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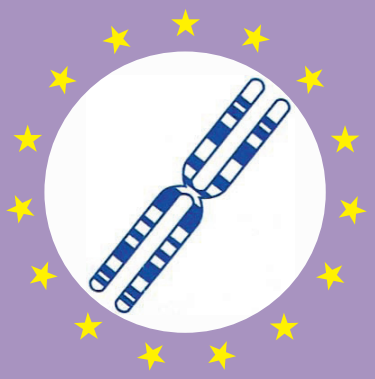

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No. 56 July 2025

Contents	*Page*
15th European Cytogenomics Conference, Leuven, Belgium, 29 June - 1 July, 2025	**2**
Program	**2**
- Abstracts invited lectures	**8**
- Abstracts selected oral presentations	**22**
- Abstracts poster presentations	**29**
--- Abstracts read by title	**94**
Literature on Social Media	**95**
E.C.A. Structures	**106**
- Board of Directors	**106**
- Committee	**107**
- Scientific Programme Committee	**107**
E.C.A. News	**107**
E.C.A. Fellowships	**107**
Minutes of the E.C.A. Board meeting March 2025	**108**
European Diploma in Classical and Molecular Cytogenetics, Nîmes 2026	**110**

E.C.A. on Facebook

As mentioned in earlier Newsletters, E.C.A. is on Facebook.
You will find announcements of interesting articles, related to cytogenomics or to biology in general, and also pictures and stories from social events related to E.C.A. and its members. Also our E.C.A. conferences will be covered on Social Media.
You can see the weekly posts and announcements via the direct link

https://www.facebook.com/Cytogeneticists/ or on the updated E.C.A. website **http://www.e-c-a.eu/**

You will find a selection of interesting Facebook posts in this Newsletter starting at page 96.
Please contact us (mariano.rocchi@uniba.it) if you wish to share an interesting news item or a pertinent article.

15th European Cytogenomics Conference, Leuven, Belgium
29 June - 1 July, 2025
Program

Conference program online: http://www.biologia.uniba.it/SEC/Leuven/ECA_conference.html
Permanent Working Groups online: http://www.biologia.uniba.it/SEC/Leuven/PWG.html

Sunday June 29	**A1:D23**	**Room**
9:30-12:45	**Hands-on workshops**	
14:30-17:30	***Permanent Working Groups*** - *Detailed program see page 6*	
14:30-16:30	***Animal, plant, and comparative cytogenetics (P. Heslop-Harrison)***	**ALO 05.100**
16:30-17:30	***Chromosomes' integrity, stability, and dynamics (J. Garcia-Sagredo - E. Volpi)***	
15:30-17:30	***Clinical and molecular approaches to cytogenetic syndromes & cytogenomics (J. Vermeesch - A. Lindstrand - D. Sanlaville)***	**GA01**
14:30-16:30	***Neoplasia (H. Rieder - P. Caria)***	**ALO 07.100**
16:30-17:30	***Prenatal diagnosis (R. Pinto Leite - J.-M. Dupont)***	

18:00-19:00	**Opening lecture - Evan E. Eichler: Complete chromosomes and complex genomes Chaired by Mariano Rocchi and Joris Vermeesch**	**GA0**
19:00	**Kick-off party**	

Monday June 30			
8:30-10:15	**Plenary session 1 - Structural variation in health and disease Chaired by Joris Vermeesch and Anna Lindstrand**		**GA0**
8:30-9:00	**Alexander Reymond**	The pleiotropic spectrum of proximal 16p11.2 CNVs	
9:00-9:30	**David Porubsky**	Structural variation of 22q11.2 region in normal and diseased human population	
9:30-10:00	**Tobias Marschall**	Mapping structural variation in the pangenome	
		selected oral presentation	
10:00-10:15	**Nivin Moustafa-Hawash**	Optical genome mapping in the clinic reveals germline and somatic findings that may influence the treatment approach	
Coffee break			
10:45-12:15	**Plenary session 2 - Complexity of cancer genomes Chaired by Roberta Vanni and Barbara Dewaele**		**GA0**
10:45-11:15	**Jonas Demeulemeester**	Multiomic long-read sequencing to improve diagnosis and care of genomically complex sarcomas	
11:15-11:45	**Stefano Santaguida**	Mechanistic insights into the consequences of chromosome segregation errors on cell physiology	

		selected oral presentations	
11:45-12:00	**Amber Verhasselt**	Optical genome mapping is a powerful diagnostic tool in non Hodgkin lymphoma	
12:00-12:15	**Şule Altiner**	Cytogenetic profile of hematological malignancies with complex karyotype a single center study from Turkey	
Poster session			
12:30-14:30		**Applied Spectral Imaging symposium**	
	Jana Limbergová	Next-gen cytogenetics: Applications of AI and digital FISH in diagnostics	**ALO 05.100**
	Yarin Hadid		
	Lee Kaplan		
14:30-15:30	**Concurrent Session 1 - Meiosis and Mitosis Chaired by Jean-Michel Dupont and Elisabeth Syk Lundberg**		**GA0**
14:30-15:00	**Marta De Ruijter-Villani**	Meiosis/mitosis transition	
15:00-15:30	**Carolina Villarroya-Beltri**	Mosaic variegated aneuploidy in development, ageing and cancer	
14:30-15:30	**Concurrent Session 2 - Automation and AI in Clinical Genetics Chaired by Barbara Dewaele and Thierry Lavabre-Bertrand**		**GA1**
14:30-15:00	**Claudia Haferlach**	Application of AI in hematological diagnostics	
15:00-15:30	**Robert Kuhn**	Online resources at UCSC	
Coffee break			
15:45-17:30	**Plenary Session 3 - Clinical Cytogenomics Chaired by Damien Sanlaville and Orsetta Zuffardi**		**GA0**
15:45-16:15	**Thomas Bourgeron**	The genetic architecture of autism: from medicine to neurodiversity	
16:15-16:45	**Jesper Eisfeldt**	Long read genome sequencing in clinical cytogenomics	
16:45-17:15	**Andrea Ciolfi**	DNA methylation profiling as a diagnostic tool	
		selected oral presentation	
17:15-17:30	**Dominik Režný**	Precision approaches in clinical cytogenomics the role of optical genome mapping and long read sequencing in structural variant detection	
17:30-20:00	**Poster session**		
18:00	**ECA General Assembly**		**GA0**

Tuesday July 1			
8:30-10:30	**Plenary Session 4 - Animal, Plant and Comparative Cytogenomics** **Chaired by Pat Heslop-Harrison and Mariano Rocchi**		**GA0**
8:30-9:00	**Aurora Ruiz-Herrera**	Evolution and function of 3D chromatin folding	
9:00-9:30	**Julie Sardos**	Diversity and diversification in banana: how in silico chromosome painting opens new perspectives for the conservation and use of an iconic fruit	
9:30-10:00	**Pat Heslop-Harrison**	What cytogenomics has done, and is doing, for agriculture in our world	
		selected oral presentations	
10:00-10:15	**Simon Mallet**	Interstitial telomeric sequences and accumulation of dna damage hallmarks of genomic ınstability ın cancer resistant wild vertebrates	
10:15-10:30	**Fengtang Yang**	Genomic complexity and evolutionary plasticity ın dugesia japonica revealed by multi ploidy chromosome level assemblies	
Coffee break			
11:00-12:15	**Concurrent Session 3 - Nuclear organisation and disease** **Chaired by Emanuela Volpi and Pat Heslop-Harrison**		**GA1**
11:00-11:30	**Martin Mensah**	Nucleolar dysfunction in rare genetic diseases	
11:30-12:00	**Cristina Cardoso**	Epigenetic reprogramming and disease	
		selected oral presentation	
12:00-12:15	**Lusine Nazaryan-Petersen**	Detection of structural variants by short read whole genome sequencing and interpretation for genetic diagnosis	
11:00-12:15	**Concurrent Session 4 - Clonal correction of constitutional chromosome imbalances** **Chaired by Damien Sanlaville and Orsetta Zuffardi**		**GA0**
11:00-11:30	**Diane Van Opstal**	Placental cytogenetic studies provide a glimpse into the black box of early embryogenesis	
11:30-12:00	**Alfredo Brusco**	Somatic recombination and the removal of the structural variant: any phenotypic outcome?	
		selected oral presentation	
12:00-12:15	**Anikó Ujfalusi**	Evaluation of X-ınactivation pattern ın carriers of X chromosome aberrations and DMD gene mutations	
Poster session			
12:30-13:15	**Illumina symposium**		**GA1**
12:30-12:45	**Drew Ellershaw**	Introduction	
12:45-13:05	**Inga Nagel**	Addressing clinical challenges in rare diseases through long-range insights by a novel genome sequencing technology	
13:05-13:15		Q&A	

14:00-15:45	**Concurrent Session 5 - Accreditation and workshop on ISCN Chaired by Franck Pellestor and Harald Rieder**		**GA0**
14:00-14:30	**Konstantin Miller**	ISO15189 and cytogenetic laboratories	
14:30-15:45	**Jean-Michel Dupont**	Workshop on ISCN 2024	
14:00-15:15	**Concurrent Session 6 - Applied Cytogenotoxicity Chaired by José Garcia Sagredo and Joan Blanco**		**GA1**
14:00-14:30	**Alba Hernadez Bonilla**	Genotoxicity and carcinogenicity of long-term micro- & nano-plastics exposure: current understanding and future directions	
14:30-15:00	**Ans Baeyens**	Chromosomal radiosensitivity testing for inborn errors of immunity	
		selected oral presentation	
15:00-15:15	**Marlene Ek**	Long-read genome sequencing enhances diagnosis of pediatric neurological disorders	
Coffee break			
16:15-17:30	**Plenary Session 5 - Prenatal Diagnosis and Preimplantation Chaired by Elisabeth Syk Lundberg and Rosario Pinto Leite**		**GA0**
16:15-16:45	**Alan Handyside**	PGT, with a focus on aneuploidies	
16:45-17:15	**Nathalie Janel**	Prenatal treatment of chromosomal anomalies	
		selected oral presentation	
17:15-17:30	**Charlotte Tardy**	Transforming prenatal cytogenetics rapid chromosomal rearrangement characterization with Nanopore sequencing	
17:30-18:30	**Closing keynote - Joris Vermeesch: Cytogenomics, where we are and where we are heading Chaired by Mariano Rocchi and Jean-Michel Dupont**		**GA0**
18:30	**Closing ceremony**		

****Rooms**** The rooms of plenary and concurrent sessions (GA0 and GA1) are on the same floor as the reception area, posters, and company booths. Due to the building's underground levels, this is considered the 4th floor. Consequently, rooms ALO 0**5**.xxx, AL0 **6**.xxx, and AL0 **7**.xxx are located one, two, and three floors above the GA0/GA1 rooms, respectively.

Permanent Working Groups - Sunday June 29 14:30-17:30		
14:30-16:30	**Animal, plant, and comparative cytogenetics (P. Heslop-Harrison)** **ALO 05.100**	
14:30-14:35	**Coordinator**	Welcome and foreword by PWG Coordinator
14:35-14:50	Andreas Houben	Does chromoanagenesis play a role in the origin of B chromosomes?
14:50-15:05	Alla Krasikova	Retrotransposable elements drive transcription of tandem repeats
15:05-15:20	Ioana Nicolae	Cytogenetic investigations in Romanian Black and White Spotted cattle
15:20-15:35	Lyubov Malinovskaya	Germline-restricted chromosome during embryogenesis in sand martin (riparia riparia)
15:35-15:50	Ahmet L Tek	A novel model for functional centromere composition in soybean and Glycine soja
15:50-16:05	Alessia Daponte	Unraveling the genetic architecture of centromeres with CENdetectHOR
16:05-16:20	Paulina Tomaszewska	Repetitive DNA sequences mark genome boundaries in the terrestrial orchid epipactis zinn
16:20	**Coordinator**	General discussion and Conclusive remarks
16:30-17:30	**Chromosomes' integrity, stability, and dynamics (J. Garcia-Sagredo, E. Volpi)** ***Exploring new chromosomal paradigms for precision medicine and early disease detection*** **ALO 05.100**	
16:30-16:40	**Coordinators**	Welcome and foreword by PWG Coordinators
16:40-16:50	Ulrike Mau-Holzmann	Multiple Variable Chromosomal Aberrations in Primary Fibroblasts: Further Hints to Chromosomal Instability as a Long-Term Effect Even Years After Irradiation
16:50-17:00	Claudia Oliveira	The DEB Test Beyond Fanconi anaemia: A new look into chromosome instability
17:00-17:10	Zuzanna Graczyk	Impact of sperm fractioning on chromosome positioning, chromatin integrity and DNA methylation level
17:10-17:20	Radhia M'kacher	Telomere Dysfunction, DNA Breaks, Chromosomal Aberration Formation and the Dark Side of the Centromere
17:20	**Coordinators**	Conclusive remarks and new initiative announcement by PWG Coordinators
15:30-17:30	**Clinical and molecular approaches to cytogenetic syndromes & cytogenomics (J. Vermeesch, A. Lindstrand, D. Sanlaville)** **GA1**	
15:30-15h35	**Coordinators**	J. Vermeesch - A. Lindstrand - D. Sanlaville
15h35-15h45	Paola Evangelidou	A rare and complex case of a male patient with DiGeorge – like phenotype, carrying three different mosaic copy number variants on chromosome 22
15h45-15h55	Caroline Schluth - Bolard	FGF14 disruption by constitutional chromoanagenesis as a cause of spinocerebellar ataxia
15h55-16h05	Leslie Kulikowski	Resolving the Unresolved: Epigenomic Profiling as a Diagnostic Tool for Copy Number Variants of Uncertain Significance
16h05-16h15	Martine Doco-Fenzy	Invdupdel Or Duptrp Rearrangements Revisited Using Array-CGH And Optical Genome Mapping

16h15-1625	Lusine Nazaryan-Petersen	Detection Of Structural Variants By Short Read Whole Genome Sequencing And Interpretation For Genetic Diagnosis
16h25-16h35	Marlene Ek	Long Read Genome Sequencing Enhances Diagnosis Of Pediatric Neurological Disorders
16h35-16h45	Igor Lebedev	X Chromosome Cnv Reclassification Integrating X Inactivation Status For Improved Pathogenicity Assessment
16h45-16h55	Esmee Ten Berk de Boer	Investigating X Chromosome Inactivation Patterns In X Autosome Translocations Using Long Read Sequencing And The T2t Genome Assembly
16:55-17:30	**Coordinators**	General discussion and Conclusive remarks
14:30-16:30	**Neoplasia (H. Rieder - P. Caria)**	**ALO 07.100**
14:30-14:35	**Coordinators**	Welcome and foreword by PWG Coordinators
14:35-14:45	Tadeusz Kałużewski	Evaluation of the Utility of TERT Promoter Mutations in the Early Detection of Urothelial Cancer
14:45-14:55	Marija Dencic Fekete	Distribution of gene aberrations in chronic lymphocytic leukemia by NGS testing in a Serbian patient cohort
14:55-15:05	Marie-Bérengère Troadec	What is wrong with the deletion of chromosome region 5q in myelodysplastic syndrome? Identification of a novel actor of the sensitivity to lenalidomide of MDS with del(5q)
15:05-15:15	Uliana Lykhova	Beyond t(12;21): unveiling the hidden layers in all karyotypes
15:15-15:25	Laura Yissel Rengifo	Dynamic Follow Up of Tumor Burden in Multiple Myeloma Through Analysis of ccfDNA Markers
15:25-15:35	Seon Y Kim	Detection of measurable residual disease using fluorescence in situ hybridization compared with multiparametric flow cytometry in patients with B- lymphoblastic leukemia
15:35-15:45	Hila Lederman Nachmias	New Insights Affecting Classification, Prognosis and Treatment of Multiple Myeloma Using Optical Genome Mapping
15:45-15:55	Soumaya Mougou-Zerelli	Mapping Cancer Risk in Constitutional Chromosomal Deletions: A Cytogenetic Analysis
15:55-16:30	**Coordinators**	General discussion and Conclusive remarks
16:30-17:30	**Prenatal diagnosis (R. Pinto Leite - J.-M. Dupont)**	**ALO 07.100**
16:30 -16:35	**R. Pinto Leite**	Introduction
16:35 -16:45	A.Vardanyan	Retrospective analysis of cytogenetic findings in pregnant women at risk following first-trimester screening: insights from NIPT in Armenia
16:45 - 16:55	M.A. Caro Miro	Circuit of prenatal screening with free circulating fetal DNA in the balearic islands
16:55 - 17:10	R. Pinto Leite	NIPT in Europe, Result of the PWG survey
17:10 - 17:20	K.Cassinari	First Prenatal Case of Jumping-like Translocations: Unraveling Complex Chromosomal Rearrangements
17:20 - 17:30	N.Chatron	Comparative Efficacy of cfDNA and aCGH in Detecting Chromosomal Aberrations Post-Miscarriage

Abstracts - Invited Lectures

Opening lecture

Complete chromosomes and complex genomes

Evan E. Eichler

Department of Genome Sciences and Howard Hughes Medical Institute,
University of Washington, Seattle, WA

Advances in long-read sequencing have enabled telomere-to-telomere (T2T) sequencing of genomes essentially providing for the first time sequence resolved chromosomes. This advance has meant that all forms of genetic variation can be discovered including previously under-appreciated complex patterns of genetic variation in regions previously regarded as inaccessible to sequence and assembly. I will present our most recent work sequencing diverse human and nonhuman primate (NHP) genomes including the development of human pangenomes. The data provide new insights into genetic diversity and the mutational processes shaping genomes. This is leading to new genetic associations, the discovery of pathogenic variants previously missed by short-reads, the identification of new duplicated genes and candidates for selection in specific human populations and species-specific changes. Specifically, we are finding that inversions and segmental duplications are intimately linked leading to the emergence of newly minted genes at the edges whilst simultaneously creating genomic instability predisposing our genomes to rearrangement associated with disease. Assembly-based variant discovery has the potential to provide a complete understanding of the evolution of every basepair of the human genome and an improved model of the genetic changes especially neurodevelop-mental genes that make us uniquely human.

L1 The pleiotropic spectrum of proximal 16p11.2 CNVs

Alexander Reymond

Center for Integrative Genomics
University of Lausanne, CH

Recurrent 600kb-long genomic rearrangements at 16p11.2 BP4-5 represent one of the most common causes of genomic disorders. They are mediated by human-specific duplications that appeared at the beginning of the modern human lineage, suggesting that their expansion has a possible evolutionary advantage that outweighs chromosomal instability.
These copy number variants (CNVs) are among the most frequent genetic causes of neuro-developmental and psychiatric disorders, as they are found in 1% of individuals with autism spectrum disorders and schizophrenia. They were also originally associated with reciprocal defects in head size and body weight, but have since been associated with a plethora of phenotypic alter-ations, albeit with high variability in expressivity and incomplete penetrance. Revealing the complex and variable clinical manifestations of these CNVs is crucial for accurate diagnosis and personalized treatment strategies for carriers.
The 16p11.2 BP4-5 CNVs showcase variable expressivity and pleiotropy, as they are deleterious enough to be enriched in clinical cohorts but not enough so to be absent from population cohorts.

L2 Structural variation of 22q11.2 region in normal and diseased human population

David Porubsky[1,2], DongAhn Yoo[1], Philip Dishuck[1], Nidhi Koundinya[1], Erika Souche[3], William T. Harvey[1], Thomas Webber[2], Vasiliki Tsapalou[2], Katherine M. Munson[1], Kendra Hoekzema[1], Daniel Chan[4], Tiffany Leung[4], Marta S. Santos[3], Patrick Hasenfeld[2], Eva B.

Garagorri[2], Jan O. Korbel[2], Joris R. Vermeesch[3,5], Peter Lansdorp[4,6], Evan E. Eichler[1,7]

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[5]Department of Human Genetics, Centre for Human Genetics, University Hospitals Leuven, Leuven, 3000, Belgium
[6]Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada
[7]Howard Hughes Medical Institute, University of Washington, Seattle, WA 98195, USA

The chromosome 22q11 microdeletion syndrome is the most common recurrent genomic disorder in the human population. Rearrangement breakpoints are mediated by large copy-number polymorphic segmental duplications (SDs) aka low copy repeats (LCR22A-D) that have been challenging to characterize and reconcile at a population genetic level. We fully sequence-resolved the genomic architecture of 135 chromosome 22q11 haplotypes from a diversity panel of the 1000 Genomes Project samples. We find that the majority of the copy-number variation is polarized to the most proximal LCRA copy where 50 distinct structural configurations have been observed ranging from ~189 kbp to ~2.15 Mbp (11-fold length variation). Most of this variation is driven by a higher-order cassette of 105 kbp in length, flanked by 25 kbp long inverted repeats. This repeat structure harbors *GGT2* protein-coding genes and transcribed pseudogenes that emerged in the human-chimp ancestral lineage and specifically expanded in the *Homo* genus 1.0 [0.8-1.2] million years ago (MYA). We identified and validated a total of 9 distinct inversion polymorphisms including four recurrent ~2.28 Mbp inversions extending across the critical region from (LCRA-D) and two smaller inversions (LCRA-B and LCRB-D) each observed only once in this study. We sequenced and assembled two parent-child duos and one trio and show that LCRA-D deletion breakpoints map to the 105 kbp repeat unit while inversion breakpoints associate with the 25 kbp repeat unit nearby palindromic AT-rich repeats (PATTRs). In two of three cases, the rearrangements occurred on parental haplotypes involving larger LCR22A structures and show more complex unequal crossover events associated with gene conversion and multiple breakpoints. Our findings suggest that specific haplotype configurations will be both protective and susceptible to chromosome 22q11 microdeletion.

L3 Pangenome based analysis of structural variation

Tobias Marschall
Heidelberg, Germany

Breakthroughs in long-read sequencing technology and assembly methodology enable the routine de novo assembly of human genomes to near completion. Such assemblies open a door to exploring structural variation (SV) in previously inaccessible regions of the genome. The Human Pangenome Reference Consortium (HPRC) and the Human Genome Structural Variation Consoritum (HGSVC) have produced high quality genome assemblies, which provide a basis for comparative genome analysis using pangenome graphs.
First, we will ask how a pangenomic resource like this can be leveraged in order to better analyze structural variants in samples with short-read whole-genome sequencing (WGS) data. In a process called genome inference implemented in the PanGenie software, we can use a pangenome reference to infer the haplotype sequences of individual genomes to a quality clearly superior to standard variant calling workflows. This process allows us to detect more than twice the number of structural variants per genome from short-read WGS and therefore provides an opportunity for genome-wide association studies to include these SVs.

Second, we introduce Locityper, a tool specifically designed for targeted genotyping of complex loci using short and long-read whole genome sequencing. For each target, Locityper recruits and aligns reads to locus haplotypes and finds the likeliest haplotype pair by optimizing read alignment, insert size and read depth profiles. Locityper accurately genotypes up to 194 of 256 challenging medically relevant loci (95% haplotypes at QV33), an 8.8-fold gain compared to 22 genes achieved with standard variant calling pipelines. Furthermore, Locityper provides access to hyperpolymorphic HLA genes and other gene families, including KIR, MUC and FCGR.

L4 Comprehensive multimodal profiling to advance sarcoma precision oncology and clinical care

Jonas Demeulemeester[1,2,3], Robert A. Forsyth[1,2,3], Jef Baelen[4], Laurens Lambrechts[1,2,3], Isabelle Vanden Bempt[4]

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[2]VIB Center for AI and Computational Biology, Leuven, Belgium
[3]Department of Oncology, KU Leuven, Leuven, Belgium
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Background: Sarcomas represent 1-2% of adult cancers but encompass over 100 subtypes, posing unique challenges for diagnosis and treatment. Current genetic testing relies on multiple sequential assays, each providing limited insight while delaying clinical decisions. Notably, up to 20% of soft tissue sarcomas show no known molecular markers with standard approaches. There is an urgent need for comprehensive molecular profiling to improve diagnosis, guide therapy selection, and advance precision oncology for sarcoma patients.
Methods: We are implementing an innovative multimodal profiling approach leveraging three complementary technologies: (1) Fiber-Seq for simultaneous genome-wide detection of mutations, DNA methylation, and chromatin accessibility; (2) Nanopore direct RNA-seq to capture full-length transcripts and their modifications; and (3) data-independent acquisition mass spectrometry for deep proteome quantification. We are aiming to profile 375 sarcomas, prospectively collected at diagnosis. Containerized analysis workflows will be implemented to enable reproducible processing of this complex data, with results delivered through standardized clinical reporting templates designed for molecular tumor boards.
Results: Our pilot Fiber-Seq data on a diverse sarcoma cohort demonstrates the feasibility of comprehensive multiomic profiling, revealing previously undetectable alterations with potential therapeutic relevance. We anticipate identifying clinically actionable insights in over one-third of cases, impacting both diagnosis and treatment selection. We will also strive to accelerate sarcoma research through responsible data sharing and providing open-source analysis workflows.

L5 Mechanistic insights into the consequences of chromosome segregation errors on cell physiology

Stefano Santaguida

European Institute of Oncology and University of Milan

Genome integrity is maintained through faithful chromosome segregation at each cell division, in which one copy of a duplicated chromosome is deposited in each daughter cell. Errors in this process lead to aneuploidy, a condition in which cells carry an abnormal karyotype. Aneuploidy is the most common chromosome aberration in humans and is a widespread feature of solid tumors. To shed light on how aneuploidy contributes to tumorigenesis, it is crucial to determine how this condition impacts normal cells and to determine how it affects cellular functions. By inducing mitotic errors in otherwise pseudo-diploid cell lines, our lab is investigating

the immediate consequences of chromosome mis-segregation on cell physiology. Here, I will present our findings on the interaction between micronuclei, a common byproduct of chromosome mis-segregation often found in aneuploid cells, and components of the autophagic machinery. I will discuss the implications for micronuclei recognition by autophagic proteins and how this process modulates wellcharacterized features of micronuclei, including their ability to trigger inflammation and their capacity to provide an optimal substrate for chromothripsis.

L6 Meiotic-to-mitotic transition and chromosome segregation errors in non-rodent mammalian embryos

Marta de Ruijter-Villani[1,2,3]

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[2]Hubrecht Institute, KNAW, Utrecht, the Netherlands
[3]Division Woman and Baby, University Medical Centre Utrecht, Utrecht, the Netherlands

The transition from meiosis to mitosis is a pivotal process in early development. One of the most remarkable features of this transition is the shift from acentrosomal to centrosomal spindle assembly. The centrosomes, composed by two centrioles surrounded by peri-centriolar material (PCM), are the main microtubule-organizing centres in somatic cells and critically regulate the formation of the spindle, its positioning and bipolarization and the correct segregation of the chromosomes. In mammals, oocytes lose their centrioles during oogenesis, while in sperm cells, centrioles are so heavily remodeled during spermiogenesis that they no longer resemble canonical ones. At fertilization, sperm- derived centrioles are introduced in the fertilized oocyte's cytoplasm, however, we recently demonstrated that centrosomes play a minor role during zygotic spindle assembly and are often mal-positioned (not at the spindle poles). We used a combination of quantitative real-time imaging of bovine zygotes, fixed-cell analysis and small-molecule perturbation to investigate the transition from meiosis to mitosis and the effects of centrosome positioning on chromosome segregation fidelity.
Live imaging showed that in 57% of zygotes, the centrosomes were mal-positioned, while in 26% of the zygotes the centrosomes showed impaired microtubule nucleation (non-visible centrosomes). Accurate chromosome segregation occurred in all zygotes with correctly positioned centrosomes, whereas errors were observed in 56% of the zygotes with mal-positioned and in 69% of the ones with non-visible centrosomes. The centrosome containing the sperm-proximal-centriole aways associated with the maternal pronucleus, while the one containing the sperm-distal-centriole associated with the paternal pronucleus. Centrosome positioning dictated cleavage plane. When the division plane was parallel to the pronuclear-interface, segregation errors were more frequent (89% vs 52%).
Inhibiting centriole biogenesis did not increase mal-positioning or segregation errors but caused cell arrest at the two-cells stage. Inhibiting centriole maturation impaired PCM recruitment and microtubule nucleation from the centrosomes in a similar fashion as in wild type non-visible centrosomes but did not affect spindle assembly and bipolarization.
Our results show that, although dispensable for spindle assembly in the first cell cycle, centrosomes play a key role in ensuring correct chromosome segregation in mammalian zygotes and are necessary for cycle progression at the two cell stage.

L7 Mosaic variegated aneuploidy in development, ageing and cancer

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Mosaic variegated aneuploidy (MVA) is a rare genetic disorder in which aneuploid cells affecting different chromosomes are continu-

ously generated and eventually comprise 10–40% of the patient's total cells. MVA is characterized by various developmental defects and, depending on the mutation, an increased susceptibility to cancer. Despite its rarity, MVA offers a unique clinical context for understanding the consequences of aneuploidy in humans. By analyzing blood samples from MVA patients and mouse models with chromosome numbers alterations, we are investigating cell-autonomous and non-cell autonomous consequences of aneuploidy in humans.

L8 Application of AI in hematological diagnostics

Claudia Haferlach

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Artificial intelligence (AI) in the field of haematological diagnostics is rapidly evolving. A variety of applications facilitate and improve the work of doctors and scientists in diagnostics. AI, through machine learning (ML) and deep learning (DL) algorithms, has demonstrated remarkable capabilities in analyzing complex datasets, surpassing traditional diagnostic methods in both speed and accuracy. The application of AI in hematological diagnostics encompasses several key areas, including the automated analysis of blood samples, the automated sorting of chromosomes to karyotypes, and the prediction of disease progression and treatment outcomes. AI algorithms have been successfully implemented to perform differential blood counts identifying and classifying various blood cell types with high precision. This automation not only enhances the efficiency of diagnostic processes but also minimizes human error, leading to more reliable results.

Predictive analytics offers the potential to revolutionize the management of hematological diseases by forecasting disease progression and response to treatment. By analyzing patterns in historical patient data, AI models can predict outcomes with a high degree of accuracy, facilitating personalized treatment plans and improving patient prognosis. Despite the promising advancements, the integration of AI into clinical practice faces challenges, including data privacy concerns, the need for extensive high quality datasets to train AI models, and the requirement for clinicians to adapt to new technologies. Moreover, the interpretability of AI decisions remains a significant hurdle, necessitating ongoing research to develop more transparent AI systems. In conclusion, the application of AI in hematological diagnostics holds immense potential to enhance diagnostic accuracy, streamline laboratory workflows, and personalize patients treatment. As AI technologies continue to evolve, their integration into hematology promises to usher in a new era of precision medicine, characterized by more efficient, accurate, and personalized care.

L9 Online resources at UCSC Genome Browser

Robert Kuhn

UCSC Genome Browser, Santa Cruz, US

The UCSC Genome Browser is a widely used graphical viewer that offers access to a variety of clinical CNV data in an intuitive interface. A brief overview will be offered to show where to find useful datasets and features and how to preserve Browser views for future use or for sharing with colleagues. The Browser features a coordinate-based display of data, allowing views of data from a wide variety of sources at locations of interest. Convenient link-outs to the original data providers give easy access to more detailed data.

L10 The genetic architecture of autism: from medicine to neurodiversity

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The genetic contribution to autism is high (>80% of heritability), but its architecture involves a complex combination of rare and common variants. Autism shares genetic variations with other conditions such as attention deficit hyperactivity disorders (ADHD), intellectual disability, and epilepsy, but little is known about the factors that contribute to the diversity of the clinical trajectories. Remarkably, if rare variants with strong effects are most often associated with intellectual disability, common variants taken altogether are in contrast positively associated with intelligence. In this presentation, I will introduce recent results that shed new light on the inheritance of autism and on some of the underlying mechanisms. For example, I will illustrate how genes associated with autism shape brain connectivity by regulating gene expression and synaptic function. Finally, I will present how we are currently studying Resilience to understand why some carriers of genetic variants seem to be protected from adverse symptoms while others have more difficulties to thrive in the society.

L11 Long read genome sequencing in clinical cytogenomics

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Clinical genetic laboratories often require a comprehensive analysis of chromosomal rearrangements/structural variants (SVs), including large events like translocations and inversions, supernumerary ring/marker chromosomes and small deletions or duplications. Understanding the structure and complexity of these events, as well as their clinical consequences requires accurate detection of their breakpoint junctions. While short-read WGS is well established as a first-tier diagnostic test, it still has limitations; especially for resolving complex or balanced SVs. In this context, long-read WGS has emerged as a promising alternative with the potential to capture the complete scope of structural variation in the human genome.
Recognizing the promise and challenges of long-read WGS, we have performed a series of pilot projects, exploring and developing the potential of long-read WGS in clinical cytogenomics. These projects include a national pilot project including 16 carriers of known cytogenetically visible aberrations, as well as a prospective study including 100 probands, which were analyzed using long-read and short-read WGS in parallel.
Through these studies, we have developed a national long-read WGS pipeline, dubbed Nallo, optimized laboratory protocols for both ONT and PacBio sequencing using clinically available DNA, and established procedures for the characterization of complex rearrangements based on the long-read sequencing data. Overall, we find that the long-read WGS data provides valuable insights for clinical cytogenomics, however its clear that novel reference genomes, algorithms and interpretation tools are needed to fully benefit from the data, especially for labs already performing comprehensive short-read WGS analyses. Herein we detail the results our long-read WGS pilot projects, as well as our planned prospective study including over 1000 rare disease genomes.

L12 DNA methylation profiling as a diagnostic tool

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DNA methylation (DNAm) is a key epigenetic mark consisting in the covalent addition of a methyl group at cytosine's C5 position. This reversible modification regulates gene expression in a dynamic and finely controlled fashion,

which is required for the control of cellular processes and developmental programs from the early embryo stages in humans. As a consequence, somatic cells exhibit a definite and stable DNAm pattern, specifically contributing to the control of the specific lineage-related gene expression programs.

Alteration of the epigenetic regulatory molecular mechanisms controlling the DNAm status of the genome has been recently reported to underlie an increasing number of human rare congenital disorders (RDs) with genetic or teratogenic etiology. Studies conducted over the past years in many of these diseases have shown that unique and specific genome-wide DNAm patterns can result from the underlying causal gene defects and could be used as sensitive biomarkers, which are commonly referred as "DNAm signatures" or "episignatures". Therefore, genomic DNA obtained from peripheral blood is generally used by applying microarray technology combined with supervised and unsupervised classification approaches, allowing to confirm or rule out a clinical diagnosis based on an existing DNAm signature.

Although the application of genomic sequencing technologies has proven its eKicacy in the diagnostic workflow of RDs in the last two decades, a significant proportion (up to 50%) of these "unclassified" conditions remain undiagnosed. Moreover, this technological advancement has deepened the gap between our capacity to read the DNA sequence and our ability to interpret genome variation, as documented by the growing prevalence of variants of unknown significance (VUS) in diagnostic test reports. The use of genome-wide DNAm array analysis can hence represent a new highly informative complementary diagnostic tool for an increasing number of genetic and non-genetic RDs, allowing to validate or reject a clinical diagnosis in cases where genomic sequencing is inconclusive, as well as to support functional reclassification of VUS.

L13 Evolution and function of 3D chromatin folding

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Studies examining the evolution of genomes have been mainly focused on sequence conservation. However, the inner working of a cell implies a tightly regulated crosstalk between complex gene networks, controlled by small dispersed regulatory elements of physically contacting DNA regions. How these different levels of chromatin organization crosstalk in different species underpins the potential for genome evolutionary plasticity. I will provide an overview on the evolution of chromatin organization, discussing on general aspects of the mode and tempo of genome evolution to later explore the multiple layers of genome organization. We propose that both genome and chromosome size modulate patterns of chromatin folding and that chromatin interactions facilitate the formation of lineage-specific chromosomal reorganizations. Overall, analyzing the mechanistic forces involved in the maintenance of chromatin structure and function of germ line is critical for understanding genome evolution, maintenance, and inheritance.

L14 Diversity and diversification in banana: how in silico chromosome painting opens new perspectives for the conservation and use of an iconic fruit

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With the rise of genomics, the characterization of crop genetic resources has entered a new era. Here, we present how the SNP-based characterization of ancestry along chromosomes – the in silico chromosome painting approach - is game changing for the conservation and the use of banana genetic resources. Banana is a vegetatively propagated crop presumably composed of clonal cultivars and clonal cultivar groups. Using in silico chromosome painting enables to provide fine-scale genomic identity to cultivars and cultivar groups. Doing so, it allows the identification of fixed clonal diversification events such as mitotic recombination and indels, sometimes providing a unique genomic signature to specific varieties. It also allowed to identify pluri-clonal cultivars groups in which the different varieties result from different sexual events. By enabling the characterization of a hidden component of banana diversity, this method can be used for the routine management of ex-situ collections, notably for gap analysis and for the regular check of the genetic integrity of the germplasm. These findings also constitutes a first path towards a wider and wiser use of banana genetic resources in breeding, notably through the selection of targeted ancestral genomic regions in breeding lines parents. Finally, these discoveries could also trigger the direct use of existing banana genetic resources to buffer the effects of climate change on traditional agrosystems.

L15 What cytogenomics has done, and is doing, for agriculture in our world

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Agriculture and farming has been enormously successful in producing more, higher quality, food for the huge increase in human population to more than 8 billion people. About half of the improvement in yields has come from better ways to grow the crop, and half from genetics. From classical cytogenetics to cytogenomics, information about chromosomes, genomes, ploidy and meiosis has underpinned the improvement in crops including their yields and resistances to biotic (disease) and abiotic (environmental) stress. In this talk, I will explore examples from our work in a wide range of species – Brassica, oats and other cereals, forage grasses, bananas, and sheep, goats and bovids – where chromosome biology has underpinned genetic improvements in diploid and polyploid species, helping to understand and exploit the diversity in wild and cultivated relatives. In situ hybridization and genomic probes have been valuable in following introgression and substitutions of alien chromosomes, and understanding the nature of hybrids which include many of the most successful grass and brassica crops. Repetitive DNA, including transposons, are some of the most rapidly evolving sequences, and I will show examples where they can be used as markers for crop breeding, and themselves lead to diversity and modulation of gene expression including agronomic and abiotic (environmental) or biotic (disease) resistance traits. Genome assembly combined with chromosome analysis has shown how species change during evolution and in breeding timescales, and can direct ways to improve crop genetics. With the immense challenges of increasing agricultural sustainability – with current practices causing pollution, loss of soil and water, and greenhouse gas emissions – and given the static human population, outside Africa, we are at a point where we can continue genetic improvement of crops, exploiting biodiversity and cytogenomics approaches to reduce the impact of food production on the environment and solve real-world agricultural challenges. Further details, presentation slides, and references are available from www.molcyt.org .

L16 Nucleolar dysfunction in rare genetic diseases

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Background: Brachyphalangy, polydactyly and tibial aplasia syndrome (BPTAS) is an extremely rare and complex multiorgan malformation disorder of unknown cause. A patient with BPTAS had a novel de novo frameshift mutation at the start of the C-terminal acidic intrinsically disordered region (IDR) of the HMGB1 protein. HMGB1 was previously associated with a neurodevelopmental disorder. The role of mutations in such IDRs is not well understood. IDRs are known to drive phase separation and the formation of biomolecular condensates, but their functions remain largely unclear.
Objective: To investigate the role of mutations in IDRs in BPTAS and to determine whether similar mutations affect the properties and functions of condensates in general.
Materials and methods: Genome, exome and targeted sequencing were performed in five unrelated individuals with BPTAS. Droplet formation assays were performed with wild-type and mutant HMGB1. Microscopy and fluorescence recovery after photobleaching (FRAP) techniques were used with U2OS cells expressing HMGB1 and other protein variants. Databases such as ClinVar, COSMIC, 1000

Genomes and dbSNP were searched for pathogenic variants in IDRs.
Results: Patients with BPTAS had de novo frameshift mutations in HMGB1 that replaced the acidic IDR of the protein with an arginine-rich basic tail. This change altered the phase separation behaviour of HMGB1 and increased its partitioning in the nucleolus, leading to nucleolar dysfunction. A screen of more than 200,000 known variants in C-terminal IDRs revealed 624 frameshift mutations resulting in similar arginine-rich tails. Increased nucleolar partitioning occurred in 12 out of 13 variants tested, with several also disrupting rRNA biogenesis.
Conclusion: Frameshift-induced IDR-swapping represents a novel disease mechanism and is responsible for BPTAS. This mechanism may also shed light on the functional consequences of many known pathogenic variants that have been observed but not yet functionally characterized.
Reference: Mensah*, Niskanen*, et al. Nature 2023, PMID:36755093

L17 Epigenetic reprogramming and disease

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From yeast to man, the genome is non-homogenously packed within the cell nucleus. This spatial compartmentalization is highly dynamic during development and in disease and regulates genome activity. Heterochromatin is the highly compacted form of chromatin and hallmarked by high DNA methylation in mammals. MeCP2 and other members of the methylcytosine binding domain protein family are DNA methylation readers and have also been reported as heterochromatin organizers [1]. *MECP2* gene mutations were found in *circa* 90% of patients with a human neurological disorder called Rett syndrome and affect chromatin organization [2,3]. Binding of MeCP2 protein to heterochromatin protects methylcytosine from further oxidation by the TET (Ten-Eleven Translocation) dioxygenase enzymes, thus, lowering transcriptional noise [4]. By combining liquid-liquid phase separation (LLPS) analysis and single-molecule tracking with quantification of local MeCP2 concentrations *in vitro* and *in vivo,* we explored the mechanism of MeCP2-driven heterochromatin compartmentalization and dynamics. We show that MeCP2 alone forms liquid-like spherical droplets via multivalent electrostatic interactions and with isotropic mobility. Crowded environments and DNA promote MeCP2 LLPS and slow down MeCP2 mobility. DNA methylation, however, restricts the growth of heterochromatin compartments correlating with immobilization of MeCP2. Furthermore, MeCP2 self-interaction is required for LLPS and is disrupted by Rett syndrome mutations [5]. In summary, we modelled the *in vivo* heterochromatin compartmentalization as well as MeCP2 concentration and heterogeneous motion using a minimal *in vitro* system. Furthermore, we compare it with other MBD family members as well as heterochromatin protein 1 family.

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L18 Placental cytogenetic studies provide a glimpse into the black box of early embryogenesis

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Objective: Confined placental mosaicism (CPM) is a type of chromosomal mosaicism present in the placenta but not in the fetus, and it was discovered in the eighties of last century through the use of chorionic villus sampling (CVS) for

prenatal diagnosis. It affects 1-2% of CVS cases and therefore was a rare phenomenon for a long time. It regained attention after the introduction of non-invasive prenatal testing (NIPT) that is applied at a much larger scale than invasive prenatal diagnosis. Since NIPT investigates placental cell-free DNA in maternal blood to identify fetuses at risk for a chromosome aberration, the numbers of CPM increased being the major origin of discordant results of NIPT (NIPT abnormal and fetus normal).

The aim of this study was to confirm CPM involving a trisomy or structural chromosome aberration (SA) in the placenta after delivery, in cases with abnormal NIPT but normal or sometimes differently abnormal follow-up of the fetus. Additionally, we examined the distribution of abnormal cells over the different placental lineages of cytotrophoblast (CTB) (trophectoderm origin) and mesenchymal core (MC) (inner cell mass origin) to study their embryonic origin.

Methods: Four chorionic villus (CV) biopsies from four placental quadrants were requested in cases of abnormal NIPT where CPM was assumed based on follow-up investigations during pregnancy. Both cell lineages of the placental CV, cytotrophoblast (CTB) and mesenchymal core (MC), were analyzed separately with SNP array.

Results: A total of 117 placentas were investigated. If CPM involved a trisomy, it could be confirmed in 67 % (59/88) of the placentas. Three quarters of the CTB and MC biopsies from these mosaic placentas were uniformly normal (57 %) or abnormal (20 %), and only a minority showed mosaicism. Among 16 cases of proven CPM where first trimester CV were examined as well, 11 had chromosomally normal CV results during pregnancy.

If NIPT detected a SA, it could be confirmed in 55% (16/29) of the placentas. In 11/16 cases, exactly the same chromosome aberration as detected with NIPT, all with a normal fetus, was confirmed in the placenta. In 5/16 confirmed cases, the SA showed to be involved in complex mosaicism involving different abnormal cell lines of which only one ended up in the fetus which was different from the NIPT result in 4/5 cases (and pathogenic in 2/5), while the rest, including the cell line detected with NIPT, remained confined to the two placental lineages, especially to the CTB.

Conclusion: Cytogenetic investigations of term placental biopsies suspected to be affected with CPM involving a trisomy did not reveal the chromosome aberration in one third of the placentas. This seems to be caused by the patchy pattern in which chromosomally abnormal cells are distributed over the placenta with the majority of the biopsies being uniformly normal. These observations seem to fit recent findings that every bulk placental sample taken randomly is in fact derived from a single parental branch that is genetically distinct. Further CPM research, including its clinical impact, requires the analysis of more than four biopsies to get insight into the extent of the affected part of the placenta.

If CPM involved a SA, confirmation in the term placenta was only achieved in about half of the cases. In one third of these, the SA showed to be involved in complex feto-placental mosaicism despite only one normal or abnormal cell line in amniotic fluid. This warrants genome-wide confirmatory analysis of the fetus when NIPT shows a SA. Further, these complex cases resemble what is seen in preimplantation embryos, confirming that complex mosaicism in these embryos are not artefacts, but a biological phenomenon.

L19 Somatic recombination and the removal of the structural variant: any phenotypic outcome?

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Within the intricate landscape of the human genome, structural variants can be spontaneously reshaped or eliminated through the dynamic process of somatic recombination. This cellular self-correction unfolds through diverse mechanisms, each with the potential to dramatically alter an individual's phenotype.

Imagine a scenario where a detrimental inherited genetic anomaly is silently repaired in a subset of cells during an organism's development; this is the essence of "revertant mosaicism," a phenomenon increasingly recognized in conditions like Primary Immunodeficiency Diseases and Diamond-Blackfan Anemia. In these cases, the wholesale replacement of a mutated chromosomal segment via copy-neutral loss of heterozygosity (CN-LOH) can restore gene function in clonal cell populations, sometimes leading to a milder disease course or, remarkably, spontaneous remission.

The story of somatic recombination is not always one of straightforward rescue. In the realm of hematological malignancies, CN-LOH frequently emerges, not to correct, but to consolidate a cell's oncogenic trajectory by duplicating existing cancer-driving mutations or unmasking recessive tumor suppressor genes. This highlights the dual nature of somatic recombination: a guardian of genomic integrity that can, under certain pressures, become an instrument of clonal selection and disease progression. Indeed, the ever-expanding field of clonal hematopoiesis research reveals how both monogenic predispositions and the subtle interplay of polygenic inheritance can steer the fate of hematopoietic stem cells, with somatic recombination events acting as critical junctures in their clonal evolution.

Sometimes, the genetic narrative involves an early post-zygotic drama where an inherited unbalanced translocation, a major genomic disruption, is partially "rescued". Through mitotic recombination, a mosaic state can arise where some cells retain the imbalance while others achieve a corrected, albeit sometimes uniparentally disomic, segmental constitution. The clinical outcome of such events is a complex interplay between the proportion of corrected cells, the tissues involved, and the developmental window during which the correction occurs. Even in cases like Shwachman-Diamond Syndrome, a ribosomopathy, somatic genetic rescue can occur through acquired mutations in a different gene, *EIF6*, which alleviate the primary defect in ribosome assembly, showcasing the ingenuity of cellular adaptation.

The ability to detect these subtle yet significant genomic alterations using tools like SNP arrays and advanced sequencing techniques has revolutionized our understanding. However, the mosaic nature of these events presents diagnostic challenges, urging a multi-tissue approach and careful interpretation. Unraveling these narratives of spontaneous genomic correction and alteration not only deepens our knowledge of fundamental genetic mechanisms but also holds promise for predicting disease trajectories and potentially inspiring novel therapeutic avenues that harness or mimic these natural rescue pathways.

L20 ISO15189 and cytogenetic laboratories

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The new edition of ISO 15189:2022, Requirements for Quality and Competence in Medical Laboratories, is the international basis for accreditation of medical laboratories. Reason for the update was the alignment with ISO/IEC 17025 - General requirements for the competence of testing and calibration laboratories concerning non-medical laboratories and the general principles of ISO 9001 - Quality management systems – Requirements.

New aspects of the revised standard relate to impartiality and confidentiality of medical laboratories, requirements regarding patients, measurable objectives, risk management, process requirements, requirements for internal quality control of examination procedures, participation in external quality assessment, requirements for reports, data and information management including aspects of cybersecurity, and risk management in emergency situations.

Practical examples of how to avoid non-conformances with a focus on new requirements of implementing the ISO 15189:2022 will be given.

L21 Workshop on ISCN 2024

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Since the 70's and the rise of medical cytogenetics, ISCN has been a reference document for harmonisation of karyotype writing. Numerous iterations of this nomenclature have included major technical advances in molecular cytogenetics as well as improved rules for depicting complex results, but at the same time incorporated some redundances and inconsistencies between different chapters.
The new ISCN 2024 has been reviewed extensively with a brand-new chapter 4 presenting an overview of the general rules applying for all techniques, while specific recommendations as well as many new examples are available in each technology specific chapters. A new chapter 9 is devoted to optical genome mapping technique and the sequencing chapter 11 has been extended with many new examples. Finally, the chapter 10 which deals with region specific assays has been also extensively reviewed to include region specific analysis with any technique and a new part for methylation analysis nomenclature.
Following an overview of the main changes in the nomenclature rules, an interactive presentation of key examples will allow the participants to challenge their knowledge on ISCN.

L22 Genotoxicity and carcinogenicity of long-term micro- & nanoplastics exposure: current understanding and future directions

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Micro- and nanoplastics (MNPLs) are emerging pollutants that are now ubiquitous across all environmental compartments. Increasing evidence indicates that humans are chronically exposed to these particles via inhalation and ingestion, and that their small size facilitates absorption, systemic distribution, and bioaccumulation. While the biological effects of MNPLs are currently the subject of intensive research, the long-term consequences of chronic exposure remain largely underexplored. Among the most critical endpoints from a human health risk perspective are genotoxicity and carcinogenicity. This presentation will provide an overview of the current state of knowledge regarding the genotoxic and carcinogenic potential of MNPLs, with particular emphasis on the methodologies developed and the findings obtained within the framework of the EU-funded PlasticHeal project (www.plasticheal.eu/en). Key research priorities and persisting knowledge gaps will also be discussed, with the aim of informing future research and advancing MNPLs risk assessment strategies.

L23 Chromosomal radiosensitivity testing for inborn errors of immunity

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Inherited defects in the human immune system, known as inborn errors of immunity (IEI), encompass a wide range of genetic disorders that impair innate and/or adaptive immune responses. Among these, certain comprise defects in DNA repair factors, leading to (severe) combined immunodeficiencies, bone marrow failure, heightened risk to malignancies, and increased sensitivity to ionizing radiation (radiosensitivity, RS). Detecting RS is clinically relevant, particularly for tailoring radiation-based treatments and optimizing patient care. In this study, chromosomal radiosensitivity was evaluated in a diverse cohort of 107 IEI patients using the G0 cytokinesis-block micronucleus assay. The analysis revealed considerable heterogeneity in RS levels among different genetic and clinical categories. Pronounced RS was consistently

observed in all patients with ataxia-telangiectasia, as well as in single cases with FANCI and ERCC6L2 deficiencies, whereas no marked RS was detected in the remainder of the cohort. Age influenced both spontaneous and radiation-induced micronuclei (MN) formation, but clinical manifestations such as recurrent infections, immune dysregulation, or malignancy did not correlate with elevated MN frequencies. These findings highlight the need for targeted RS testing in patients with suspected DNA repair defects, especially those with ataxia-telangiectasia, to guide safer therapeutic decisions.

L24 PGT, with a focus on aneuploidies

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Chromosome aneuploidy is a major cause of pregnancy failure, miscarriage and rarely, fetal abnormalities or congenital disorders, after normal or assisted conception. Hence, preimplantation genetic testing for aneuploidy (PGT-A) is now widely used to select viable euploid embryos for transfer following IVF and biopsy of a small number of the outer, extraembryonic trophectoderm cells at the blastocyst stage. Chromosome gains and losses arising from errors during meiosis, prior to fertilisation, result in trisomies and monosomies, respectively, affecting all cells of the embryo. Segregation errors and other abnormalities of mitosis following fertilisation, however, are also common. Depending on when they occur, mitotic aneuploidies only affect a variable proportion of cells in the embryo leading to chromosome mosaicism. In addition, chromosome breaks, and other abnormal events can cause gain or loss of whole or part of a chromosome arm causing segmental aneuploidies. Depending on the chromosomes involved and the proportion of affected cells, these aneuploidies may contribute to developmental arrest as the embryo makes the transition to embryonic gene expression before the blastocyst stage, which occurs in about half of human embryos following IVF. Genome-wide single nucleotide polymorphism (SNP) genotyping using microarrays or NGS based methods and parental haplotyping enables the detection of both meiotic and mitotic, whole chromosome and segmental aneuploidies at high resolution. The ability to distinguish meiotic and mitotic aneuploidies may have important implications for PGT-A in clinical practice by minimising the discard of embryos with only mitotic aneuploidies of unknown clinical outcomes.

L25 Prenatal treatment of chromosomal anomalies

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Down syndrome (DS) is a genetic disease characterized by a supernumerary chromosome 21. Intellectual disability (ID) is the constant and major feature of disability associated with DS. ID might be caused by several defects in neurodevelopmental processes. Among them, neuroinflammation and microglial activation have been reported in DS fetus and children. Some studies suggest that anti-inflammatory treatment in mouse models of DS could rescue this phenotype. The synthetic Pre-Implantation Factor (sPIF) is a peptide known to have immune-modulatory, anti-inflammatory, and neuroprotective effect, and has the advantage to pass the blood brain barrier. We therefore investigated the potential effect of sPIF in cognitive deficit and microglial activation at juvenile and adult stages of Dp(16)1Yey mice, a mouse model of DS, by administration during gestation and until weaning. For this, behavioral tests, immunefluorescence assays and cell quantification were evaluated. Treatment with sPIF has no negative effect on vital functions, and enhanced the Dp(16)1Yey pups' social communication in response to maternal separation. Moreover, it rescued the impairment in hippocampal-dependent working memory in adult Dp(16)1Yey mice. At the cellular level, treatment with sPIF restores hippocampal neurogenesis and

microglial activation. At the molecular level, treatment with sPIF restored the level of DYRK1A, a protein that is involved in cognitive impairments in DS. Taken as a whole, we demonstrated the neuroprotective effects of sPIF treatment in a mouse model with chromosomal anomalies. When combined with the literature data, our present results further strengthen the hypothesis whereby the cognitive dysfunction linked to gene deregulation can be corrected, adjustment of DYRK1A being one of the explanations for the positive behavioral effects demonstrated.

Closing keynote - Cytogenomics, where we are and where we are heading?

Joris Vermeesch

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Cytogenomics - the integration of cytogenetics and genomics - has transformed our understanding of chromosomal structure, function, and variation in health and disease. Over the past two decades, advances in molecular techniques such as array-based comparative genomic hybridization, next-generation sequencing, and single-cell genomics have propelled the field beyond traditional karyotyping, enabling higher-resolution and genome-wide insights into chromosomal abnormalities. This talk will explore the current state of cytogenomics, highlighting key applications in clinical diagnostics, cancer genomics, reproductive medicine, and rare disease research. It will also address the challenges that remain, including interpretation of structural variants, the integration of multi-omic data, and the clinical utility of emerging technologies. Looking ahead, the field is poised for further evolution with the rise of long-read sequencing, spatial genomics, and AI-driven analytics. These innovations promise to refine our understanding of genome architecture and function, uncover previously undetectable anomalies, and personalize genomic medicine. By mapping both the achievements and the future directions of cytogenomics, this presentation aims to provide a comprehensive overview of a field at the frontier of genomic science and clinical application.

Abstracts - Oral Presentations

O1 - Optical Genome Mapping in the Clinic Reveals Germline and Somatic Findings that may influence the Treatment Approach

Nivin Moustafa-Hawash [1], Christina Srouji [1], Avraham Frisch [2], Baher Krayem [2], Nira Arad-Cohen [3], Tsila Zuckerman [2], Tamar Paperna [4], Karin Weiss [4]

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Background: Optical Genome Mapping (OGM) is a new genome-wide cytogenetic technology. OGM uses imaging of ultra-long labeled single DNA molecules to generate genomic assemblies, highlighting any structural change present, both balanced and unbalanced, at an unprecedented resolution. Thus, OGM can revolutionize our understanding of hematological neoplasms but can also uncover germline structural variants (SV). We aimed to evaluate the advantages of clinical OGM over standard-of-care cytogenetics used for hemato-oncology and its effect on clinical management.

Methods: Bone marrow aspirates from 552 adult and pediatric patients diagnosed with various hematological malignancies were analyzed by OGM for clinical diagnosis, following technology-specific methods.
Results: In 276 cases (50%), OGM detected SVs relevant to prognosis, tumor surveillance, or therapy decisions. In 162/276 abnormal cases (57%) OGM identified new SVs that were undetectable by our previous cytogenetics workflow, including a partial duplication of KMT2A, deletions of PAX5, IKZF1, TET2, CUX1, cryptic translocations, and others. In 14 cases (2.5%), suspected germ-line SVs were identified, with relevance to neoplasia (NF1, RUNX1 and DNMT3A), or incidental (DMD), requiring genetic counseling. In addition, we detected novel SVs suspected as tumor-related, and several recurrent SVs, possibly unique to the Israeli population.
Conclusions: OGM testing uncovers unexpected SVs, both somatic and germline that alter patient management and may increase the load of genetic counseling in hemato-oncology patients. The identification of novel SVs may lead to new treatment and surveillance options, but requires further investigation.

O2 - Optical Genome Mapping is a Powerful Diagnostic Tool in Non-Hodgkin Lymphoma

Amber Verhasselt [1], Geneviève Ameye [2], Justine Vanhevel [2], Thomas Tousseyn [3], Johanna Vets [4], Lucienne Michaux [2], Katrina Rack [2], Barbara Dewaele [2], Jolien de Bie [2]
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Non-Hodgkin Lymphoma (NHL) is a heterogeneous hematological malignancy, characterrized by structural variants (SV) and Copy Number Alterations (CNA) essential for classifycation. The gold standard genetic tests, Chromosome Banding Analysis (CBA) and Fluorescent in-situ Hybridization (FISH), are labor-intensive and have limited resolution. Moreover, CBA needs a viable cell culture and FISH is a targeted technique.
Here, we applied Optical Genome Mapping (OGM) on 110 NHL samples. OGM fluorescently labels Ultra-High Molecular Weight DNA isolated from fresh frozen tissue. The subsequent labeling pattern is then compared to a reference genome for genome-wide high-resolution SV and CNA calling.
Informative results were obtained in 94% of all cases. The overall concordance between OGM and CBA/FISH for clinically relevant aberrations was high in our cohort and OGM detected 166 of 180 aberrations reported by CBA/FISH (92,2%). In total, 14 variants were missed by the software. Most were present in small (sub)clones or polymorphic lymphoma entities with low tumor cell percentages. Based on these results and interphase FISH on uncultured cells, a detection threshold of 10-15% malignant cells was established.
Interestingly, OGM was capable of revealing extra clinically relevant information in 40% of patients, as well as clarifying complex karyotypes or unidentified material, for example by revealing partner genes in clinically relevant translocations, thus supporting the creation of a diagnostically and/or prognostically relevant genetic profile. On top of this, OGM proved capable of rescuing 27 samples with CBA failure due to distinct reasons, where OGM detected clinically relevant aberrations in all samples.
In conclusion, OGM shows high concordance with CBA/FISH in NHL, identifying clinically relevant aberrations and revealing unexpected or novel genetic information independent of cell culture. OGM could thus be used in the diagnostic evaluation of NHL, able to replace both CBA and FISH.

O3 - Cytogenetics Profile of Hematological Malignancies with Complex Karyotype. A Single Center Study from Turkey

Şule Altiner [1], Arzu Vicdan [1], Nüket Yürür Kutlay [1], Timur Tuncali [1], Halil Gürhan Karabulut [1], Hatice Ilgin Ruhi [1]

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Cytogenetics is still an important method for the evaluation of hematological malignancies. Although recurring chromosomal abnormalities correlate with subtypes, complex karyotype(CK) has utmost prognostic value related with overall survival.

Cytogenetic data of patients with CK detected at the Department of Medical Genetics, Ankara University Faculty of Medicine in a period of eight years were examined within the scope of this study.

Bone marrow or peripheral blood samples of 16.437 patients were examined and 387 of them (2,35%) were found to have complex cytogenetic abnormalities. Out of these, 209 (54%) were males. 30 of the patients(7,7%) were in the pediatric age group. The mean ages of patients when CK was detected were 9,2 years (median:9,5years) and 57 years (median:60years) in pediatric and adult group, respectively. Multiple myeloma (MM) was the leading hematological malignancy regarding CK (22,48%), followed by acute myeloid leukemia (AML) (22,2%) and myelodysplastic syndrome (MDS) (17%). CK is generally considered to be a strong predictor of poor outcome. Upon examining survival data, we found that 34,1% of patients with CK died within an average of 7,5 months (median:4months) following CK detection.

When we analyze on patient basis, chromosome 1 related changes were detected in 71% of MM patients. Monosomal karyotype was detected in 48% of AML. It is noteworthy that 80% of Ph+ acute lymphoblastic leukemia (N:4/5)had double Ph. High CK was detected in 62% of chronic lymphocytic leukemia (N:5/8). 17p deletion was detected in 11,8% of all patients.

Complex karyotype maintains its value in hematological malignancies. Although new generation genome-wide detection can be done with some methods, conventional cytogenetic method which is labor intensive is still more accessible in practice. This study is important both in terms of showing the power of conventional cytogenetics in CK detection and in terms of being the most comprehensive data for Turkey.

O4 Precision Approaches in Clinical Cytogenomics. The Role of Optical Genome Mapping and Long Read Sequencing in Structural Variant Detection

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Structural variation (SV) in the genome is one of the major causes of human genetic diseases. Its detection in clinical practice is still based on traditional methods of classical and molecular cytogenetics, which often fail to accurately determine breakpoints in translocations, inversions and the detection of complex cytogenetic rearrangements. In recent years, however, new technologies based on the analysis of long DNA molecules have emerged that could overcome these limitations.

In this study, we focused on comparing optical genome mapping (OGM) and long-read whole genome sequencing (LR-WGS, Oxford Nanopore Technologies) for the detection of SV in patients with neurodevelopmental disorders (NDDs). The main aim was to assess the efficiency, accuracy and practical applicability of both methods in clinical practice and to compare their results with previous cytogenetic analyses.

The diagnostic potential of these methods was tested in five patients with NDDs who had complex or unresolved cytogenetic findings. Both methods were able to detect all previously reported genetic alterations. OGM proved to be more effective for initial screening due to a lower number of variants detected and clearer visualisation of the results. LR-WGS was more accurate in determining the exact breakpoint locations and detailed characterisation of genes involved in rearrangements, but it generated a massive amount of data, making analysis and interpretation more difficult.

Our results suggest that a combination of OGM for rapid screening and LR-WGS for detailed SV analysis may be an optimal diagnostic approach. However, further development of analytical tools is needed for more efficient processing and interpretation of LR-WGS data.

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O5 - Interstitial Telomeric Sequences and Accumulation of DNA Damage Hallmarks of Genomic Instability in Cancer Resistant Wild Vertebrates

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Studying cancer in non-model organisms provides an opportunity to identify mechanisms that could be leveraged for the development of innovative therapies, such as the well-known case of elephants with TP53 gene duplications. However, the characterization of genomic instability—through telomere instability and the accumulation of DNA damage— in cancer-resistant wildlife remains largely unexplored. The aim of this study is to investigate genomic instability in these species by assessing telomere instability and DNA damage accumulation.

Materials and Methods:

Ten cancer-resistant wild animal species were included in this study. Primary fibroblast cell lines and circulating lymphocytes from each species were analyzed. Five primary human fibroblast cell lines served as controls. Cytogenetic preparations were performed, followed by telomere staining on cytogenetic slides. Telomere analysis, including telomere length and aberrations, was conducted, alongside the assessment of chromosomal instability biomarkers such as micronuclei (MN), nucleoplasmic bridges (NPBs), and nuclear buds (NBUDs).

Results:

Telomere analysis of primary fibroblast cell lines from the ten cancer-resistant species and human controls revealed the exclusive presence of interstitial telomeric sequences (ITS) in eight out of ten cancer-resistant species. The fluorescence intensity of these ITS accounted for more than 40% of the total telomere signal intensity at chromosome ends. The presence of ITS is correlated with a higher rate of telomere doublets. Interestingly, ITS were also significantly associated with an increased frequency of MN, NPBs, and NBUDs, indicating genomic instability in the primary fibroblast cell lines. These findings were further confirmed using circulating lymphocytes.

Conclusion:

By analyzing a large cohort of primary fibroblast cell lines and circulating lymphocytes, we demonstrate for the first time a correlation between interstitial telomeric sequences and the accumulation of DNA damage. These findings highlight a novel paradigm linking cancer resistance and genomic instability in wild animal species.

O6 - Genomic Complexity and Evolutionary Plasticity in Dugesia Japonica Revealed by Multi Ploidy Chromosome Level Assemblies

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Planarians are well known for their remarkable regenerative capacity and serve as important model organisms for studying stem cell biology and tissue regeneration. However, the complex nature of their genomes, characterized by high repetitiveness, variable ploidy, and limited genomic resources, has posed significant challenges for genome assembly and functional analysis. Dugesia japonica, a widely studied planarian species, exhibits diverse karyotypes, including diploid, triploid, and mixoploid, making it a valuable system for investigating genome evolution and structural plasticity.

Here, we generated and analyzed four high-quality, chromosome-level genome assemblies representing different ploidy states of D. japonica, utilizing a combination of PacBio HiFi, ONT ultralong reads, Illumina sequencing, and Hi-C scaffolding. The haploid genome size was estimated at 1.8–1.9 Gb, making it one of the largest planarian genomes reported to date. The assemblies revealed a highly AT-rich and repeat-dense genome (GC content 26.6%–27.0%, repeat content 75%–79%), with DNA transposons—particularly Maverick elements—dominating the repetitive landscape. These elements were not only conserved across ploidy types but also preferentially inserted in promoter regions, suggesting potential roles in gene regulation and genome architecture.

Structural variation analysis uncovered extensive genomic diversity among individuals, including large-scale chromosomal inversions and abundant SNPs and SVs, underscoring the genome's dynamic and polymorphic nature. While significant improvements were achieved in genome contiguity and accuracy, challenges remain in assembling telomeric and centromeric regions due to the genome's repetitive and AT-rich nature.

This work provides the most comprehensive genomic resource to date for D. japonica and offers novel insights into the roles of repetitive elements in genome organization and evolution. It lays a foundation for future studies on regeneration, genome plasticity, and transposon-mediated regulation in planarians and other complex metazoans.

O7 - Detection of Structural Variants by Short Read Whole Genome Sequencing and Interpretation for Genetic Diagnosis

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Structural variants (SVs) have been associated with many human diseases and phenotypes, therefore accurate identification and clinical interpretation of SVs is crucial for genetic diagnosis, treatment and prevention within many disease areas. Within the frame of National Genome Center in Denmark, whole genome sequencing (WGS) is performed for patients within different disease groups, e.g. patients with rare diseases, hereditary cancer, endocrinological disorders, immune deficiency, heart disease, psychiatric disorders, kidney failure etc. In addition, a rapid comprehensive WGS-analysis with a 2–3-week turnaround time is performed for intensively ill children to assist acute and long-term clinical decisions.

In the department of Clinical Genetics (Rigshospitalet, Copenhagen, Denmark), we have used WGS as first-line diagnostic test for more than a year and hence developed a comprehensive pipeline for SV-detection, enabling identification of all types of structural events: recurrent and non-recurrent copy-number variations (deletions and duplications), insertions and non-tandem duplications, mobile element insertions, inversions, balanced and unbalanced

translocations, as well as complex genomic rearrangements, such as chromothripsis and chromoanasynthesis. Furthermore, we also identify numerical chromosomal abnormalities, mosaicism and uniparental disomy. A group of specialists consisting of molecular biologists and medical doctors with both cytogenetic and molecular genetic backgrounds, participate in clinical interpretation of the identified SVs. The diagnostic yield of a likely pathogenic/pathogenic SVs detected in our WGS pipeline depends on the patient group analyzed and is e.g. ~5% in the intensively ill children cohort.

O8 - Evaluation of X Inactivation Pattern in Carriers of X Chromosome Aberrations and DMD Gene Mutations

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Introduction: X chromosome inactivation (XCI) normally is a random process (50:50) in which the maternal and the paternal X chromosome have the same chance of being inactivated in all cells. The preferential inactivation of either the maternal or paternal X chromosome results in a skewed pattern (> 75:25) that influences the clinical manifestation of X-linked diseases. Evaluation of XCI pattern in female carriers of X-linked disorders is of clinical significance for providing accurate genetic counseling.
Aim: Our aim was to investigate the XCI pattern in carriers of structural aberrations of chromosome X and Duchenne muscular dystophy (DMD), and to provide a more accurate genotype-phenotype correlations.
Methods: We used HUMARA assay that relies on the methylation status of the methylation-sensitive restriction enzyme (Hpall) binding site present close to polymorphic CAG repeats in the AR gene. Three rare cases of del(Xq), one case with t(X;12), and two DMD carriers were studied.
Results: The XCI pattern was random (58:42) in the case with del(X)(q26.2) and no symptoms. Skewed XCI pattern (100:0) was detected in an infertile female with del(X)(q2?4q2?6) and no phenotype abnormalities; in a symptomatic Rett syndrome patient with del(X)(q28) (85:15); in an asymptomatic t(X;12) carrier (88:12). Non-random XCI pattern was revealed in both symptomatic (97:3) and asymptomatic (77:23) DMD carriers.
Conclusion: The XCI results were consistent with the phenotype of the patients: symptomatic carriers had a preferential inactivation of the X-chromosome carrying the normal allele, while healthy females showed random XCI pattern or inactivation of the aberrant chromosome X. Based on our results, evaluation of XCI pattern provide a more accurate genotype-phenotype correlation and personalized genetic counseling in cases of X-linked genetic diseases.
Supported by EKÖP-24-2.

O9 - Long Read Genome Sequencing Enhances Diagnosis of Pediatric Neurological Disorders

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Neurological disorders are heterogeneous group of conditions that may present as intellectual disability, neurodevelopmental delay, motor delay, or hypotonia. Their genetic background includes a diverse range of variant types, with short-read genome sequencing (GS) achieving a diagnosis for approximately 35% of the individuals, depending on cohort characteristic. Among these, the majority involves single

nucleotide variants (SNVs) and small insertions/deletions (INDELs). However, structural variants (SVs) and short tandem repeat (STR) expansions constitute an important proportion of the findings, yet remain a challenge for short-read sequencing methods. The challenge lies in their repetitive nature and size, which is something that long-read sequencing may overcome.

In this prospective study, we included 100 children and adolescents (≤20 years) referred for short-read GS due to neurological disorder. Each underwent standard clinical evaluation and long-read GS (Oxford Nanopore Technologies). Bioinformatic analysis included pipelines for SNV/INDELs, SVs and STRs, with in-silico panels targeting intellectual disability (1,568 genes) and neuromuscular disorders (1,035 genes).

Pathogenic variants were detected in 29% of the individuals, of which 34% (10/29) carried SVs or an STR expansion. They involved simple rearrangements, including four deletions (n=4), a duplication, an inversion and a translocation, as well as complex rearrangements, including a terminal del-inv-dup rearrangement of chromosome 9 and a mosaic ring chromosome 18. Additionally, we found five SVs, of which three were complex, that were classified as benign after thorough evaluation.

Long-read GS proved valuable in characterrization and evaluation of structural variants in individuals with neurological disorders. It is likely to provide new insights into normal variation, shorten the diagnostic odyssey, and enhance genetic diagnostics for this patient group.

O10 Transforming Prenatal Cytogenetics Rapid Chromosomal Rearrangement Characterization with Nanopore Sequencing

Charlotte Tardy [1], Flavie Diguet [1], Quentin Testard [2], Claire Bardel [2], Sylvie Bernard-Beufe [3], Vincent Jauffret [3], Marianne Till [1], Damien Sanlaville [1], Mathilde Pujalte [1], Nicolas Chatron[1]

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Balanced chromosomal rearrangements detected during prenatal karyotyping are often incompletely characterized, limiting its clinical utility as variant interpretation is restricted to « cold VUS » if the rearrangement is inherited from a healthy parent or « hot VUS » if de novo. Forty percent of de novo balanced rearrangements carried by symptomatic patients could be considered pathogenic after breakpoint characterization in a postnatal setting.

Our ARPAGON(Analysis of Rearrangements in Prenatal Assessment using Genomic Oxford Nanopore Sequencing) project aims at demonstrating the feasibility of such characterization in a time window compatible with pregnancy management. Two micrograms of DNA extracted from amniotic fluid cell culture were converted into genomic library using the LSK114 kit and 50Gb were sequenced on an R10.4 PromethION flowcell (Oxford Nanopore Technologies, Oxford, UK). Dorado v0.6.3 was used for basecalling using HAC+5mc_5hmC mode before alignment on GRCh38 using Minimap2. SVIM, Sniffles2 and Sawfish were used for structural variant calling. Calls were filtered on quality scores and karyotype information.

To date, we have included three fetuses harbouring a reciprocal translocation identified via fetal karyotyping, prompted by ultrasound anomalies and confirmed balanced after CMA. All three were succesfully characterized in less than 8 days after metaphases'observation with two additional weeks required for PCR junction confirmation so that the result could be used in diagnostic setting. For patients 1 and 3 characterizations were considered non contributive. For patient 2, harbouring a t(4;11)(q35;q23)dn, KMT2A intron 1 was disrupted most likely leading to haploinsufficiency, known to be responsible for Wiedemann Steiner syndrome. The variant was reclassified as pathogenic. All SV pipelines identified the three rearrangements. Our findings confirm that nanopore sequencing surpasses conventional methods for resolving balanced chromosomal rearrangements and is

compatible with prenatal testing. Inclusions are ongoing before rapid transfer to diagnostics.

Abstracts - Poster presentations

1. Animal and Plant Cytogenomics

P1006 - Does Chromoanagenesis Play a Role in the Origin of B Chromosomes?

Andreas Houben [1], Jianyong Chen [1], Gihwan Kim [1], Ali Mohammad Banaei -Moghaddam [2], Jörg Fuchs [1], Taoran Liu [1]
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B chromosomes (Bs) exist in addition to the standard (A) chromosomes in a wide range of species. The process underlying their origin is still unclear. We propose pathways of intra- and interspecific origin of B chromosomes based on known mechanisms of chromosome evolution and available knowledge of their sequence composition in different species. We speculate that a mitotic or meiotic segregation error of one or more A chromosomes initiates via chromoanagenesis the formation of a proto-B chromosome. In the second step, proto-B chromosomes accumulate A chromosome- and organelle-derived sequences over time, most likely via DNA double-strand break (DSB) misrepair. Consequently, the original structure of the early stage proto-B chromosomes becomes masked by continuous sequence incorporation. The similarity between A chromosome sequences integrated into B chromosomes and the original sequences on the donor chromosomes decreases over time if there is no selection pressure on these sequences on B chromosomes.

P1009 - Retrotransposable Elements Drive Transcription of Tandem Repeats

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Transcription of evolutionarily divergent tandemly repetitive DNA is required for the maintenance of centromere and telomere regions of chromosomes. Despite numerous examples of tandem repeat transcripts in a wide range of species, there is lack of information on how tandem repeat transcription is initiated and terminated, and how tandem repeat-containing RNAs are processed during and after transcription.
Here, we aimed to estimate the transcriptional activity at centromeres on all chicken chromosomes, including sex and dot chromosomes, during the diplotene stage of oogenesis. We first analysed oocyte nuclear and cytoplasmic total strand-specific RNA-seq profiles along the complete telomere-to-telomere assembly of the chicken genome. These data were compared with RNA-FISH visualisation of nascent transcripts on isolated lampbrush chromosomes.
The Cen1, Cen2, Cen3, Cen4, Cen7, Cen8 and Cen11 repeat arrays were transcriptionally silent. In the centromere regions of chicken acrocentric chromosomes, the 41-bp CNM and PO41 repeats form higher-order repeats. According to oocyte nuclear RNA-seq and RNA FISH data, most CNM repeat clusters at centromere regions are transcriptionally inactive. At the same time, CNM arrays at sub-telomeres are actively transcribed. We found that active transcription of telomere-derived RNAs is initiated from the long terminal repeats of LTR retrotransposons. We

then showed that transcription of tandem repeat arrays on the chromosome arms is also initiated at the promoters of retrotransposable elements. In all cases observed, transcription of tandemly repeated DNA on the lateral loops of lampbrush chromosomes was carried out by RNA polymerase II. Co-transcriptional splicing of tandem repeat-containing RNAs, as assessed by immunolocalisation of splicing factors, was dependent on repeat type. The results obtained suggest a crucial role for active retrotransposon promoters in the regulation of tandemly repeated non-coding RNA synthesis.

The research was carried out using the equipment at the Molecular and Cellular Technologies Resource Centre.

P1051 - Bivalent Marker Dynamics in Protamine Expression Unraveling Chromatin Compaction Mechanisms

Liliana Burlibasa [1], Alina-Teodora Nicu [1]
University of Bucharest, Genetics, Bucharest-Romania [1]

A distinctive feature of mammalian spermatogenesis is the extensive chromatin remodeling that occurs during the final stages of differentiation, characterized by histone replacement with protamines, leading to an extraordinary level of DNA compaction. This transition is closely linked to global epigenetic modifications throughout sperm differentiation. In this study, we investigated the dynamics of H3K4me3 and DNA methylation at the Prm1-Prm2-Tnp2 loci. Immunohistochemistry and chromatin immunoprecipitation (ChIP) assays were employed to dissect key aspects of chromatin compaction during murine spermatogenesis. ChIP analysis provided novel insights into the interplay between histone methylation and DNA methylation. Furthermore, bisulfite sequencing revealed distinct DNA methylation patterns across different spermatogenic cell types, including pachytene spermatocytes, round spermatids, and mature spermatozoa. Understanding the epigenetic landscape of spermatogenic cells could contribute to deciphering the molecular mechanisms underlying male infertility.

P1054 - Cytogenetic Investigations in Romanian Black and White Spotted Cattle

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Since chromosome abnormalities are very often associated with developmental anomalies, embryonic death and various levels of infertility which generate reproductive failures, the role of cytogenetic investigations becomes a very important tool for the genetic improvement of livestock and the relationship with the reproductive performances at the farm level. For this reason, during the last five years, karyotype analyses was performed on a group of 78 females of the Romanian Black and Spotted breed, raised on the farm of The Research and Development Institute for Bovine, Balotesti, Romania. The results of cytogenetic screening developed in the last five years in the frame of three national projects, revealed normal karyotype for 51 females and chromosomal instability for 27 females. The group of the 27 females, presented a high percentage of abnormal cells (mono-and bichromatidic Xq breakages, mono-and bichromatidic autosomal breakages, lost fragments and gaps). The phenotypic effects were expressed by reproductive disturbances (repeated inseminations, lack of oestrus and loss of pregnancy), 6 cases of congenital malformations, a case of foetal abnormality and 2 cases of freemartine female. The high number of SCEs/cell in the chromosomes of the females with reproductive disturbancies could be related with the environmental pollution and the biological effects of the toxic agents on the genetic material integrity.

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P1093 - Unraveling the Genetic Architecture of Centromeres with CENdetectHOR

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Background: centromeric regions are characterized by arrays of satellite DNA that can organize into Higher-Order Repeats (HORs). Analyzing these complex structures has been challenging due to their repetitive nature and rapid evolution, resulting in precise HOR annotation achieved only in human centromeres. The advent of long-read sequencing technologies has enabled comprehensive sequencing of these regions, but the increasing data volume necessitates bioinformatics tools that can efficiently handle large datasets, provide thorough analyses, and require minimal prior information for new genomes. Methods: we developed CENdetectHOR, a computational tool designed to identify and analyze HOR arrays in centromeric regions across diverse organisms without requiring a priori information. CENdetectHOR employs a systematic workflow that detects repetitive regions, extracts non-overlapping monomers, clusters them into families, and conducts phylogenetic analyses to identify HOR arrays. We validated its application using the human telomere-to-telomere (T2T) genome assembly and extended it to the T2T genomes of great apes. Results: CENdetectHOR annotated 160 HORs across 24 human chromosomes, with compositions ranging from 2 to 42 families, matching previous annotations while identifying HOR variants in 21 chromosomes — an achievement previously possible through precomputed hidden Markov models. Additionally, we completely annotated HORs in great ape genomes for the first time in both assembled haplotypes, allowing for comparative assessments of centromeric region variability within the same genome and among species.
Conclusion: CENdetectHOR is a powerful tool for advancing research on centromere structure and evolution. It provides a detailed landscape of HORs in great apes and enhances our understanding of their evolutionary history.

P1137 - Repetitive DNA Sequences Mark Genome Boundaries in the Terrestrial Orchid Epipactis Zinn

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Epipactis is mostly a Eurasian genus with a south-central distribution, widespread in Europe, but the species can be found in the temperate and subtropical climates. The taxonomic classification of this genus is very complex due to the morphological similarities between many species, which result from adaptation to local environments, and changes in floral architecture that facilitate the transition between cross- and self-pollination. The systematics of this genus is considered provisional by many scientists due to the varying number of distinguished species depending on the taxonomic approach. Regardless of the classification system, identifying different species, especially infraspecific categories, can be challenging due to the wide range of observed phenotypic plasticity. The combination of cytogenetic and bioinformatic tools seems promising for the analysis of genome structure and the determination of intergenomic relationships between even very closely related species. In particular, the analysis of rapidly evolving repetitive DNA sequences, including satellite sequences, rDNA, transposons or retrotransposons, can support phylogenetic

reconstruction. In this regard, our goal was to analyze the repeatome of selected Epipactis species and define genome-specific repetitive DNA elements. Our analyses showed that two groups of Epipactis species evolved independently. The genomes of Epipactis species belonging to the Helleborine complex, in contrast to E. palustris and E. gigantea, are distinguished by the presence of the Tekay retrotransposon and an unusual amplification of Arabidopsis-like telomeric repeats.

2. Clinical Cytogenomics

P1007 - Duplication of 13q. A Rare Chromosomal Abnormality

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Duplication of 13q is a barely known chromosomal abnormality; and shows phenotypic differences from Patau syndrome. It is often derived from a balanced translocation in one of the parents. We examined a female infant born to healthy parents due to multiple anomalies, severe infection and multiorgan failure. Her anamnesis was burdened by late-recognized cardiac malformations followed by sepsis, temporary cholestasis with hepatomegaly, intestinal necrosis, transient renal failure and one pathologic femur fracture. Extended examinations during hospitalization revealed cortical and bilateral optic nerve atrophy, hypoplastic corpus callosum and abnormal shape of kidneys. After a long inpatient period she showed delayed, but gradually improving psychomotor and somatic development. Giemsa-banded karyotyping revealed a 46,XX,der(13)t(13;14)(q22;q11) karyotype, confirmed by fluorescent in situ hybridization (FISH). Array comparative genomic hybridization (arrayCGH) (CytoScan 750, Affymetrix) refined the breakpoints of the der(13): arr[GRCh38]13q11q21.33(18,862,148_68,694,987)x3. Family investigation showed a balanced reciprocal translocation in the mother and the grandmother: 46,XX,t(13;14)(q22;q11).
The patient's phenotype partially overlapped with other cases described in the scientific literature, but some features might also be explained by delayed recognition of the childs heart abnormality. Our report broadens the knowledge about genotype-phenotype correlations in cases with a duplication of 13q and helps to determine the expected symptoms.

P1008 - Copy Number Variations in Males with Unexplained Azoospermia

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Many genetic changes can underlie male infertility, primarily manifested as sexual dysfunction, oligoasthenospermia, azoospermia, abnormal seminal plasma, and immune infertility. Problems during spermatogenesis are reflected in lower, irregular, or absent sperm production. In cases of idiopathic azoospermia, genetic causes are highly probable. In this study, we investigated genomic copy number variations (CNVs), focusing on microdeletions or microduplications on the Y chromosome and autosomes in regions potentially linked to male infertility. From an initial cohort of 400 male patients evaluated in our infertility clinic, we selected 51 individuals who met strict inclusion criteria: non-obstructive azoospermia, normal karyotype or balanced chromosomal rearrangements, no Y chromosome microdeletions, no CFTR gene mutations, and absence of environmental or medical factors known to impair spermatogenesis. Array-CGH was performed. We identified four pathogenic CNVs

and three VUS, together representing 14% of the study group. The pathogenic variants included: one duplication on 15q11.1q11.2 and three deletions on Yq11.223q11.3. VUS were detected on autosomes: two on 15q11.1q11.2 and one on 8p11.21p11.1.
Structural abnormalities of the Y chromosome often adversely affect spermatogenesis. We noted that the analysis of CNVs using microarrays could be a complementary method for diagnosing male infertility, especially regarding large deletions on the Y chromosome, which are not covered by the standard analysis of Y microdeletions using the PCR method. Array-CGH could also be the method of choice when the male infertility is associated with microdeletions or microduplications on autosomal chromosomes

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P1011 - Developing Del2phen a Novel Phenotype Description Tool for Chromosome Deletions

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Information on the health-related consequences of rare structural chromosome disorders is often limited, posing challenges for both patients and clinicians. The Chromosome 6 Project aims to bridge this knowledge gap for structural aberrations involving chromosome 6 by providing reliable, aberration-specific clinical information directly to parents of affected children. To achieve this, detailed phenotype and genotype data is collected directly from parents worldwide and supplemented with data from literature reports, resulting thus far in a dataset of over 500 individuals. This comprehensive data pool was used to develop Del2Phen, a software tool that generates aberration-specific phenotype information for chromosome disorders. Del2Phen identifies individuals with a deletion or duplication similar to that of a new patient (index) and produces a clinical description for the index based on phenotypic features observed in these genotypically similar individuals. Genotypic similarity is determined using existing knowledge on the haploinsufficiency effect of genes and established gene-phenotype relationships. The optimal genotypic similarity parameters for chromosome 6 deletions were evaluated, which lead to thorough and reliable clinical descriptions based on sufficiently large groups of individuals with highly similar deletions. Although currently optimized for chromosome 6 deletions, Del2Phen can also be applied to deletions involving other chromosomes and is easily adapted for use on duplications, given sufficient data is available. Del2Phen can already be used to expedite data analysis for chromosome disorders, thus aiding healthcare professionals in delivering appropriate clinical care. Lastly, this tool will be integrated into an interactive website designed for parents of children with a chromosome 6 aberration, providing essential health information in a timely and accessible manner.

P1016 - Cytogenetic Analysis of a Complex Ring Chromosome 5 with 5p15.2 Duplication in a Child with Congenital Developmental Delay

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Background. Ring chromosomes 5 are rare findings, only 1.3% of reported all human ring chromosomes. We report a clinical case in which a newborn child's karyotype is represented by two cell lines - one with ring chromosome 5, which has a duplication of segment 5p15.2, and a line with monosomy of chromosome 5.

Materials and methods. Clinical, standard karyotyping, FISH analysis using TelVysion probes (5ptel, 5qtel, 5p15.2(Cri-du-Chat loci)). Discussion. Child from the fourth pregnancy, with diagnosed intrauterine growth retardation at 26 weeks. Delivery at 37 weeks by cesarean section. Weight 1460, height 41 cm, Apgar 5/6 points. Genetic counserling in the Center for Medical Genetics took place on the 15th day.Phenotype:physical developmental delay, microcephalic head, forehead sloping backwards, large first finger, large eyes. Neonatal thrombocytopenia, heart defects: pulmonary artery stenosis, ventricular septal defect; congenital foot deformities.

Standard chromosomal analysis showed a female karyotype with two cell lines: the 90% of the has one normal chromosome 5 and a ring chromosome 5 with a duplication of segment 5p15.2 in the short arm; 10% of the cells was with a monosomy of chromosome 5.

FISH analysis showed that 86% of the cells had three signals at the 5p15.2 locus, two of which were on ring chromosome 5, which is in favour of duplication in the short arm of ring chromosome 5; 14% had one signal at the 5p15.2 locus of chromosome 5, which confirms monosomy 5. The absence of syndrome Cri-du-Chat is indicated by the presence of subtelomeric regions 5ptel and 5qtel on the ring chromosome 5. Result: mos 46,XX,der(5)r(5)(p15.3q35.3) dup(5)(p15.2p15.2)[27]/45,XX,-5[3].ish der(5) (5ptel+,D5S721/D5S23++,5qtel+)[173]/5(5ptel, D5S721/D5S23,5qtel)x1[27].

Conclusion. Chromosomal rearrangements require the use of different laboratory methods of different levels of resolution to understand the mechanisms and and nature of formation.

P1017 - A case with both SMARCA2 pathogenic variant and 14q24.1-q32.33 deletion with the only finding hypocalciuric hypercalcemia

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Nicolaides Baraitser Syndrome (NCBRS) (MIM #601358) is characterized by sparse scalp hair, prominence of the interphalangeal joints and distal phalanges due to decreased subcutaneous fat, characteristic coarse facial features, microcephaly, seizures, short stature, and developmental delay/intellectual disability caused by SMARCA2 gene included in the BAF (mammalian SWI/SNF complex) chromatin remodeling complex. 14q24-q32 deletion (vary in size) shows a non-specific dysmorphic appearance and neurological developmental delay.

We present a 65-year-old female case referred with familial hypocalciuric hypercalcemia in the current report with a heterozygous pathogenic SMARCA2 p.A1201V variant and a 14q24.1-q32.33 deletion (37,693 Mb). After whole exome sequencing (WES), two heterozygous pathogenic variants were detected in the SMARCA2 and F8 genes which are not related to familial hypocalciuric hypercalcemia. Because the diagnosis of hypercalcemia cannot be done with WES, array-CGH (Comparative Genomic Hybridisation) analysis was performed and the result showed a deletion of the 14q24.1-q32.33 region. The segregation analysis could not be performed because the parents were not alive. Her son was analysed for the same two variants detected with WES, he had only F8 heterozygous variant. The variant SMARCA2 NM_003070.5: c.3602C>T p.(A1201V) was reported with a mild phenotype for NCBRS in the literature. Our case was 65-year-old woman without any complications related to NCBRS and 14q24-q32 deletion. She had no dysmorphic features, but an antisocial life.

In the present review we aimed to present a surprising case who has both a pathogenic variant SMARCA2 NM_003070.5:c.3602C>T p.(A1201V) and a 14q24-q32 deletion aiming to better characterize the clinical spectrum and evaluate possible genotype-phenotype correlation

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P1021 - A Rare Case of a Carrier of Two Different Balanced Chromosomal Rearrangements

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We present a case of a carrier of two different balanced chromosome rearrangements. A phenotypically normal couple had had 4 spontaneous abortions. Chromosome analyses showed that the woman had a normal, 46,XX, karyotype. The husband was a carrier of two different balanced chromosomal rearrangements: a balanced reciprocal translocation - 46,XY,t(7;8)(q32;q24.1) and a pericentric inversion - inv(9)(p12q21.32). Such association between two balanced anomalies is a rare event. Each of the two rearrangements give an increased risk of producing unbalanced gametes; the risk is amplified by the presence of two rearrangements. We consider that this couple may benefit from artificial reproductive techniques with preimplantation diagnosis.

P1024 - Investigation of 30 Couples with Infertility with Fluorescent In Situ Hybridization (FISH) and Correlation with their Karyotypic Findings

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Background: Cytogenetic aberrations are important prognostic and diagnostic indicators in infertility.
Aim: The purpose of this study was to define the chromosomal abnormalities of the sex chromosomes of 30 couples with infertility problems by using Fluorescent in situ hybridization (FISH) and the SHOX marker (Cytocell) that detects the centromere of X chromosome (CepX) and chromosomal regions Xp22.33/Yp11.32/Yq12. The study also explored the correlation between FISH findings and patients' medical histories.
Methods: The study material consisted of peripheral blood samples from 30 couples who experienced infertility between 2021 and 2024 . Each partner underwent molecular cytogenetic FISH analysis with the SHOX marker that detects the centromere of X (CepX) and the chromosomal regions Xp22.33/Yp11.32/Yq12 in 150 interphase nuclei per patient.
Results: In men, all karyotypes were normal (46,XY), while in women, 4/30 (13.3%) had an abnormal karyotype involving a Robertsonian translocation [46,XX,der(13;14)(q10;q10)], a reciprocal translocation [46,XX,t(4;6)(p15~16; q13)] and 2 X chromosome mosaics (46,XX/ 45,X). FISH analysis showed a normal hybridization pattern for Yp11.32 and Yq12 regions in 100% of men. However, abnormalities were detected in the Xp22.33 and CepX regions in 3 out of 30 men (10%), all of whom exhibited low-level XXY mosaicism, affecting approximately 3–3.5% of their cells. In females, an abnormal hybridization pattern was detected in 9/30 (30%) with low mosaicism of the X chromosome (45,X and 47,XXX) in 3-11% of analyzed cells.
Conclusions: The high frequency of chromosomal alterations even in a low percentage of cells in infertile couples makes cytogenetic testing useful for choosing an appropriate therapeutic protocol. The contribution of chromosomal alterations in gametogenesis can lead to recurrent pregnancies/ miscarriages. Genetic counseling is considered a necessary tool for the appropriate guidance of the couple.

P1025 - Optical genomic mapping (OGM) and whole-genome sequencing (WGS) reveal a double reciprocal chromosomal translocation (RCT) and a chromosome 13 rearrangement in an infertile male with normozoospermia

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Structural aberrations involving more than two breakpoints on at least chromosomes are known as complex chromosomal rearrangements (CCRs) and have been described in >250 publications to date. Approximately 160 cases concerned male CCR carriers, the vast majority of whom are infertile or experience reproductive failures, including 9 normozoospermic cases. Reduced fertility arises from gametogenesis arrest due to disrupted pachytene chromosomal pairing. Depending on the number of chromosomes and breakpoints involved, CCRs are classified into four main types. Type III characterized by the presence of two or three independent reciprocal or Robertsonian chromosome translocations, has been observed in only 12 cases to date.

We performed the comprehensive characterization of a novel normozoospermic CCR case with reproductive failures using classical GTG banding, fluorescent in situ hybridization (FISH), whole genome sequencing (WGS), optical genomic mapping (OGM), preimplantation genetic testing for structural rearrangements (PGT-SR; Ion ReproSeq), and sperm quality tests.

OGM analysis revealed double reciprocal chromosome translocation ogm[GRCh38] t(2;9)(q32.2;q21.13)(189,561,373;73,326,540), ogm[GRCh38] t(12;8)(p12.1;q24.22)(24,660,805;13,094,226) and ogm[GRCh38] 13::13 (q32.3::q21.3)(100,997,502::70,268,176). WGS did not reveal any SNV variants causative for infertility. Evaluation of ejaculated spermatozoa revealed: ~35% of genetically normal/ balanced cells for each RCT (meiotic segregation pattern by FISH), 71% of properly protaminated cells (assessed by aniline blue staining), and 77% of sperm cells with high reproductive potential (hyaluronian binding assay, HBA). PGT-SR analysis of five blastocysts showed a variety of trisomy and monosomy events related to translocated fragments.

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KR and ZG contributed equally

P1028 - Ring Chromosomes in Hong Kong 173 Cases Diagnosed Through a 23 Years Period in Two Centers

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Introduction

Constitutional ring chromosomes (RC) are rare, occurring in 1 in 50,000 newborns. Despite attempts to coin the term "Ring Syndrome", significant clinical and cytogenetic heterogeneity exists. The importance of deep phenotyping and comprehensive evaluation is becoming increasingly apparent with time.

Methods

This retrospective cohort review summarizes the clinical and genetic findings of 173 affected fetuses and individuals diagnosed from two major clinical and laboratory genetics units in Hong Kong from year 2000 to 2022.

Results:

A total of 40 fetuses and 133 postnatal individuals with RCs from 173 apparently unrelated families were included. The male to female ratio is 70:103. Twenty-three fetuses (57.5%) presented with abnormal antenatal screening related to advanced maternal age; high risk result for first trimester combined Down syndrome screening or non-invasive prenatal testing. Twelve fetuses (30.0%) presented with structural anomaly on morphology scan. Amongst postnatally ascertain-

ned individuals, 48 subjects (36.1%) presented with short stature, followed by 15 subjects (11.3%) presented with developmental delay/ intellectual disability. Amongst subjects with parental testing arranged, 7/72 (9.7%) of affected individuals were found to have familial RCs inherited from apparently unaffected parent.
All RCs with chromosomal origin unequivocally identified in our cohort contained material from a single chromosome. No complex RCs (i.e., RCs composed of different chromosomes) were identified. Ring chromosome X predominates our cohort (n=43; Antenatally ascertained n= 4; 9.3%; Postnatally ascertained n=39, 90.7%), followed by r(13) (n= 17; Antenatally ascertained n=7; 41.2%; Postnatally ascertained n=10, 58.8%). 44 subjects (25.4%) had RCs originated from an acrocentric chromosome. 41 subjects had RCs of unknown chromosomal origin
Conclusions:
Future studies will be necessary to systematically characterize the composition and nature of RCs in order to improve understanding and lead to a more personalized management plan.

P1030 - Prenatal Sex Discrepancy between NIPS and Phenotype. A Rare Y Chromosome Rearrangement with Neocentromere Formation

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Background

Since July 2017, non-invasive prenatal screening (NIPS) for common aneuploidies has been routinely offered to all pregnant women in Belgium, with optional disclosure of fetal sex. When discrepancies arise between NIPS-predicted sex chromosomes and the phenotypic sex observed on ultrasound or at birth, further genetic investigations are recommended.
Method
NIPS performed at an external laboratory suggested a female fetus. However, prenatal ultrasound revealed a male phenotype and intrauterine growth restriction. The parents declined invasive prenatal testing. At birth, the newborn was phenotypically male, presenting with hypospadias, unilateral cryptorchidism, corneal opacities, mild hypotonia, and feeding difficulties. Initial genetic workup on lymphocytes included molecular karyotyping (Cytoscan750k SNP-array, Affymetrix). Due to the findings, additional cytogenetic investigations, including standard karyotyping and FISH analysis, were conducted.
Results
Chromosomal microarray identified a 6 Mb terminal gain of Ypter→Yp11.2, a 4 Mb interstitial gain of Yq11.221→Yq11.222, and an >8 Mb terminal loss of Yq11.222→Yqter. Standard karyotyping revealed 47,X,der(Y), +sSMC. FISH further confirmed the sSMC as an sSMC(Y) with two SRY signals. The presence of a neocentromere on the sSMC(Y) was established by the absence of hybridization of the Y-specific alpha-satellite DNA probe in all cells. The sSMC(Y) was ultimately identified as neo(Y), with the final karyotype described as 47,X,der(Y)(:p11.2→q11.221:),+neo(Y)(pter→p11.2::q11.221→q11.222→neo→q11.222→q11.221::p11.2→pter).
Discussion
This complex duplication Y with neocentromere formation explains the NIPS/genotypic discordance but is unlikely to fully account for the phenotype. As paternal DNA was unavailable, the inheritance of the Y-chromosomal abnormalities could not be determined. Further genetic investigations, including whole-exome sequencing, were proposed but declined by the family. This case underscores the critical role of complementary cytogenetic techniques in characterizing structural rearrangements for precise genetic counseling to proband and the family. To our knowledge, this specific rearrangement has not been previously reported.

P1031 - Utility of Optical Genome Mapping in Routine Cytogenetics Laboratory Workflow. A Presentation of Two Cases

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Background
Optical Genome Mapping (OGM) detects both copy number variants (CNVs) together with structural variants (SVs) and can potentially be employed as a valuable tool in cytogenetics laboratories. Our laboratory started validating OGM against standard of care (SOC) services such as Chromosome Microarray Anaysis (CMA), karyotyping and Fluroscence in-situ hybridisation (FISH).
Method
We present two cases from our early study.
Results
Case 1: A 15-year-old girl with hypotonic quadriplegic cerebral palsy, history of microcephaly and global developmental delay, suspected Rett syndrome, with some relatives suffering from probable genetic conditions was referred for CMA. CMA showed a loss of 2.23 Mb at 6p12.2p21.1. OGM confirmed this loss and found an additional inter-chromosomal translocation, t(2;6)(p22.3;q21), which results in the disruption of LTBP1 gene.
Case 2: Prenatal CMA performed on a fetus showed a 40.08 Mb terminal pathogenic gain at chromosome 3q25.32->qter and a 19.46 Mb pathogenic terminal loss at chromosome 5p14.3->pter. Parental karyotypes were performed and the father's karyotype showed 46,XY,t(3;5)(q25.3;p14) at 550 band level. OGM refined the cytoband to 3q25.32 and 5p14.3.
Discussion
OGM gave additional information of a t(2;6) segregating within the family of case 1 and may suggest that some her family members may have unbalanced karyotypes from malsegregations of the balanced karyotype. OGM has the potential of replacing CMA and karyotype analysis.
For case 2, OGM improved the resolution of conventional karyotyping and can better validate the breakpoints of CMA findings in the fetus.
Conclusion
OGM helps to fill the gap which might be missed by CMA and the integration of OGM into the clinical workflow can help clinicians gain better understanding of chromosomal aberrations.

P1036 - Molecular Characterization of Human Ring Chromosomes and Complex Genomic Rearrangements Using Optical Genome Mapping and Short Read Genome Sequencing

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Constitutional ring chromosomes (CrC) and complex genomic rearrangements (CGRs) are ultra-rare chromosomal alterations, and few cases have been fully characterized by optical genome mapping (OGM). This study aimed to perform molecular characterization of breakpoint junctions (BPJs) of CrC and CGRs. The sample comprised six individuals with CrC [CrC of 6, 7, X (three individuals), and Y] and four individuals with CGRs. Methods included: Chromosomal microarray analysis (CMA), using the CytoScan™ HD or 750k chips from Affymetrix®, and OGM, using the Bionano Genomics Saphyr

System, performed for all cases; and 10x short-read genome sequencing (GS), performed for autosomal rings and CGRs. CMA showed copy number variations (CNVs) in five cases with rings and three cases with CGRs and was unable to show CNVs in one case with low-mosaicism (20%) r(X). OGM allowed the correct identification of BPJs of all CrC except the r(Y), including the low-mosaicism r(X), and revealed a complex configuration of r(7), with an inv-dup-del rearrangement in the p arm. OGM also allowed the characterization of CGRs, revealing three patients with exceptional complex chromosomal rearrangements (CCRs) harboring three to five chromosomes and six to 24 BPJs and one patient with a CGR involving the p arms of chromosomes 2 and 9, with nine BPJs. OGM also found all CNVs found by CMA. GS validated the BPJs found by OGM and refined these breakpoints at the base-pair level in the autosomal rings and two CGR patients. Short-read GS could not fully characterize two cases with exceptional CCRs. In conclusion, besides reinforcing the need to use different methods to characterize CGRs, this study contributes to gaining insights into the genomic architecture of ultra-rare chromosomal alterations. Financial support: FAPESP, CAPES, CNPq.

P1038 - Developmental Delay and Dysmorphic Features Unravel a Marker Chromosome with a Neocentromere Derived rom Chromosome 8

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Introduction: Marker chromosomes (mar) are small structurally abnormal chromosomes not identifiable by conventional cytogenetics that may be derived from any chromosome. Neocentromeres are newly formed centromere in any chromosome, in a different location from normal and, unlike natural centromeres, they usually lack highly repetitive sequences. Mar are very rare and the presence of a neocentromere in a marker chromosome is even rarer.

Material and methods: We report the clinical case of a young man, evaluated in medical genetics consultation at 16yo, referred for oral cleft, first child of a nonconsanguineous couple. He presented with complete primary and secondary palate cleft and unilateral lip cleft, prognathism, macrocephaly, intellectual disability, global developmental delay, behavioural disorders and obesity. Chromosome GTL banded metaphases analysis was performed in peripheral blood cultures according to standard methods. Molecular cytogenetic studies included MLPA technique using panels P250-B2 and P070-B3 SalsaMLPA(MRC Holland), FISH centromeric #8, subtelomeric #8 probes (Vysis-Abbot) and AffymetrixCytoScan HD array.

Results: The patients karyotype revealed a supernumerary mar in all cells. MLPA P250-B2 showed GATA4, MSRA and PPP1R3B probes increase, all in 8p23 region. MLPA P70-B3 showed a FBXO25 probe increase, in 8p subtelomeric region; 8p23.3 Subtelomeric FISH probe was present in both mar extremities. Chromosome 8 centromeric probe did not show a signal in mar. Patients karyotype:
47,XY,+mar.ish der(?8)(8S504+,D8Z1-,D8S504+).rsa 8p23.3(FBXO25)x4,8p23.1(PPP1R3B,MSRA,GATA4)x3.
Patients array was arr[hg19] 8p23.3(158049_699220)x4,8p23.1(7044046_11936001)x3,
confirming the karyotype.

Discussion: A rare case of mar with a neocentromere is presented. The authors highlight the importance of the combination of high resolution banding with molecular cytogenetic techniques for identifying mar. FISH analysis is essential in these cases to determine the presence of neocentromeres, allowing a better chromosomal characterization and adequate genetic counselling for the patient and family.

P1041 - Unravelling a Complex Case of del(9)(p24) and Subtelomeric del(4q) in a 46 XY Female Patient

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Introduction

Disorders of sexual development (DSD) are defined as any congenital condition in which the development of chromosomal, gonadal or anatomical sex is atypical. A phenotypic 46,XY female is an individual with a typical male karyotype who develops female physical characteristics. This may have several causes. Small telomeric deletions of 9p are known to be associated with XY sex reversal. The typical 9p deletion syndrome has (OMIM#158170) a trigonocephaly phenotype; minor anomalies, intellectual disability and ambiguous genitalia may be present in up to 70% of patients.
Material and methods:
A 37 yold woman with intellectual disability and ovarian agenesis was referred from a fertility consultation for karyotyping. Chromosome analysis of GTL banded metaphases from peripheral blood cultures was done, followed by MLPA Subtelomeres P070-B3, Salsa® MLPA® (MRC Holland) panel and a FISH probe for 4q subtelomeres (Vysis - Abbott)
Results
In addition to the presence of 46,XY, the karyotype revealed a structural anomaly, a deletion in chromosome 9 short arm, in 9p24. MLPA subtelomeric regions panel showed the deletion in 9p and also a deletion in 4q, this latter confirmed by FISH. The karyotype was thus: 46,XY,del(9)(p24).rsa 4q35.2,9p24.3(P070-B3) x1.ish del(4)(q35.2q35.2)(D4S2930-).
Discussion
We believe that the combination of these chromosomal aberrations contributed to the unusual clinical features exhibited by the patient. This case highlights the importance of comprehensive cytogenetic analysis in identifying and characterizing complex chromosomal abnormallities. The combination of del(9)(p24) and 4q subtelomeric deletions in a female patient with a 46,XY karyotype presents a particularly challenging diagnostic scenario. Our findings provided valuable information regarding the potential phenotypic consequences of these chromosomal aberrations and enabled a more adequate genetic counselling.

P1043 - FGF14 Disruption by Constitutional Chromoanagenesis as a Cause of Spinocerebellar Ataxia

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Hereditary cerebellar ataxias constitute an heterogeneous group of neurological diseases associating gait alteration, limb incoordination, dysarthria and abnormal eye movement. The FGF14 gene is linked to a late-onset form of spinocerebellar ataxia (SCA27B), due to intronic GAA-repeats and an earlier form (SCA27A) that can begin in childhood.
We report here a 7-year-old girl that was adressed for developmental and speech delay, hypotonia, ataxic gait, altered fine motor skills, ptosis and oculomotor apraxia. Brain MRI showed vermis hypoplasia. Sequencing a panel of 419 genes involved in parkinsonism, abnormal movements and ataxia was inconclusive. Chromosomal

micro-array (CMA) identified a 1.96Mb one-copy loss in 2p25.1p24.3 involving 5 genes and classified as variant of unknown significance (VOUS). Then, genome sequencing showed a complex de novo chromosomal rearrangement involving 4 chromosomes, chromosomes 2, 6, 13 and 21, and 58 breakpoints. It resulted in 3 deletions of 1987kb (2p25.1p24.3, detected by CMA), 41kb (21q21.2) and 18.5kb (21q21.1), all considered as variant VOUS. This complex rearrangement was further confirmed by karyotype and FISH.

Analysis of breakpoints signature showed mainly blunt-end and some microhomologies (one to three nucleotides). Three breakpoints presented small templated insertions of 5 to 11 nucleotides. This was in favor of a chromothripsis mechanism. Among the nine disrupted coding genes, FGF14 could explain the patient phenotype.

FGF14 is known to cause SCA27A mainly through single nucleotide heterozygous variations. However, cytogenetics mechanisms were already reported such as deletion or disruption by a reciprocal translocation breakpoint. We report here the first case of SCA27A due to chromoanagenesis disruption. Despite the high complexity of the rearrangement, the impact is quite limited with only one gene responsible for the phenotype. It also emphasizes the importance for structural variation exploration of the genome to resolve diagnosis odyssey.

P1045 - A Personalized Genomic Medicine Approach to Rare Genomic Disorders Associated with Simple Chromosomal Structural Variants

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Rare genomic disorders (GD) arise from cytogenomically visible or cryptic, simple or complex structural variants (SVs) and/or copy number variants that cause OMIM disorders, syndromes, or potentially as-yet unidentified conditions. Diagnosing disorders associated with such variants based solely on clinical features, or interpreting the clinical significance of SVs, is inherently challenging. We implemented a precision genomic medicine (PGM) approach that integrates long-insert and short-insert genomic sequencing (siGS) with blood transcriptome analysis in 29 probands with rare GDs, seemingly linked to simple chromosomal rearrangements. Using this approach, we identified disease-causing or plausible variants in 26 of 27 probands with clinical phenotypes. Four variants implicated FLT1, SSBP3, YIPF5, and SPATC1L as novel disease-causing candidate genes. Among the 26 probands with identified variants, 21 were diagnosed with an OMIM disorder, while five were linked to previously uncharacterized conditions. The diagnostic yield exceeded 90%, with 66% classified as rare GDs and 33% as rare disorders. Pathogenic mechanisms included a cryptic variant, digenic inheritance involving different variant types, and X/autosome translocation leading to a position effect on ZC4H2, with skewed X-chromosome inactivation, among others. Of the affected genes,

18 were autosomal dominant, and 13 of these were involved in chromatin remodeling and transcriptional control. Transcriptome analysis improved the prediction of two disease-causing candidate genes, revealed altered expression in disrupted genes or those affected by a position effect, identified nonfunctional fusion transcripts, and highlighted allele-specific skewed X-chromosome inactivation. In summary, addressing the complexity of rare GDs requires a cost-effective PGM approach centered on siGS, integrating comprehensive genomic variant profiling, comparative phenotypic analysis, reverse phenotyping, transcriptome analysis, and convergent genomic data analysis. This approach reduces the diagnostic odyssey for patients, while contributing to the annotation of the coding and non-coding morbid genome.

P1048 - Comprehensive Analysis of Copy Number Variations in Tunisian Patients with Congenital Heart Defects

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Congenital heart defects (CHDs) pose a significant global health burden, affecting one million newborns annually. Understanding the genetic causes of CHDs is crucial for improving diagnosis, management, and genetic counseling. Copy number variations (CNVs) play a key role in CHD pathogenesis, either as direct causes or contributors to multifactorial risk. Nevertheless, advancements in technology, such as chromosomal microarray analysis (CMA) and whole-genome sequencing (WGS), have transformed diagnostic capabilities.

This study involves a comprehensive analysis of 20 Tunisian patients with syndromic CHDs referred to our Genetics department. Initial CMA investigations revealed pathogenic CNVs in 20% of cases. These included in one case an association of 11 MB deletion at 9p24.2 and a 10 MB duplication at 20pter. The second CNV was a 1.2 MB deletion at 15q26.2 coupled with an 11 MB duplication at 2q36.3. The third case presented a deletion in 17q21.32 spanning 113 Kb, and the fourth case involved a duplication at 8q22.1.By establishing genotype-phenotype correlations through these CNVs, we identified genes known to be associated with CHDs, such as NR2F2, DOCK8, and KANSL1. The NR2F2 gene at 15q26.2 is linked to cardiac malformations, underscoring its importance in cardiac development. Similarly, DOCK8 at 9p24.3 is implicated in congenital cardiac malformations due to its cardiac tissue expression. KANSL1 deletion results in Koolen de Vries syndrome,

which includes CHDs, mental delay, hypotonia, and dysmorphic features. These findings provide valuable insights into CHD pathogenesis, and underscore the CNVs pathogenesis in syndromic CHDs enhancing clinical management and genetic counseling by accurate more risk assessment. The ongoing analysis of WGS data from a larger cohort will elucidate the CHDs genetic architecture identifying novel genetic variants and pathways involved

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P1049 - Copy Number Variations (CNV) Found in Tunisian Patients with Corpus Callosum Malformations

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Corpus callosum malformations (CCMs) are a group of heterogeneous brain abnormalities affecting approximately 1 in 4,000 births. They commonly manifest as complete or partial agenesis of the corpus callosum and are frequently associated with chromosomal or genetic abnormalities, complicating prenatal diagnosis.

This study aims to assess the diagnostic yield of conventional and molecular cytogenetic approaches in a cohort of 105 Tunisian patients screened between 2010 and 2024. Karyotyping was systematically performed, while array comparative genomic hybridization (array CGH) was conducted on 54 individuals along with FISH to confirm the chromosomal anomalies if observed.

Array CGH identified 18 copy number variations (CNVs) in 17% of diagnosed cases, including pathogenetic deletions (14q12, 4p, 1q43q44, 1p32, 5p14.3, 5q35, 16q, 18p, and 9p21) and duplications (4q, 18p, 15q13.1, 2p23.2, and 15q11.2). Additionally, three variants of uncertain significance (VUS) were detected at 1q31.1, 20q11.22, and 12q12.

Genotype-phenotype correlations revealed known CCM-associated genes, such as ZNF238, FOXG1, and NFIA, along with novel candidate genes, including BRINP3, PLD5, FMN2, and PRKD1. These genes are implicated in neuronal migration, callosal axon maintenance, and embryonic midline formation. Gene interaction analysis using STRING and Pathway Commons suggested potential functional interactions, particularly within pathways related to neuronal development and axon guidance, enhancing our understanding of the genetic complexity underlying CCMs.

Our findings highlight the significant role of CNVs in CCM. Further studies are needed to determine the pathogenicity of rare CNVs associated with CCM. Integrating next-generation sequencing (WES/WGS) with array CGH could improve diagnostic accuracy and genetic counseling, ultimately enhancing prenatal diagnosis and expanding knowledge of CCM molecular mechanisms.

P1052 - Invdupdel or duptrp Rearrangements Revisited Using Array CGH and Optical Genome Mapping

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Introduction : Inverted duplication deletion [invdupdel] are complex and rare chromosomal rearrangement that combines most often a distal deletion and an inverted interstitial duplication of a chromosome arm. They often affect the short arm of chromosome 8 clinically featuring neuro-developmental delay, mild to severe cognitive impairment, heart congenital defects and brain abnormalities as previously reported.

Method : We have studied invdupdel from different chromosomes 4p, 8p, 9p,11q and Xp. The patients were referred in a prenatal or postnatal context. They all presented an abnormal phenotype. We used different techniques such as array-CGH, Optical Genome Mapping(OGM) and FISH in order to characterize the complexe rearrangements and compared the results.

Results : The chromosomal abnormalities were homogeneous or presented mosaicism either in the same culture or in different cultures or tissues. As expected, the CNVs (deletion/duplication) were identified by Array-CGH and OGM but the inversions were only proven using FISH or OGM. We noticed discrepancies in the length of the telomeric CNVs between array-CGH and OGM. The FISH technique could confirm the underestimated length of deletions with CMA or OGM. In some cases a triplication was associated with the invdupdel or only a duplication. The position of the CNVs (deletion, duplication and triplication), on the same chromosome was easily detected using OGM. The FISH showed the different clones with the rearranged distal chromosomal regions resulting from mosaicism. Associated triplications were identified, they are rarely reported in the litterature. Retrospectively the triplications (Trp) were observed in some of our cases with invdupdel or dup that had not been reported.

Conclusion : the comparison of techniques like CMA, OGM and FISH is useful to better characterize the structure and the mitotic instability of some complex chromosomal rearrangements namely invdupdel, delinvduptrp, or duptrp.

P1057 - Characterization of Complex Chromosomal Structural Variation. A Comparison of Cytogenetic Methods

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Complex chromosomal structural variants (SV) often require a combination of cytogenetic methods, such as karyotyping, fluorescence in situ hybridization (FISH) and chromosomal microarray (CMA), to fully characterize the chromosome structure. While G-banding remains the gold standard in describing complex chromosomal rearrangements at low resolution, newer high-resolution methods, such as optical genome mapping (OGM), allow for the detection of both balanced and unbalanced rearrangements, with limitations in certain complex regions of the genome. Our goal was to evaluate the utility of these techniques in elucidating the complexity of various types of chromosomal rearrangements and consider the advantages and limitations of each.
We performed OGM on 28 pediatric cases previously tested by standard-of-care methods, such as G-banding, FISH and CMA. Six cases with complex chromosomal rearrangements were selected and results compared.
Chromosome rearrangements with multiple breakpoints and junctions confined to a single chromosome were investigated in two cases, one with chromosome 4 and the other with chromosome 7 involvement. Rearrangements of a supernumerary chromosome 8 and chromosome 15 were studied in two other cases. A case with a 1q jumping translocation to the 20p and 13q subtelomeric regions and a case of an SRY-positive XX karyotype were also analyzed. OGM analysis detected cryptic complex rearrangements beyond the resolution of G-banding, however, the karyotype and targeted FISH analyses better described the chromosome structure in certain complex and repetitive regions of the genome, which are known limitations of OGM.
No single method is sufficient to accurately describe complex structural rearrangements, and a combination of techniques is often required. Such comparison studies may help to refine the SV detection algorithms for high-resolution mapping and sequencing technologies, thereby increasing the diagnostic yield and improving our understanding of the mechanisms underlying these complex structural variations.

P1061 - De Novo Deletion 18p in a Female with Short Stature and Premature Ovarian Failure. A Case Report

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Deletion 18p syndrome is a rare chromosomal disorder caused by the partial deletion of the short arm of chromosome 18, with an estimated incidence of 1 in 50,000 live births.
We report a 24-year-old female patient with short stature and premature ovarian failure, in whom cytogenetic testing revealed a de novo 18p deletion.
The patient was born preterm as a firstborn, following an uncomplicated pregnancy. She experienced mild psychomotor delay, began walking at 18 months, and underwent strabismus surgery at five years. Despite these delays, her cognitive development remained normal. She has significant emotional sensitivity and anxiety, which have impacted her daily life. Additionally, she has chronic anemia and persistent short stature, with menarche occurring at 10 years. At the age 24, she was diagnosed with premature ovarian insufficiency, and Turner syndrome was suspected by her gynaecologist.
Conventional and molecular karyotyping confirmed a de novo deletion of the short arm of chromosome 18.

This case highlights the necessity of genetic evaluation in patients presenting with a variable spectrum of unexplained growth deficiencies and ovarian dysfunction, offering crucial insights into the diverse phenotypic manifestations of 18p deletion.

P1064 - Mosaic Trisomy 14 in a Child with Multiple Congenital Anomalies Due to an unstable Robertsonian Translocation Involving Chromosomes 14 and 22

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We report on a 2 years old female child with a complex clinical phenotype including global developmental delay, muscular hypotonia, joint hypermobility, atrial septal defect, macrocephaly, and facial dysmorphic signs. A first chromosome analysis showed a balanced dicentric Robertsoian translocation between chromosome 14 and 22 in 10 metaphases. Uniparental disomy 14 could be ruled out by microsatellite analysis. Whole exome analysis was negative. Micorarray analysis performed two month later with a second blood sample revealed trisomy 14 in mosaic form. Reanalysis of the chromosome slides could detect a second cell line with an unbalanced dicentric Robertsonian translocation between two chromosomes 14 in about 10 % of the analysed cells. Thus we conclude that the mosaic trisomy 14 was caused by the instablility of the Robertsonian translocation; there are now several published reports of such unstable Robertsonian transloctions. While pure trisomy 14 is not compatible with life, mosaic trisomy 14 is a rare but well documented genetic syndrome mainly characterized by variable global developmental retardation, congenital anomalies, pigmentary skin lesions, and dysmorphic signs. This case again demonstrates the usefulness of conventional chromosome analysis in the era of NGS analyses.

P1065 - Cytogenetic and Molecular Characterisation of Chromoanasynthesis in a Child with Multiple Congenital Anomalies

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Genomic and chromosomal disorders are often known to be caused due to structural chromosome rearrangements resulting in gene disruption, gene fusion and abnormal gene dosage as mechanisms responsible for abnormal phenotypes.
With the advancements in sequencing technologies and molecular cytogenetics methods, it is now possible to better characterise these structural rearrangements and define more precisely the mechanism of formation of the rearrangement.
We present a case of a 2 year old girl born of non-consanguineous marriage with multiple congenital anomalies, including, bilateral cleft lip palate, post axial polydactyly and bilateral retinoblastoma. Standard G-banded karyotype showed an abnormal chromosome 13 and chromosomal microarray was further performed to characterise the abnormality. CMA showed a large deletion ~19Mb encompassing cytobands q13.3-q21.1 and ~ 18Mb duplication q31.1-q33.2. Also observed were two smaller duplications of ~6.3 Mb in the cytoband q21.1-q21.31 and ~1.7 Mb in the cytoband q31.1-q31.1.
To further characterise the rearrangement optical genome mapping and long read nanopore sequencing were performed. Our analysis suggests a complex eight break rearrangement encompassing the cytobands 13q13.3 to 13q33.2, suggestive of chromoanasynthesis, which has resulted in complex rearrangement involving deletion and duplications with micro homology at breakpoints.
We highlight the importance of high resolution cytogenomic investigations to delineate complex structural rearrangements and improved understanding of the underlying mechanisms

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P1068 - Unraveling Genetic Variability in Reproductive Failure a Novel Approach to Infertility Diagnosis

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Infertility and spontaneous miscarriages represent a significant issue in human reproductive health, with approximately 30% of cases classified as idiopathic infertility, meaning no identifiable cause can be determined through conventional diagnostic analyses [1]. Recent studies suggest that small balanced chromosomal rearrangements, such as inversions and submicroscopic translocations, may play a key role in reproductive failure [2,3]. However, current genomic analysis technologies have limitations in detecting such structural variants [4,5,6]. Our project aims to identify genetic variants underlying reproductive failure using Single-cell Template Strand Sequencing (Strand-seq), an innovative technology that enables the detection of inversions and translocations with a resolution of up to 1 kb and a false positive rate of 0.003%, overcoming the limitations of traditional methodologies [7,8]. The analysis will be conducted on a total of 50 couples with idiopathic infertility, that fulfill specific criteria. So far, 33 couples have already been recruited for the study. The protocol includes isolating mononuclear cells from peripheral blood, extracting DNA, preparing sequencing libraries, and performing bioinformatics analysis to identify chromosomal abnormalities potentially associated with infertility and recurrent implantation failure [9]. The expected results include the creation of a detailed map of the most frequently associated inversions and translocations linked to recurrent pregnancy loss and idiopathic infertility, the characterization of the genes involved, and the evaluation of how these rearrangements affect meiosis and lead to the formation of unbalanced gametes [10,11]. The results of this study will provide new tools and insights into the genomic basis and predisposing factors of infertility. Additionally, they will contribute to the development of a diagnostic tool to assess the likelihood of success in couples planning a pregnancy or undergoing preimplantation genetic testing, based on their specific genetic background.

P1069 - A Rare Y Autosome Reciprocal Translocation t(Y;17) Found in a Patient with Azoospermia

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Introduction: Y autosome translocations are relatively rare in humans. During normal meiosis in male, the X and Y chromosomes recombine, synapsing at the PAR regions and formed the sex vesicle at pachytene. This complex is necessary for normal spermatogenesis. Y autosome translocations often result in a disruptive effect and leads to spermatogenetic arrest and azoospermia. Case report and Cytogenetic Analysis: We report about a 35-year-old healthy man with infertility due to azoospermia. Family history was normal. Cytogenetic revealed a balanced reciprocal translocation including chromosomes Y and 17 in all 25 observed metaphases: 46,X,t(Y;17)(p11.32; q12). FISH analysis with subtelomere probe for Yptel (DXYS129) and Yqtel (DXYS154) showed a normal signal pattern for the X and Y chromosomes. These analyses pointed out that

the breakpoint positioned distal to the Yp subtelomere probe with an apparently intact Y chromosome. 17qtel probe (D17S2200) localised on derivative Y chromosome.
Conclusion: The presence of an intact PAR-region, together with the absence of Y chromosome microdeletions in the AZF-regions indicate that the azoospermia may be due to the translocation, through a disturbance in meiotic pairing and segregation.

P1070 - Maternally Inherited Gain Xq24 Encompassing the CUL4b Gene Causative for X Linked Intellectual Disability

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X-linked intellectual disability (XLID) accounts for approximately 5 to 10 % of all inherited cases of intellectual disability in males. To date, CUL4B variants have been identified in 3 % of XLID cases. Specifically, truncating variants in the gene have been associated with X-linked intellectual disability, Cabezas type (OMIM #300354), which is characterised by developmental delay, intellectual impairment with significant speech impairment and short stature.
The CUL4B gene encodes a scaffold protein of the cullin 4B-RING ubiquitin ligase (E3) complex, named Cullin 4B. It is involved in the ubiquitin-dependent proteasomal degradation process. The mechanisms underlying the neurological disorders in patients with CUL4B variants remain to be elucidated.
We report on the case of a 9-year-old boy with severe developmental delay and autism spectrum disorder. Utilising oligonucleotide array comparative genomic hybridisation (aCGH), we identified a gain of chromosomal material of Xq24, encompassing the complete CUL4B gene, with a size of approximately 814 kilobases.
To the best of our knowledge, only one family with a comparable non-disruptive CUL4B duplication has been published in the literature to date. The male patients present with borderline IQ, overweight, stereotypies and attention deficit hyperactivity disorder.
In our case, a maternal inheritance was proven using aCGH. Subsequent analysis of X inactivation in the mother indicated a clearly shifted X-inactivation pattern.
Our report provides further evidence that triplosensitivity of CUL4B is a causative factor for XLID. Additionally, this case report emphasizes the critical role of CUL4B gene alterations in male patients with developmental delay. Therefore, this gene should be considered for routine diagnostics for patients with suspected XLID.

P1072 - A Complex Chromosomal Translocation in a Young Girl with Mental Retardation

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Complex chromosomal rearrangements (CCRs) are rare structural changes which commonly involve many breakpoints with random reassembly, and can embrace a single or several chromosomes. In clinically affected patients most apparently balanced CCRs turn out to be unbalanced at the molecular level. Here, we report on a nine year old girl presenting adiposity and mild intellectual disability with language impairment. Two seizures were noted at the age of eight. Conventional karyotyping revealed an apparently balanced CCR involving chromo-

somes 2, 7 and 13. This aberration was confirmed by whole chromosome painting fluorescence in situ hybridization (FISH). Breakpoints of the translocation t(2;7;13)(p15;p13;q14.3) were specified via locus specific FISH probes. Array CGH analysis excluded related chromosome imbalances. Further parental cytogenetic analysis revealed normal karyotypes in mother (46,XX) and father (46,XY) assuming a de novo event in the index patient. Clinical trio exome analysis showed no variants comprising ACMG (American College of Medical Genetics and Genomics) class 4 and 5. Currently the girl‘s phenotype cannot be explained by the results using the aforementioned cytogenetic and molecular methods. Further molecular approaches (a. o. optical genome mapping, whole genome sequencing, DNA methylation analysis, functional analysis of regulatory gene segments) could resolve this case.

P1075 - Chromosomal Abnormalities in Reproductive Health: Data from Cytogenetic Analysis in a Greek Cohort the Last Decade

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Background:
Chromosomal abnormalities play a significant role in reproductive challenges. Advances in cytogenetic analysis have facilitated the detection of chromosomal aberrations in individuals undergoing cytogenetic evaluation.
Materials and Methods:
Between 2014 and 2024, 2.372 individuals underwent cytogenetic investigation. These were classified based on the reason for referral which included infertility, recurrent miscarriages, IVF and screening using data from the Laboratory of Medical Genetics, Athens University. Retrospective analysis of data allowed characterization and prevalence of findings across the different groups.
Results:
Infertility: In females 5% presented mosaicism of sex chromosomes, while 1% reciprocal translocation. In males 6% was diagnosed with Klinefelter syndrome, 1% presented mosaicism of sex chromosomes and 1% reciprocal translocation.
Recurrent miscarriages: Males and females presented similar percentages;1% sex chromosome mosaicism ,1% reciprocal translocation and 1% Robertsonian translocation. In males 1% also presented inversions.
IVF: In females cytogenetic analysis revealed sex chromosome mosaicism (1%) and Robertsonian (1%) and reciprocal (1%) translocation.
Screening: In females 3% presented sex chromosome mosaicism, while 2% structural aberrations. In males 1% was diagnosed with Klinefelter syndrome, while in 2% a structural abnormality was revealed.
Conclusion:
Cytogenetic analysis in individuals tested revealed numerical and structural aberrations that are in line with the literature. This study underscores the importance of conventional karyotype as a diagnostic tool in individuals undergoing genetic evaluation during reproduction and enhances clinical management towards improved reproductive outcomes

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P1076 - A Family with Multiple Recurrent Copy Number Variations Associated with Increased Risk for Neurodevelopmenetal Disorders

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Recurrent CNVs represent a group of genomic disorders that predispose to neurodevelopmental disorders (NDDs), and most are associated with variable expressivity and reduced penetrance.
A pair of siblings presented with mild intellectual disability, motor delay, incoordination, and craniofacial minor anomalies. The older, 9-year-old child's additional symptoms include dysdiadochokinesis and monomorphic spike wave dicharges identified on EEG, but no history of seizures. The 3.5 years old younger sibling has absent speech, generalized hypotonia, inappropriate laughter, motor stereotypies, reduced eye contact and reduced social reciprocity. She is currently undergoing evaluations for autism spectrum disorder. The mother has a history of dyslexia and speech articulation difficulties, meanwhile the father has borderline intelligence.
Multiplex ligation-dependent probe amplification analyses were performed using the commercially available P245 and P297 probemixes. The results showed that both siblings carry the NDD-associated BP4-BP5 15q13.3 recurrent microdeletion including CHRNA7 gene (ClinGen HI score: 3). Furthermore, the older sibling carries two additional microduplications of recurrent regions 1q21.1 (distal, BP3-BP4, including GJA5 gene; ClinGen TS score: 2) and 16p13.11 (BP2-BP3, including MYH11 gene; ClinGen TS score: 2). Both microduplications have been linked to NDDs with low penetrance, although further data is required to evaluate the association. Genetic testing of the parents revealed that the 15q13.3 microdeletion was inherited from the mother, whereas the 1q21.1 and 16p13.11 microduplications were present in the father. Karyotypes were normal for all family members. The grandparents were not available for testing.
In summary, we present a family with variably expressed NDDs and multiple recurrent CNVs. Interestingly, the less severley affected sibling carried all three CNVs, and the minimally affected mother carried the 15q13.3 microdeletion. Our findings showcase the difficulties associated with genotype-phenotype correlation of recurrent CNVs.

P1077 - Decoding Complex Chromosomal Rearrangements and Their Genetic Impacts

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Whole Genome Sequencing (WGS) is currently a method of choice for genetic analyses, as it allows for the detection of both single nucleotide variation and cytogenetic rearrangements. Since most breakpoints occur in intronic region, which are not accessible by classic methods like Whole Exome Sequencing, and as it offers better resolution than karyotyping and chromosomal microarray analysis (CGH-array), WGS is increasingly used in first intention.
We describe here the case of a patient presenting with upper and lower limb hexadactylies, cryptorchidism and moderate intellectual deficiency as his main symptoms. Given these various clinical signs and in the absence of abnormalities in the karyotype and CGH-array, WGS was performed as part of the Plan Médecine France Génomique (PFMG).
This patient suffers from a de novo Complex Chromosomal Rearrangement (CCR) suggesting a chromothripsis involving several different regions on the short arm of both chromosome 7 and 11, disrupting GLI3 and STIM1, well known OMIM morbid genes. The chromothripsis leads to loss of function of GLI3, explaining the hexadactyly and perineal malformations. However, the consequences on STIM1 seem unclear, since its main pathogenic mechanism is a gain of function. Several other biological experiments are ongoing to determine the level of implication of STIM1 in our patient's phenotype, whether leading to loss of function or gain of function affecting other transcripts.

P1078 - Maternal Cryptic inv(16)(p13.3q24.3) Leading to Opposite Recombinant Chromosomes 16 in two Daughters

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We report on a family in which the mother is carrying a large cryptic pericentric inversion 16 (undetectable at the 550-band resolution level). Each of her daughters inherited the inversion in a recombinant form.
Chromosome and FISH analyses were initially conducted on the now 28-year-old daughter following a conspicuous SNP-array finding, prompted by developmental delay and seizures. The array analysis showed a terminal deletion 16p13.3 (1,53 Mb) and a terminal duplication 16q24.3 (579 kb). These results were confirmed by FISH. Additional FISH analysis on the maternal chromosomes revealed a hybridization pattern consistent with a pericentric inversion.
The healthy 27-year-old sister of our index patient sought genetic counseling to assess her carrier status for the maternal pericentric inversion before starting a family. Chromosome analysis was - like in mother and sister - without any findings at the 500-band resolution level. Surprisingly, the FISH analysis showed signals consistent with a terminal duplication 16pter and a terminal deletion 16qter on one chromosome 16 - opposite to the recombinant chromosome 16 diagnosed in the sister. Array analysis confirmed these results, presenting a 305 kb deletion 16q24.3 and a 1,5 Mb duplication 16p13.3.
We will discuss the exiciting question: what would be the behavior of the recombinant chromosome 16 during meiosis?

P1079 - Comparative Evaluation of CNVs Detection. A Case Study of Optical Genome Mapping and Long Read Whole Genome Sequencing versus Chromosomal Microarray

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The contribution of copy number variations (CNVs) to the pathogenesis of various diseases has been increasingly recognized. Chromosomal microarray (CMA) remains the gold standard for genome-wide CNVs analysis. However, emerging cytogenomic techniques, such as optical genome mapping (OGM) and long-read whole-genome sequencing (LR-WGS), offer the potential to not only detect structural variations but also to provide more detailed insights into CNVs.
In this study, we compared and evaluated the CNV profiles obtained using CMA (Agilent), OGM (Bionano), and LR-WGS (Oxford Nanopore Technologies) in a patient with neurodevelopmental symptoms and negative classical cytogenetic results. Our primary aim was to assess the success and accuracy of CNVs detection by OGM and LR-WGS, relative to the CMA method, which is firmly established in clinical diagnostics.
The CMA analysis identified a duplication and a deletion of the chromosome 12, both of which were also detected by OGM and LR-WGS. Notably, LR-WGS provided a more detailed and comprehensive view of the affected regions, offering refined coordinates of the CNVs and a deeper examination of the associated genes.
This case report suggests that OGM and LR-WGS hold significant potential for CNV detection in clinical practice. However, it is crucial to understand the limitations of these methods and integrate them carefully into diagnostic algorithms for optimal clinical utility.

P1080 - Multiple Non Contiguous Interstitıal Deletıons in 5q21q22.1 Including the CHD1 Gene Identified in a Boy with Developmental Delay and Severe Language Impairment.

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Intellectual disability (ID), developmental delay (DD), and behavioural disorders are complex neurodevelopmental conditions associated with multifactorial etiologies, including genetic factors. Chromosomal microarray analysis (CMA) is a valuable tool in identifying copy number variations (CNVs) contributing to neurodevelopmental disorders.
Here we report a 4-year-old male with DD, severe language impairment, behavioral disturbances, macrocephaly, facial dysmorphisms, and delay walking (at 20 months). He was born to nonconsanguineous parents. Family history is significant for maternal intellectual disability and paternal neonatal hypoxic-ischemic encephalopathy, which resulted in hemiparesis and language impairment.
CMA revealed three heterozygous interstitial deletions: 2.12Mb at 5q15q21.1(97929163-100045362), encompassing the CHD1 gene; 684Kb at 5q21.3(104580978-105264711), a gene-free region; and 3.69Mb at 5q21.3q22.1 (107047547-110727429), including the SLC25A46 gene. Parental segregation studies revealed that all three deletions were maternally inherited. Although the identified non-contiguous losses may suggest a complex chromosomal rearrangement (CCR), no further studies were performed.
Interstitial deletions of the middle region of the long arm of chromosome 5 are rare, and cases of CCR involving only this chromosome are even more rare. Most of the CCR are associated to intellectual disability.
Missense variants in CHD1 have been associated with Pilarowski-Bjornsson syndrome, a neurodevelopmental disorder characterized by ID, DD, dysmorphic features, and apraxia of speech. However, deletion involving this gene are rare and may lead to speech abnormalities in the absence of intellectual disability (ID) or other major neurodevelopmental disorders. This phenotypic variability suggests that both CHD1 deletions and missense variants may exhibit variable expressivity or incomplete penetrance.
This case highlights a possible link between CHD1 deletion and an autosomal dominant complex neurodevelopmental disorder and the diagnostic utility of cytogenetic studies in identifying complex genetic etiologies underlying CCR.

P1081 - Exome Sequencing Identifies Copy Number Variants Associated with 22q11.2 Deletion Syndrome Like Phenotype

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22q11.2 deletion syndrome (22q11.2DS) is a well-characterized disorder with variable clinical manifestations. However, overlapping phenotypes may arise from other chromosomal aberrations. We present two patients with 22q11.2DS-overlapping phenotypes in whom standard genetic testing did not detect the 22q11.2 deletion.
The patients were admitted with syndromic congenital heart defects and global developmental delay. Patient 1 exhibited an atrial

septal defect (ASD), a ventricular septal defect (VSD), hypermetropia, and minor anomalies. Patient 2 presented with ASD, VSD, bilateral hearing impairment, recurrent infections, cleft palate, kyphosis, inguinal hernia, and minor anomalies. Initial fluorescent in situ hybridization (FISH) using the N25 and TUPLE 22q11 probes and multiplex ligation-dependent probe amplification (MLPA) using the MRC-Holland SALSA MLPA P250 probemix did not reveal pathogenic copy number variations (CNVs). To identify causative variants, exome sequencing (ES) with CNV analysis was performed. CNVs were validated using G-band karyotyping.

Patient 1 was found to have an 8p23.3p23.1 (6.2 Mb) deletion and a 4p16.3p15.2 (23.7 Mb) duplication. Patient 2 carried an 18q22.1q23 (14.49 Mb) deletion and a 20p13p11.23 (19.62 Mb) duplication. The overlapping phenotypes associated with these CNVs accounted for the clinical presentation in both patients and originated from parental balanced translocations. Prenatal cytogenetic testing is crucial for these carrier families.

Our findings emphasize the heterogeneous background of the 22q11.2DS-like phenotype and the importance of genetic testing in identifying patients with a dual diagnosis. Additionally, we highlight the critical role of G-band karyotyping in validating findings from ES-based CNV analysis

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P1082 - Optical Genome Mapping is a Powerful Tool for Detecting Clinically Significant Variants and Chromosome Abnormalities in Hematological Diseases

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Conventional cytogenetics is widely used to diagnose hematological malignancies and to assess their prognosis. Optical genome mapping (OGM) has demonstrated remarkable efficacy in identifying structural rearrangements. It can detect number anomalies, such as aneuploidy or small copy number variants with a greater resolution than conventional cytogenetic techniques. Here, we evaluate the use of OGM in routine diagnostic hematological cytogenetics.

We carried out a retrospective study of 20 patients with hematological malignancies. All patients underwent a standard diagnostic (karyotype +/- FISH) and OGM. OGM were analyzed in single-blind conditions by two operators. We compared the results obtained between OGM and conventional cytogenetics. We confirmed each variant of clinical significance with complementary techniques.

Twenty samples were analyzed: 50% B-ALL (n=10), 20% AML (n=4), 15% T-ALL (n=3), 10% MDS (n=2), and 5% of other diagnostics. In 70% of cases, OGM detects an additional clinically significant variant compared to standard techniques. These variants mainly include cryptic variants that were not visible in the karyotype (CDKN2A deletion (n=8), IKZF1 deletion (n=3)). OGM has also identified rare cryptic structural variants not seen on karyotype or FISH: t(12;15) with ETV6::NTRK3 fusion, t(X;14) with IGH::CRLF2 juxtaposition, fusion(9;9) with PAX5::JAX2 fusion, chromotrypsis of chromosome 8, a t(12;22) with EP300::ZNF384 fusion. OGM missed a variant identified by conventional techniques in 35% of cases: 2 arm-to-arm translocations (centromeric region) with no loss or gain of chromosomal material, an inversion of chromosome 14, a dicentric chromosome, and aneuploidy with low clonality and hyperdiploidy.

OGM can identify rare events of prognostic interest that are not visible with standard cytogenetic techniques. It also explains complex chromosome rearrangements. However, it has some limitations, notably for Robertsonian translocations and arm-to-arm translocations.

OGM is a very valuable diagnostic tool for hematological malignancies.

P1090 - Biological Implementation of Optical Genome Mapping in Recurrent Miscarriages and Implantation Failure. A Comprehensive Evaluation

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Introduction: Karyotyping has long been considered the gold standard for identifying genetic causes of implantation failure and recurrent miscarriages. Recently, Optical Genome Mapping (OGM) has emerged as a promising method for detecting both balanced and unbalanced structural variations as well as copy number variations. This study aims to evaluate the effectiveness of OGM in comparison to karyotyping for diagnosing genetic abnormalities in couples with a history of recurrent miscarriages or implantation failure, with the goal of incorporating OGM into routine biological practice for these indications.
Materials and Methods: A comparative study was carried out with 45 couples who had a history of miscarriages or implantation failures. Each couple underwent both OGM and conventional karyotyping. The results obtained from these two methods were compared.
Results: A concordance rate of 95% was observed between OGM and karyotyping. OGM demonstrated superior precision in identifying breakpoint locations in cases of translocations. However, in 5% of cases, OGM showed false positives and false negatives, particularly in reciprocal translocations concerning centromeric or telomeleric regions, as well as in Robertsonian translocations.
Conclusion: Optical Genome Mapping has proven to be a valuable diagnostic tool for couple with recurrent miscarriage or implantation failure. However, OGM may produce false results in cases of Robertsonian translocations and variants concerning centromeres and telomeres. Given these limitations, we have opted to perform a minimalist karyotyping approach, analyzing only two metaphases, in combination with OGM as the primary diagnostic tool in our laboratory. We will present the results from patients who have undergone this combined approach.

P1094 - Enhancing Clinical Cytogenetics: Automated Detection of Chromosomal Aberrations Using Telomere and Centromere Staining

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Clinical cytogenetics employs various cytogenetic assays, including conventional and molecular cytogenetic techniques, to detect chromosomal aberrations. However, these techniques present inherent challenges, such as lengthy processing times from sample collection to result and the need for highly skilled personnel. Therefore, there is a growing need for methods that can overcome these limitations. Here, we demonstrate that the introduction of telomere and centromere (TC) staining successfully addresses these challenges while significantly enhancing the efficiency of clinical cytogenetics through the development of automated approaches.
Materials and Methods
A total of 100 cytogenetic slides from patients with hematological diseases and genetic disorders were analyzed. TC staining was performed using the Aging Kit Cell Environment. Image segmentation was carried out using neural networks and multi-class classification algorithms capable of automatically detecting chro-

mosomal aberrations. In cases involving complex karyotypes, this technique can be combined with the M-FISH technique for highly reliable detection of chromosomal abnormalities.
Results
The integration of TC staining into cytogenetic analysis significantly improves the efficiency and robustness of chromosomal aberration detection. Additionally, TC staining enables the analysis of telomeric and centromeric sequences. For automated analysis, our software achieved a chromosome segmentation precision of 98%, paving the way for a new era in cytogenetic investigations and the development of next-generation cytogenetic technologies.
Conclusion
The introduction of TC staining in cytogenetic analysis, combined with automation, represents a major advancement in patient management and the establishment of comprehensive cytogenetic databases. This innovation enhances diagnostic accuracy, reduces processing time, and lays the foundation for the future of clinical cytogenetics

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P1095 - Prenatal Diagnosis of a Recombinant Chromosome from a Parental İnsertion: from Karyotype to Whole Genome Sequencing, The Cytogeneticist's Eye Remains Necessary!

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Introduction/Objectives:
The use of next-generation sequencing technologies plays an essential role in prenatal genetics. They make karyotyping and standard cytogenetics obsolete. Although these technologies are able of identifying all fetal genome variations, the eye of the cytogeneticist remains necessary to understand chromosome mechanisms.
Materials/Patients and Methods:
Mrs. H. was followed for her first pregnancy. During the 2nd trimester ultrasound examination, a polymalformative association of the fetus with intrauterine growth retardation was shown. Mrs. H. was offered the opportunity to participate in a blinded study of whole-genome sequencing in parallel with routine cytogenetic testing: chromosomal analysis by aCGH and standard karyotyping. Mrs. H. gave her consent and an amniocentesis was performed.
Results:
ACPA revealed 2 copy number variations (CNVs) at the ends of chromosomes 2 and 9. The first chromosome mechanism hypothesis was the presence of a derivative chromosome resulting from a parental reciprocal translocation. A few days later, the CNVs data obtained by whole genome sequencing led to the same hypothesis. However, amniotic fluid karyotyping revealed a more complex mechanism contradicting the first hypothesis and suggesting the presence of a chromosome recombinant insertion. A second, more detailed, examination of the whole genome sequencing data, including structural variants (SV), confirmed this hypothesis. Furthermore, the insertion was confirmed to be balanced in the carrier parent with karyotype and FISH.
Conclusions:
All the fetal genetic and cytogenetic variations were available once whole-genome sequencing was completed. However, the cytogeneticist's eye was needed to reconstruct rearrangements and identify breakpoints from the sequence data.
Key words: chromosome mechanism, prenatal diagnosis, whole genome sequencing.
Declaration of interest: The authors declare that they have no conflicts of interest.

P1100 - Maternally Derived Complex Small Supernumerary Marker Chromosome 22 Associated with Cat Eye Syndrome Like Features

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Cat-eye syndrome (CES) is a rare genetic disease first reported in 1965. The estimated prevalence of CES is 1:50,000 to 1:150,000, and it is typically associated with an inverted duplicated small supernumerary marker chromosome (sSMC) derived from chromosome 22. The specific chromosomal band involved in CES causing partial triplication is 22q11.21, where chromosomal rearrangements occur due to the presence of low-copy repeats (LCR22). The phenotype of CES is extremely diverse, ranging from normal to multiple abnormalities including intellectual disabilities and dysmorphic features. To our knowledge, over 340 patients with CES have been reported to date. This study reports a patient displaying a duplication of chromosome 22pter-22q12 involving band 22q11.21 where the CES critical region is located, and 18pter to 18p11. The propositus is a three-year-old girl, born to an unrelated and healthy couple. She was referred for facial dysmorphism and psychomotor delay. Banding cytogenetic analysis revealed an sSMC resulting from abnormal 3:1 segregation of the maternal balanced translocation t(18;22). Furthermore, the origin of the sSMC was confirmed by fluorescence in situ hybridization technique. The current study emphasized the importance of molecular cytogenetic techniques such as FISH in apprehending chromosomal abnormality. In addition, it shows that partial duplication 22q11.2 to 22q12 may lead to CES-like symptoms.

P1107 - Optical Genome Mapping as a First Tier Tool for Y Chromosome Structural Variations Analysis

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The Y chromosome has a complex structure shaped by numerous evolutionary rearrangements. Its high density of repeated sequences makes it particularly susceptible to intra-chromosomal recombination and deletions during spermatogenesis. Consequently, studying this chromosome remains technically challenging and requires a precise, accessible, and user-friendly analytical method suitable for routine use. Optical genome mapping (OGM), using Bionano technology, appears promising for the analysis of such repetitive regions, although its performance in this context still needs to be fully assessed. In this study, we applied OGM to characterize previously identified Y chromosome rearrangements and used these results to benchmark the technology's relevance and accuracy in Y chromosome analysis. Five patients (3 to 32 yo), were referred for various clinical indications and found to carry Y chromosome abnormalities through conventional cytogenetic techniques, array-CGH, or whole genome sequencing. The identified anomalies encompassed a broad spectrum of rearrangements (e.g., Y deletion, isodicentric Y chromosome, ring Y chromosome, ...). OGM successfully detected previous anomalies, with a higher resolution than array-CGH. Notably, for the clinically significant AZF region, OGM demonstrated greater accuracy in detecting deletions than array-CGH. Here, we found that a

limitation is that a large portion of the Y chromosome is masked during analysis by default CNV and SV detection pipelines. In the context of investigating male infertility, it appears necessary to expand analysis parameters to better explore the Y chromosome and to manually review optical genome maps in the genome browser. To our knowledge, this is the first study to evaluate OGM for Y chromosome analysis, although it is based on a limited number of patients. Further research with a larger cohort is required to confirm these results. If validated, OGM could improve the diagnostic yield for Y chromosome disorders in male infertility.

P1109 - RORB Gene. A Novel Interstitial Microdeletion Characterized by Speech Delay and Hypertelorism

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The RORB gene, a member of the nuclear receptor superfamily, plays a critical role in regulating circadian rhythm, bone metabolism, and retinal neurogenesis. Located on chromosome 9q21.13, it spans approximately 188 kb and includes the RORB1 and RORB2 isoforms. In humans, only the RORB1 isoform has been identified, which encodes a 459 amino acid protein consisting of four key domains: N-terminal (A/B), DNA-binding (DBD), hinge, and C-terminal ligand-binding (LBD). Despite its function as a ligand-dependent transcription factor, specific ligands for RORB1 remain unidentified.
Variants in the RORB gene are associated with various clinical phenotypes, including intellectual disability, developmental delay, epilepsy, neuro-behavioral disorders, and distinct facial features (OMIM #618357). Although reports of variants in RORB are limited, previous studies have identified single nucleotide variants (SNVs) and microdeletions in the 9q21.13 region involving RORB, underscoring its critical role in neurodevelopment.
In this study, we identify a novel in-frame microdeletion of exons 2 and 3 of the RORB gene in three individuals from the same family. We provide detailed phenotypic description of affected family members and whole exome sequencing were used to pinpoint the exact deletion breakpoint. Interestingly, our patients do not exhibit epilepsy and show a milder phenotype compared to patients with microdeletions reported in the literature. This discrepancy in phenotype may be attributed to the in-frame deletion of the DNA-binding domain (DBD) of the RORB gene in our patients. This finding expands the spectrum of known RORB-related disorders, enhancing our understanding of RORB's role in human development and disease, and offering new insights into the genetic basis of neurodevelopmental disorders associated with RORB variants.

P1111 - Genetic investigation of Tunisian infertile men with globozoospermia and a report of a new DPY19L2 mutation

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Globozoospermia is a rare male infertility disorder characterized by the presence of round-

headed sperm cells lacking an acrosome, a crucial structure for fertilization. While genetic factors play a significant role in the etiology of this condition, the precise mechanisms remain elusive. Recent studies have identified mutations in the DPY19L2 gene as a major cause of globozoospermia. This gene encodes a protein involved in the development and maturation of sperm cells, particularly the formation of the acrosome. Mutations in DPY19L2 disrupt this process, leading to the production of abnormal sperm cells. However, DPY19L2 mutations account for only a subset of globozoospermia cases, suggesting the involvement of other genetic factors.

In this study, we investigate 18 Tunisian infertile men with globozoospermia. We performed in a first time a screening of DPY19L2 total deletions by a qualitative PCR. In a second time WES was realized in two DPY19L2 negative patients.

Total deletion of DPY19L2 was found in 33 % of all patients and in 60% of total globozoospermic ones. WES identified a novel DPY19L2 frame-shift mutation (c.1232_1233insA) p.Arg412 GlufsTer3 in one patient with total globo-zoospermia. The pathogenesis of this new variant is supported by In Silico prediction studies and by its absence in controls patients and different published databases.

P1117 - Clinical and Cytogenetic Presentation of Warkany Syndrome2. A Case of Mosaic Trisomy 8

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Background/Objectives: Mosaic Trisomy 8 syndrome (T8MS) or "Warkany's syndrome 2" is an autosomal abnormality with extremely variable phenotypic and cytogenetic expression rare chromosomal disorder characterized by three copies of chromosome 8 in some cells of the body [1, 2]. T8MS incidence in the general population is about 1/25,000-50,000 live births with a 5:1 ratio between males and females [1]. Since chromosomal mosaicism is frequently present in this syndrome, affected individuals show a phenotype ranging from mild dysmorphism to severe structural anomalies. Malformations, including corpus callosum agenesis and renal abnormalities, have been described by many studies [3].

Material and Methods: An 18-month-old male patient was referred to our center due to dysmorphic features. The patient's mother and father were healthy and there was no consanguineous marriage. The patient, who could control his head at 8 months and sit without support at 1 year, did not have the ability to walk or speak. In the physical examination performed on our patient, there were clinical findings such as microcephaly, frontal protrusion, upward-sloping palpebral fissures, bitemporal narrowing, wide nasal bridge, wide nasal tip, thick lower lip, curly hair, and deep palmar and plantar creases. Cell culture was performed from peripheral blood samples of our patient and his mother and father. Metaphase chromosomes obtained from cell culture were examined by staining with GTG banding method.

Results: As a result of cytogenetic analysis performed after GTG banding, trisomy 8 was detected in 4 of the 50 metaphases examined. The patient was evaluated as having mosaic trisomy 8. The patient's full karyotype and mosaicism rate were 8% mos46,XY[46]/47,XY,+8[4].

Conclusion: In conclusion, this study presents a case of mosaic trisomy 8 with different cytogenetic abnormalities. Our case also highlights the heterogeneity of clinical features and chromosomal duplications

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P1120 - X Chromosome CNV Reclassification Integrating X Inactivation Status for Improved Pathogenicity Assessment

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Copy number variations (CNVs) or gene variants on the X chromosome exhibit sex-specific clinical manifestations, influenced by X-chromosome inactivation (XCI) in females. Skewed XCI (sXCI) favoring the unaffected allele may rescue the phenotype, while loss of epigenetic compensation can lead to affected offspring (sons or daughters with random XCI, rXCI). Given the significant reproductive risk for female carriers of X-linked disorders, ACMG guidelines recommend reporting these variants because it provides the opportunity for the patient and relevant family members to pursue additional testing/counseling as needed (Riggs et al., 2020, PMID: 31690835). However, current CNV classification systems lack XCI integration. To refine interpretation of CNVs on the X-chromosome, we propose a semi-quantitative assessment of the XCI status in heterozygous CNV-carriers. In the case of rXCI, a 0 score will be assigned. If a CNV-carrier has sXCI, additional scores range from 0.45 to 0.9 (i.e., 0.025 per 1%). An sXCI of 80% is estimated at 0.45 points. An sXCI equal to 90% is estimated at 0.7 points and 95–100% is estimated at 0.9 points. We performed an aCGH analysis for a cohort of 1,175 patients with neurodevelop-mental disorders and normal karyotype. CNVs on the X chromosome were detected for 33 patients (2.8 %), including 13 maternally inherited CNVs. Three women exhibited sXCI. Reclassification allowed us to improve the prediction of the pathogenic significance of CNVs in these families including a Xq24q25 duplication with 4.8 Mb in size overlapping with region of known pathogenic Xq24 microdeletions (X-linked intellectual disability, Nascimento type, MIM #300860, 1.35 points), which was classified previously as variant of unknown significance (VUS, 0.45 points) by CNV-ClinViewer tools.
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P1127 - High Level Trisomy 8 Mosaicism in a Healthy Adult. A Rare Case with No Clinical Manifestations

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Introduction

Constitutional trisomy 8 mosaicism syndrome (T8MS), also known as Warkany syndrome, is a rare chromosomal disorder occurring in approximately 1 in 25,000–50,000 live births. It accounts for about 0.7% of spontaneous abortions and affects approximately 0.1% of recognized pregnancies. T8MS exhibits a broad phenotypic spectrum, with no established correlation between the degree of mosaicism and clinical severity. Typical features include intellectual disability, dysmorphic facial features, deep palmar and plantar creases, cardiac and renal anomalies, spinal deformities, and agenesis of the corpus callosum. In addition, T8MS has been associated with a risk of hematologic malignancies, including Wilms tumor, myelo-dysplasia, and myeloid leukemia. However, some individuals may present with normal cognitive function and no clinical signs.

Methods and results

A 60-year-old woman underwent genetic evaluation after her son was found to carry a pathogenic deletion. CMA analysis revealed that she carried the same deletion, confirming inheritance. Additionally, mosaic trisomy 8 was identified in 50–70% of cells. Karyotype analysis confirmed trisomy 8 in all examined cells, and fluorescence in situ hybridization (FISH) showed trisomy 8 in 49% of cells. A subsequent bone marrow examination confirmed complete trisomy 8 in karyotype and trisomy 8 in 56% of cells by FISH. Despite the high proportion of trisomic cells, the patient exhibited no physical, cognitive, or hematologic abnormalities.

Conclusion

This case underscores the wide phenotypic variability of T8MS and the absence of correlation between mosaicism levels and clinical severity. We report a rare instance of a healthy

adult woman with a high percentage of trisomy 8 cells, illustrating that T8MS can be compatible with normal development and health

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P1129 - Detection of Structural Variants by Short Read Whole Genome Sequencing and Interpretation for Genetic Diagnosis

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Structural variants (SVs) have been associated with many human diseases and phenotypes, therefore accurate identification and clinical interpretation of SVs is crucial for genetic diagnosis, treatment and prevention within many disease areas. Within the frame of National Genome Center in Denmark, whole genome sequencing (WGS) is performed for patients within different disease groups, e.g. patients with rare diseases, hereditary cancer, endocrinological disorders, immune deficiency, heart disease, psychiatric disorders, kidney failure etc. In addition, a rapid comprehensive WGS-analysis with a 2–3-week turnaround time is performed for intensively ill children to assist acute and long-term clinical decisions.
In the department of Clinical Genetics (Rigshospitalet, Copenhagen, Denmark), we have used WGS as first-line diagnostic test for more than a year and hence developed a comprehensive pipeline for SV-detection, enabling identification of all types of structural events: recurrent and non-recurrent copy-number variations (deletions and duplications), insertions and non-tandem duplications, mobile element insertions, inversions, balanced and unbalanced translocations, as well as complex genomic rearrangements, such as chromothripsis and chromoanasynthesis. Furthermore, we also identify numerical chromosomal abnormalities, mosaicism and uniparental disomy. A group of specialists consisting of molecular biologists and medical doctors with both cytogenetic and molecular genetic backgrounds, participate in clinical interpretation of the identified SVs. The diagnostic yield of a likely pathogenic/pathogenic SVs detected in our WGS pipeline depends on the patient group analyzed and is e.g. ~5% in the intensively ill children cohort.

P1132 - Recurrent Absence of Heterozygosity (aoh) in the Portuguese Population Clinical and Genomic Implications

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Absence of heterozygosity (AOH) occurs when genome segments are identical for both alleles, which may result from parental relatedness, chromosomal recombination, or structural rearrangements. AOH provides important insights into ancestral homozygosity, consanguinity, and uniparental disomy. Clinically, it becomes significant when involves genes harboring pathogenic variants associated with recessive disorders or when it results in uniparental disomy affecting chromosomes with imprinting genes.
To better understand the clinical implications of AOHs and assess its recurrence in the Portuguese population, a study was conducted using SNP arrays (ThermoFisher) on 646 individuals. It includes 200,000 single nucleotide polymorphisms (SNPs) and 550,000 non-polymorphic probes (copy number variants- CNVs). AOH regions were identified using Chromosome Analysis Suite (ChAS) version 4.5, selecting regions over 3Mb with a copy number of 2.
Recurrent AOH regions were most frequently observed on 3 (3p21.31–3p21.1), 11 (11p11.2–11p11.12), and X (Xq11.1–Xq12, Xq13.1–Xq21.1), with an average size of 5 Mb.
Cases within these regions were further analyzed to assess potential phenotype associations and identify additional variants that might explain the observed traits.

In the Xq11.1–Xq12 and Xq13.1–Xq21.1 regions, there are over 1,000 cases and 684 cases reported in DGV (Database of Genomic Variants), respectively. Regarding chromosome 11p11.2–11p11.12 region, 112 cases were previously described in DGV. For 3p21.31–3p21.1 region, 177 cases are recorded in DGV. Additionally, pathogenic CNVs related to the phenotype were found in 12,21% (43/352) of patients, and VUS CNVs in 31,53% (111/352). Recurrent AOH regions appear in both affected and unaffected individuals, suggesting they likely do not have any clinically significant effect on phenotype. Further studies with larger cohorts and functional analyses are needed to fully understand their potential role in genomic variation and disease susceptibility.

P1136 - Translocation of FIRRE as the Critical Event in X;autosomal Translocations Associated with Premature Ovarian Insufficiency. A Hypothesis.

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Hundreds of balanced X;autosomal translocations have been reported in women with Premature Ovarian Insufficiency (POI), where the X chromosomal breakpoints define one or more critical region(s) on Xq (Therman 1990). Previous hypotheses for these translocations have included truncation of ovarian genes and/or unknown positional effects on the X chromosome, breakpoint induced dysregulation of ovarian expressed autosomal genes or meiotic pairing disturbances. Still, the basis for the critical region is enigmatic. We collected data from 46 published POI-associated X;autosomal translocations with sufficient map data to allow a correlation at sequence level. The breakpoints are scattered over a ~60 Mb segment between Xq13.1-Xq25, without any apparent evidence for the existence of separate POI regions. This vast region overlaps with super-loops on the inactive X-chromosome, between NBDY - the most proximal, and FIRRE, the most distal super-loop anchor locus. Thus, all the translocations defining the critical region translocate FIRRE to an autosome. Moreover, three translocations ~3.4 Mb distal to the most distal POI-translocation did not have reported POI, highlighting the intervening region which include FIRRE as a positional critical region. Intriguingly, deletion of Firre in a mouse model did not dysregulate any X-linked genes, but hundreds of dysregulated autosomal genes were highly enriched for GO-terms related to mitotic and meiotic chromosome structure, function and segregation (Andergassen 2019). Furthermore, 49 genes enriched for the GO-term “Meiotic nuclear function” include known POI genes. We suggest that translocation of FIRRE to an autosome has the same effect as Firre deletion: dysregulation of autosomal genes involved in mitotic and meiotic chromosome behavior and segregation, leading to oocyte depletion and subsequently POI. To test this, further mapping, expression and PacBio methylation studies of POI-associated X;autosomal translocations is underway.

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3. Prenatal Diagnosis

P1020 - Retrospective Analysis of Cytogenetic Findings in Pregnant Women at Risk Following First-Trimester Screening: İnsights from NIPT in Armenia

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Non-Invasive Prenatal Testing (NIPT) is a genetic screening test that detects common chromosomal disorders by analyzing fetal DNA fragments in maternal blood. Performed as early as the 10th week, this highly accurate test is safe for the fetus, reassures expecting parents and reduces the need for invasive procedures like chorionic villus sampling and amniocentesis.

This retrospective study was conducted at the EcoSense Laboratory in Armenia from July 2018 to February 2025. A cohort of 1,604 pregnant women, predominantly identified as having low to high risks of aneuploidies after the first-trimester screening, underwent NIPT, which was performed at Medicover Genetics in Cyprus. High-risk chromosomal aneuploidy cases were identified in 49 patients (3% of the cohort), including 37 cases of Down syndrome (T21), 3 of Patau syndrome (T13), 2 of X-trisomy, 2 of X-monosomy, and 1 of Klinefelter syndrome.

Among the 37 pregnancies with detected Down syndrome, only 16% (6/37 patients) did not involve advanced maternal age (≥35 years). Notably, 57% (21/37 patients) had nuchal translucency (NT) measurements of 2.63.5 mm. Furthermore, only 11% (4/37 patients) were classified as high-risk (T21 risk ≥1:100) after the first-trimester screening, while 89% (33/37 patients) were in the intermediate-risk category (T21 risk 1:1011:400). These findings underscore the importance of integrating multiple risk factors for accurate T21 risk stratification. Additionally, our data confirmed that fetal fraction levels are not influenced by fetuses carrying T21, as observed in previous studies. Genetic counseling was provided to all couples with very high-risk NIPT results; however, only five underwent amniocentesis, which confirmed Down syndrome.

More importantly, the only inconclusive result for Wolf-Hirschhorn syndrome was later confirmed through diagnostic testing, highlighting NIPTs reliability for detecting microdeletions. Further validation is needed.

P1040 - The Power of Comprehensive Genetic Testing in One Family Case

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Comprehensive genetic testing is essential for ensuring accurate prenatal diagnosis. This case highlights the role of an integrated genetic approach in guiding clinical decisions.

A pregnancy was established via in vitro fertilization (IVF), following preimplantation genetic testing for aneuploidy (PGT-A) and selection of an euploid embryo. The first-trimester ultrasound revealed an increased nuchal translucency (4.5 mm), leading to chorionic villus sampling. Single nucleotide polymorphism (SNP) microarray identified a 12 Mb region of absence of heterozygosity (AOH) on chromosome 6, prompting further investigation through whole exome sequencing (WES). While no pathogenic variant was found in the AOH region, WES detected the heterozygous likely pathogenic c.1598C>G variant in PKD1 gene, associated with autosomal dominant inheritance. Following this genetic finding, an ultrasound examination was conducted on the fetus, which revealed characteristic features of polycystic kidney disease, confirming the diagnosis of autosomal dominant polycystic kidney disease (ADPKD). Parental testing, performed using Sanger sequencing, confirmed paternal transmission leading to an unexpected diagnosis of autosomal dominant polycystic kidney disease (ADPKD) also in the father.

This case illustrates the value of a multilevel genetic workflow - spanning PGT-A, SNP microarray, WES, and Sanger sequencing - in achieving a definitive diagnosis. It underscores the importance of providing comprehensive genetic analysis, ensuring accurate risk assessment and optimized patient care.

P1046 - Prenatal Diagnosis of Unusual Chromosomal Aberrations Presenting with Non-İmmune Hydrops Fetalis

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Introduction: Hydrops fetalis is characterized by abnormal fluid accumulations in two or more body cavities, such as ascites, pericardial effusion, pleural effusion, or skin edema. While non-immune hydrops fetalis (NIHF) is related to multiple etiologies, chromosomal abnormalities constitute 70% of the cases when presenting in first trimester with majority being monosomy X, trisomy 21, trisomy 18, trisomy 13 and triploidy.
Method: We reported a prenatal case with unusual multiple chromosomal aberrations presenting with NIHF at first trimester.
Results: An aged 34 non-consanguineous healthy Chinese woman, G3P1A1 with no family history of genetic disorder, intake of teratogens, or radiation exposure, presented to our unit at maturity 12 weeks with multiple fetal sonographic anomalies, including increased nuchal translucency (5mm), generalized subcutaneous edema, bilateral mild pleural effusion, absent nasal bone, and abnormal doppler with reversed a-wave pattern of ductus venosus. No cardiac anomalies were observed. Prenatal diagnosis with chorionic villous sampling was performed. Chromosomal microarray (CMA) revealed three pathogenic chromosomal imbalances, including 2.39 Mb copy loss in 2q37.3, 58.60 Mb mosaic copy gain in 6p25.3p11.1, and 72.86 Mb mosaic copy gain in 9q13q34.3. Conventional karyotyping showed mos 46,XY,add(2)(q37)dn[13]/46,XY,der(2)t(2;9)(q37;q12)dn[5]/46,XY,add(2)(q35)dn[3]/46,XY,der(2)t(2;6)(q37;p?11)dn[1]/46,XY[8]. While metaphase FISH result showed a terminal deletion on the long arm of chromosome 2, multicolor FISH result confirmed the additional material attached to the long arm of chromosome 2 originating from chromosome 9 with different segment size. As the karyotyping and FISH results of parents' blood were normal, the derivative chromosomes were likely to have arisen de novo. The pregnancy miscarried at 14 weeks.
Conclusions: While chromosomal aneuploidy is the commonest cause among NIHF at first trimester, rare multiple chromosomal aberrations could occur in which the diagnosis could be made possible by a combination of conventional karyotyping, FISH, and CMA..

P1066 - Whole Exome Sequencing. A Useful Tool in Prenatal Diagnosis

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Whole-exome sequencing (WES) has become an important diagnostic tool in both pediatric and adult patients with a range of disorders, increasingly becoming an integral diagnostic tool in medicine. Recently, WES has also been performed in the prenatal setting, and it is most often used when conventional tests (karyotype and microarray) are unable to provide a diagnosis.
A total of 165 fetuses with a mean gestational age of 17.4 weeks (range 11–32 weeks) were included in this study. We performed WES analysis using DNA from amniotic fluid (132 samples, 80%), and chorionic villi (33 samples, 20%). The analysis showed the presence of pathogenic or likely pathogenic variants in 36 (22%) cases, that were reported as causative or potentially relevant for the fetal phenotype. Fifty-four variants in 41 genes with autosomal recessive (16), dominant (26), and X-linked (2) inheritance were identified. Four cases had pathogenic variants in more than one gene potentially related to the fetal phenotype.

This study highlights the utility of WES in prenatal diagnosis in cases with a family history of genetic conditions and in fetuses with ultrasound abnormalities. With an increased diagnostic yield, prenatal WES offers important information for pregnancy and perinatal decision-making, management, and adequate counseling in fetuses with normal results after chromosomal analysis.

P1102 - Genetic Analysis of Early and Recurrent Pregnancy Loss. Challenges and Advances

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Pregnancy loss is defined as the spontaneous termination of a pregnancy before fetal viability and affects approximately one in four pregnancies. Genetic analysis of early or recurrent fetal losses is crucial for elucidating the underlying causes of miscarriage, thereby guiding clinical management and providing prognostic information to affected couples. Genetic anomalies, particularly chromosomal abnormalities, are implicated in approximately 50% to 70% of spontaneous abortions in the first trimester. Identifying these anomalies aids in understanding the etiology of pregnancy loss and offers valuable insights for future reproductive planning.
Various sample types and genetic testing methodologies are employed in this context, each with distinct advantages and limitations. Traditional cytogenetic analysis, such as karyotyping, requires viable fetal cells obtained through culture. However, this method has a success rate of only about 58% due to potential culture failures and maternal cell contamination, which can lead to inconclusive or misleading results. In contrast, molecular techniques like chromosomal microarray analysis (CMA) do not rely on cell culture, offering higher resolution in detecting chromosomal abnormalities, improving diagnostic yield, and reducing the incidence of inconclusive results. However, CMA requires a sufficient amount of fetal DNA, which may be difficult to obtain due to maternal contamination or the challenge of collecting the conceptus product.
The use of cell-free fetal DNA (cffDNA) from maternal blood has emerged as a promising method for evaluating fetal ploidy status, although large-scale validation of this approach is still required.
In this study, we present our laboratory's experience in analyzing different sample types and employing various methodologies to investigate pregnancy loss. Our findings contribute to the ongoing discussion on optimizing genetic diagnostic strategies for early and recurrent pregnancy loss, improving patient outcomes, and informing future research directions.

P1125 - Rare Prenatal Complex Chromosomal Rearrangement with 11q21-q22.1 Deletion

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Complex chromosomal rearrangements (CCR) are structural chromosomal anomalies involving more than three breakpoints in one or more chromosomes. Prenatal complex chromosomal rearrangements are rare and can cause congenital malformations if microdeletion or microduplication near the breakpoint or gene breaks exist. We report a prenatal case of vermian hypoplasia and Dandy Walker Variant. Fetal karyotype, fluorescence in-situ hybridization (FISH) and CGH array revealed a de novo complex reciprocal translocation 46,XX,t(2;4;11)(q34; q26;q21) and a 7.9Mb de novo interstitial micro-

deletion on 11q21-q22.1(Hg19 : 93,065,388-101,000,734)

Using cytogenetic molecular techniques allowed identification of CCRs and a better characterization of 11q region. Interstitial deletions at 11q region are rare, therefore genotype phenotype correlation is difficult. Various phenotypes can be associated to 11q deletions depending on the deletion size and position. Feeding difficulties, failure to thrive, speech delay, learning difficulties, dysmorphism, have been associated with 11q deletion. Our patient has cerebellar malformations already described in a 17,3Mb 11q21-q22.3 prenatal deletion. The 7,9Mb deletion reported in our case contains 30 OMIM genes, 9 are implicated in pathology. MED17 gene appears to be a core Mediator subunit of a multiprotein coactivator that is required by DNA-binding transcription factors for activation of polymerase II transcribed genes. Homozygous mutations of MED17 have been described in patients with microcephaly, development delay, seizures and brain atrophy. A 6,3Mb deletion containing MED17 has been reported in a patient with tall stature, macrocephaly, autism, delayed speech and language development echolalia and stereotypy. CNTN5 , PANX1 and GPR83 genes are expressed in central nervous system and could be candidate genes explaining the fetus cerebellar malformations. Further analysis of breakpoints at chromosomes 2 and 4, using next generation sequencing, are necessary for a better genotype phenotype correlation in our patient.

P1126 - Comparative Efficacy of cfDNA and aCGH in Detecting Chromosomal Aberrations Post Miscarriage

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Miscarriages affect 10-25% of pregnancies, with 1-5% of couples experiencing recurrent losses. Chromosomal abnormalities are a leading cause, yet traditional genetic testing on products of conception (POC) has limitations, including the need for intact tissue and absence of maternal DNA contamination. This study compares cell-free DNA (cfDNA)-based testing with array comparative genomic hybridization (aCGH) in diagnosing miscarriage etiology.

In our prospective multicenter study, we recruited 78 patients experiencing pregnancy loss between July 2023 and July 2024. Blood samples collected in STRECK tubes before curettage underwent cfDNA low-depth genome sequencing through a standard NIPT workflow, while POC samples were analyzed via aCGH post-curettage.

Of the 78 participants, 13 were excluded due to missing POC samples. Among the remaining 65, 18 yielded results from only one technique (16 cfDNA, 2 aCGH), and both failed in two cases. Maternal contamination primarily caused aCGH failures. Concordance between cfDNA and aCGH was observed in 82% (37/45). Notably, cfDNA detected 6 unique chromosomal aberrations and identified 13 out of 19 aberrations found by aCGH (aneuploidies only). Sensitivity and specificity of cfDNA testing were 68.4% and 92%, respectively.

Our findings highlight cfDNA's potential as a robust alternative to traditional POC testing, offering advantages in scenarios where maternal contamination or sample availability/integrity is problematic. Analytic thresholds to call chromosomal aberrations from cfDNA still have to be refined to the context of pregnancy loss. These results underscore the value of incorporating cfDNA-based tests into routine miscarriage investigations, including the possibility to test patients that do not require curettage.

P1128 - First Prenatal Case of Jumping Like Translocations Unraveling Complex Chromosomal Rearrangements

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Jumping and jumping-like translocations are rare chromosomal rearrangements, mostly described in hematologic malignancies and solid tumors. We report here the first constitutional prenatal case of a jumping-like translocation (JLT), identified in a fetus with multiple anomalies.

A 24-year-old woman was referred at 10 weeks of gestation for increased nuchal translucency. Ultrasound revealed intrauterine growth restriction, cystic hygroma, congenital heart defect, clubfeet, and diaphragmatic hernia. The pregnancy ended spontaneously at 21 weeks. Cytogenetic analyses (karyotyping, FISH, array-CGH) on chorionic villi revealed a complex mosaic structural rearrangement involving one recipient chromosome 15 and three donor chromosomes (2, 3, 15). Array-CGH identified a consistent 15q26.1-qter deletion and three duplications: 2q33.1-q37.3 (20% of cells), 3p26.3-p21.31 (30%), and 15q26.1 (40%). These findings were confirmed by whole-chromosome painting FISH. Parental karyotypes were normal. This rearrangement represents a de novo jumping-like translocation with one shared breakpoint and multiple donor chromosomes. The chromosomal imbalances explain the polymalformative phenotype. Attempts at detection by optical genome mapping were unsuccessful, likely due to the loss of abnormal cell lines during culture. This case supports the hypothesis of transient chromosomal instability in early embryogenesis, possibly triggered by telomere dysfunction and resulting in non-homologous end joining (NHEJ). It also highlights the utility and limitations of different genomic tools: while array-CGH and FISH were essential for diagnosis, low-level mosaicism remains challenging for some high-throughput technologies. This is the first report of a JLT in prenatal diagnosis, underlining the importance of comprehensive cytogenomic analyses in complex fetal anomalies. Current development of long-read or optical sequencing technologies may improve the detection and interpretation of such rare events.

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P1134 - Prenatal diagnosis of mosaic 45,X/47,XXX Turner syndrome in a patient with recurrent spontaneous abortions: a case report

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Turner syndrome (TS) is one of the most common sex chromosomal aneuploidies, affecting approximately 1 in 2,500 female live births. The classic form of TS (45,X) accounts for about half of all cases, typically presenting phenotypically with short stature, a webbed neck, and infertility. The remaining TS cases involve mosaic forms, with the 45,X/46,XX variant being the most common. Mosaic forms of TS have diverse clinical presentations, which make it challenging to identify

these patients. Although spontaneous pregnancies can occur in mosaic TS patients, a higher risk of recurrent miscarriage is observed.
Here we report a case of a rare mosaic TS variant 45,X/47,XXX in a patient with a history of recurrent spontaneous abortions. The patient was offered a non-invasive prenatal test (NIPT) at 12 weeks gestation as part of routine diagnostics. The NIPT analysis showed no increased risk for fetal trisomy 21, trisomy 18, or trisomy 13, but was suggestive for the presence of mosaic TS. A conventional karyotype analysis was performed, which confirmed the presence of mosaic TS 45,X/47,XXX. A total of 93 cells were analysed, revealing 36 cells with the 45,X karyotype and 57 cells with the 47,XXX karyotype. Prior to the current pregnancy, the patient suffered from 4 miscarriages.

P1138 - Circuit of Prenatal Screenıng wıth Free Circulating Fetal DNA in the Balearic Islands

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Introduction
The use of free fetal DNA circulating in maternal blood as part of prenatal screening is a significant advance. In the Balearic Islands in 2018, a joint project began to be developed with Clinical Analysts and Obstetricians from all public hospitals to internalise the genetic study of free circulating fetal DNA as a contingency and autonomous prenatal screening. The circuit and agreements of the professionals involved in this project are presented.
Material and Methods
The target population of the project is pregnant women with a combined first trimester screening test consisting of the biochemical and an ultrasound test. In the case of an intermediate risk of fetal trisomy for chromosomes 21, 18 or 13, a second line of screening is performed with free fetal DNA circulating in maternal blood. The cut-off points are defined between 1/51 and 1/1200 for both trimesters.
The VeriSeq NIPT V2 kit and Illumina analysis software are used to perform a complete genome screening on all samples.
Results
During the first year of its operation, 829 samples from the six public hospitals of the Balearic Islands were screened.
When performing the whole genome study, partial deletions and duplications were detected, as well as aneuploidies in other chromosomes. In these cases, the criterion followed was to assess on a case-by-case basis the appropriateness of confirmation by invasive testing.
Conclusions
The standardisation of prenatal screening in the Balearic Islands has presented some challenges, particularly in terms of homogenising equipment and harmonising criteria between professionals. Communication and collaboration are key to overcoming these obstacles and ensuring that everyone works to the same standards.

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4. Tumour Cytogenomics

P1004 - Improvement of Fluorescence In Situ Hybridization (FISH) Test Results in Formalin Fixed Paraffin Embedded (FFPE) Tissues

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FISH is an efficient molecular technique in detecting chromosomal abnormalities in a variety of tissue types. FFPE tissues is the most

convenient source of solid tissues for FISH studies. However, pre-analytical tissue inadequacy may account for a percentage of FISH failures.

To determine the causes and incidence of FFPE tissue FISH-failures over the past 12 years.

A retrospective review of 24,486 routine FFPE FISH cases from 2012-2023 was performed. Cases with weak/absent FISH signals were classified as non-informative. The causes for these failures were determined, and the incidence of failed/sub-optimal cases was tabulated.

142 (0.6%) FFPE cases had FISH-failure despite 2-3 repeated hybridization attempts. 64.1% (n=91) showed no DAPI staining. Such failures may be attributed to sub-optimal tissue quality/ fixation issues. FISH-failure was also noted in 16.2% (n=23) of cases with old tissue blocks ranging from 4-15 years. Loss of antigenicity is the main contributing factor in aged tissues. 9.2% (n=13) of FISH-failures also showed concordant inconclusive results with alternative molecular testing, indicating sub-optimal DNA quality as the likely cause of failure. Inappropriate/ inadequate tissue preservation was suspected in 10 overseas samples (7.0%). Finally, acid decalcified femur and phalanxes from 5 cases (3.5%) yielded no FISH results. Decalcification protocols that cause poor chromatin integrity are known causes of FISH-failures. The findings show that all our FISH-failures were attributed to pre-analytical issues. The failure rate decreased progressively from 2.7% to just 0.03% over the 12-year period.

The decline in the FISH-failure rates was attributed to better preservation methods over the years, avoidance of strong acid decalcification, and provision of freshly sectioned tissue samples. A better understanding by clinicians on the causes of FISH-failures based on laboratory feedback has led to an improvement in the FISH-success rate.

P1005 - JAK2 Mutations and Endogenous Erythroid Colony Formation in Patients with Polycythemia Vera

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INTRODUCTION:

Polycythemia vera (PV) is a chronic myeloproliferative neoplasm characterized by increased red blood cells. The most frequent genetic abnormality is the somatic JAK2V617F mutation and it occurs in more than 95% of patients. In 2-5% JAK2V617F negative PV patients were detected JAK2 exon 12 mutations. The aim of this study was to determine the frequency of JAK2V617F and JAK 2 exon 12 gene mutations and to compare the results with the presence of endogenous erythroid colony (EEC) formation.

METHODS:

Peripheral blood and bone marrow samples of 116 patients with PV were analyzed. The diagnosis of PV was established according to the bone marrow criteria of the World Health Organization (WHO). Mutation of JAK2V617F was determined by allele-specific PCR (AS-PCR) analysis. A group of exon 12 mutations (I540-E543Del, R541-E543Del, F537-K539Del, H538-K539Del, K539L,N542-E543Del) were determined by RQ-PCR mutations screening based methodology. Assay for human clonal haematopoietic progenitor cells with agar-leukocyte conditioned medium (Agar-LCM), without recombinant human erythropoietin (EPO), was used for detection of EEC.

RESULTS:

Mutation of JAK2V617F was found in the samples of the peripheral blood in 108/116 (93%) PV patients. EEC formations were obtained in the sample of bone marrow or peripheral blood in 109/116 (94%) PV patients. In 106/116 (91%) patients we detected the simultaneous presence of EEC formation and mutation of JAK2V617F. One JAK2V617F-unmutated patient, with EEC, has mutation in JAK2 exon 12 gene.

CONCLUSION:
Presence of JAK2 mutation and EEC are essential characteristics of PV. Considering these results, it is clear that the EEC formation observed in PV, is part of the JAK2-dependent activation signaling pathway.

P1018 - Detection of Measurable Residual Disease Using Fluorescence In Situ Hybridization Compared with Multiparametric Flow Cytometry in Patients with B Lymphoblastic Leukemia

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Background: Measurable residual disease (MRD) testing for B-lymphoblastic leukemia (B-ALL) is important for monitoring for relapse. Recently, highly sensitive methods have been developed and widely applied, including multiparametric flow cytometry (MFC) and next-generation sequencing. Therefore, the role of conventional MRD detection methods such as fluorescence in situ hybridization (FISH) for MRD monitoring may be questioned. We compared FISH and MFC results in follow-up samples from B-ALL patients to investigate the practical utility of FISH testing.
Method: A total of 339 bone marrow samples from 110 B-ALL patients were analyzed. In the initial diagnosis of B-ALL, four FISH probes targeting BCR::ABL1, ETV6::RUNX1, KMT2A, and CDKN2A deletion were routinely tested. During follow-up, positive FISH probes at the initial diagnosis and additional FISH probes, such as TCF3::PBX1, targeting chromosomal abnormalities detected by karyotyping or molecular testing were tested. Flow cytometry was performed using the eight-color MFC MRD panel.
Results: Of the 110 B-ALL patients, 86 patients (78%) were pediatric patients and 24 were adults. Thirteen of the patients received CAR-T treatment. MRD was detected by MFC in 118 of 339 samples (34.8%), with a median MRD percentages in positive samples of 0.46% (range, 0.01%-64.30%). Positive FISH markers usable for MRD monitoring were found in 89 patients (80.9%) ranging from 1 to 4 markers. Of the 295 samples with FISH markers, 79/97 (81.4%) MFC MRD-positive samples had a FISH-positive result, and 177/198 (89.4%) MFC MRD-negative samples had a FISH-negative result. The correlation coefficient between the percentage of FISH-positive cells and the percentage of MFC MRD clones was 0.72 ($P < 0.01$).
Conclusions: FISH testing provides useful data for detecting B-ALL MRD and is a specific marker for patient monitoring, including after CAR-T therapy.

P1022 - The Prognostic Significance of Isochromosome 17q In Myeloid Neoplasms

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Isochromosome 17q [i(17q10)] as an isolated karyotypic abnormality is rare in myeloid malignancies but is associated with distinct clinical features. It is most commonly observed in myelodysplastic/myeloproliferative neoplasms (MDS/MPN), high-risk myelodysplastic syndrome (MDS), and acute myeloid leukemia (AML). However, studies report conflicting results regarding its prognostic significance due to the heterogeneity of myeloid neoplasms.
This study examines the clinicopathologic characteristics of these patients and clarifies the prognostic impact of i(17q10) in myeloid malignancies. From 2001 to 2024, i(17q10) was identified in the karyotype of 11 patients (7 women, 4 men), with a median age of 72 years (range 48–91). Nine patients had i(17q10) as the

sole abnormality, while two had one additional cytogenetic abnormality. The disease distribution included 3 cases of myelofibrosis, 3 MDS/MPN, 4 MDS, and 1 AML. Clinical features included organomegaly (7/11), leukocytosis (8/11), anemia (7/11), multilineage dysplasia (9/11), monocytosis (2/11), hypercellular bone marrow (10/11), and bone marrow fibrosis (1/11).

Isochromosome 17q was present at diagnosis in three patients, while in eight, it emerged during disease progression (median time: 11 months). Two patients underwent allogeneic stem cell transplantation but died from complications. Two others died from unrelated comorbidities. Six progressed to AML, including one with extramedullary chloroma, all succumbing to disease progression (median survival: 14 months post i(17q10) emergence). One patient remains alive on hypomethylating therapy at 11 months.

Our findings suggest that i(17q10), even as a sole abnormality, is associated with multilineage dysplasia, aggressive disease course, and poor prognosis. Whether detected at diagnosis or acquired later, it indicates a high risk of AML transformation and reduced survival, underscoring the need for further investigation into targeted therapies.

P1023 - T Acute Lymphoblastıc Leukemia with Translocatıon t(10;14)

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Aim: The t(10;14)(q24;q11) rearrangement occurs in 5–10% of adults with T-ALL, leading to translocation of the T-cell receptor delta gene (TCRδ) at 14q11 with the TLX1 oncogene at 10q24. While TLX1 rearrangement has been associated to a favorable prognosis, it is not yet established as an independent prognostic factor. We analyzed the characteristics and outcomes of T-ALL patients with this rearrangement treated at our center.

Methods: We retrospectively studied adult T-ALL patients carrying t(10;14)(q24;q11) and treated per our center's protocols. Flow cytometry was used for diagnosis and MRD monitoring, with primer-specific PCR in two cases. Conventional karyotyping and FISH were performed at diagnosis and remission.

Results: Between 2004 and 2021, six adults (5 males/1 female), median age 55 years (range: 17–66), were identified among 73 T-ALL cases (8%). Two also had trisomy 7, trisomy 8, and del(9)(p21). Median WBC count was 24×10⁹/L. Four had a mediastinal mass, two had organomegaly, and none had CNS involvement. Immunophenotyping showed three with T-cortical and one with T-medullary ALL. One young patient received the pediatric BFM protocol, while five received less intensive regimens. All received L-asparaginase and two years of maintenance. All achieved morphological and cytogenetic remission post-induction; five reached MRD negativity after the first regimen, and one after the second. No severe toxicities occurred. Four remain in first remission (median DFS: 5 years, range: 3.5–10). Two died from non-hematologic malignancies while in remission.

Conclusions: Cytogenetic classification is crucial for risk stratification in T-ALL. The t(10;14)(q24;q11) rearrangement appears linked to favorable prognosis and sustained remission without allogeneic transplantation. Larger prospective studies are needed

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P1027 - Prognostic Biomarkers for Chronic Lymphocytic Leukemia Patient's Outcome in Albania

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Chronic Lymphocytic Leukemia (CLL) exhibits significant clinical heterogeneity with genetic abnormalities playing a crucial role in disease progression and treatment response. Among these, deletions in TP53 (17p13.1) and ATM (11q22.3) genes are of particular interest in CLL patients. Current guidelines indicate the use of Fluorescence In situ Hybridization (FISH) method to identify deletions of these genes.

This study aims to evaluate the utility of molecular cytogenetic probes as prognostic biomarkers for predicting disease progression and survival outcomes in CLL patients.

A cohort of 69 CLL patients were diagnosed clinically by the Hematological Service in the University Hospital Center Mother Teresa Tirana. They were analyzed in the molecular cytogenetic laboratory to the Clinical Genetic Laboratory Service using FISH to detect TP53 and ATM deletions from Cytocell probes and performed using MetaClass software. Patients were stratified based on the presence or absence of these deletions.

We report the results of interphase FISH analysis which detected clinical effects of double deletions P53 /ATM in 3/69 of our patients with CLL, suggesting a pathogenic role for inactivation of the tumor suppressor gene located at 17p and missing the ability to repair genetic defects from ATM deletion. In addition to the double TP53/ATM deletion, numerical abnormalities such as monosomy 11 and trisomy 14 were also identified in one patient.

Conclusion: FISH-based detection of TP53 and ATM deletions provides valuable prognostic information in CLL. Clinical effects of double deletion TP53/ATM showed high resistance to therapy, high risk for rapid progression and poor prognosis with short survival with extreme aggressiveness of the disease with one of the worst possible prognoses for malignant hemopathies in Albanian patients. Careful monitoring by modifying the dose of maintenance medication according to certain protocols and personalized therapeutic approaches should be essential for patients

P1029 - From Manual to Digital Fluorescence In Situ Hybridization (FISH) – A Time Saving Experience

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Introduction: Digital FISH analysis is an alternative approach to manual microscopic slide review. Since most manual analysis time is spent searching for cells and signals, the present study aims at assessing if digital FISH is associated with a significant reduction in analysis time.

Methods: System audit trail logs were collected retrospectively to compare the analysis time of bone marrow FISH slides in manual and digital settings. Manual analyses were performed on a capture system, and digital analyses on a scanning and review system (HiFISH, Applied Spectral Imaging). FISH slide preparation protocols were identical for both manual and digital settings, requiring classification of 250 cells by a single reviewer. FISH probes used in this evaluation included TP53/17cen, Iso(17q), del(20q) and MLL (MetaSystems). Analysis time was recorded from start to completion, and statistical significance was assessed using a Mann Whitney U test. A p-value < 0.05 was considered significant.

Results: Forty-nine slides of bone marrow specimens were included in this assessment; 26 slides were analyzed manually and 23 digitally. No significant difference was observed between the average number of cells counted manually per slide (257±45, range 200-471, median 250) and the average number of cells counted digitally per slide (241±66, range 84-356, median 250). The analysis time per slide was significantly reduced when using manual counting technique (average 23±14 minutes, range 5-58 minutes, median 19 minutes) compared to digital counting method (average 14±15 minutes, range 2-55 minutes, median 7 minutes) ($p=0.005$).

Conclusion: A 40% reduction in analysis time was observed when comparing the time spent analyzing bone marrow FISH slides manually

and digitally. In addition to the standardization resulting from the digital approach, this enhanced efficiency is poised to contribute to the expediting of turnaround times.

P1034 - Evaluation of Conventional and Molecular Cytogenetic Analysis in Plasma Cell Dyscrasias

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Background

Plasma Cell Dyscrasias (PCDs) are a heterogeneous group of hematologic malignancies caused by uncontrolled proliferation of monoclonal plasma cells leading to the overproduction of monoclonal immunoglobulins. Monoclonal Gammopathy of Undetermined Significance (MGUS) and Multiple Myeloma (MM) are the two most common disorders.

Aim

To evaluate the role of conventional and molecular cytogenetic analysis in detecting chromosomal abnormalities in patients with PCDs.

Materials and Methods

A total of 105 patients referred to Phenotypos Lab between March 2023 and December 2024 due to clinical suspicion of PCDs were included in the study. Diagnosis was established by flow cytometric immunophenotyping of bone marrow aspirates. In all patients, conventional cytogenetic analysis was performed, by analyzing 20 metaphases/patient. In 52/105 (49.5%) patients, FISH analysis was also performed, by analyzing 200 interphase cells/probe.

Results

Patients' median age was 71.4 years (range 42-94) and 52% were males. Conventional cytogenetics was successful in 102/105 (97.1%) samples. Karyotype was normal in 76/102 (74.5%) patients and abnormal in 26/102 (25.5%) patients. 1/26 (3.8) patients had a structural abnormality (del(5q)) and 25/26 (96.2%) patients had numerical aberrations: hypodiploidy (n=13), hyperdiploidy (n=10), hypotriploidy (n=1) and triploidy (n=1). FISH analysis identified chromosomal abnormalities in 22/52 (42%) cases: in one patient with failed karyotype, in 10 patients with normal karyotype and in 11 patients with abnormal karyotype. 14/22 (63.6%) patients had structural abnormalities (igh rearrangements, 17p/13q deletions) and 8/22 (36.4%) had numerical abnormalities.

Conclusions

Cytogenetic abnormalities were detected in approximately 1/4 of patients with PCDs using conventional cytogenetics and increased to 2/5 of patients using FISH. Interestingly, conventional cytogenetics identified more numerical abnormalities, while with FISH technique, more structural aberrations were observed, indicating the importance of both techniques for guiding diagnosis, prognosis and treatment.

P1037 - Beyond t(12;21) Unveiling The Hidden Layers in all Karyotypes

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What secrets are hidden within the 12;21 translocation karyotype? While often associated with a favorable prognosis, the presence of additional genetic anomalies can significantly alter a patient's outcome.

From 2022 to 2024, we examined 50 patients with 12;21 positive B Cell Acute Lymphoblastic Leukemia (B-ALL), aged 1 month to 18 years, with a male-to-female ratio of 30 (60%) to 20 (40%). Cytogenetic analysis was performed on bone marrow aspirate (BM) cells at initial diagnosis using GTG banding, FISH, and a DNA probe panel (Vysis Abbott, ZytoVision, Leica Biosystems), following ISCN 2020 guidelines. A complex molecular cytogenetic study revealed

that 27 patients (54%) had abnormal karyotypes, while 23 patients (46%) had «normal» karyotypes. The most frequent abnormalities included +21 chromosome in 7 cases (14%), associated with hyperdiploidy and favorable prognosis. Chromosome 6 abnormalities were found in 6 cases (12%), including del(6q), r(6), i(6p), and t(6;11), t(6;12;13), with del(6q) potentially being an adverse factor in ALL. Chromosome 12 abnormalities, excluding t(12;21), were observed in 5 cases (10%), including del(12p), der(12), and translocations t(12;12;21), t(12;16), t(12;13), indicating additional pathogenic events. Chromosome 13 abnormalities were present in 4 cases (8%), including del(13q), t(13;15), and t(12;13). Hyperdiploidy (≥47 chromosomes) was seen in 5 cases (10%), generally associated with a favorable prognosis, while hypodiploidy (<45 chromosomes) was detected in 3 cases (6%) and may suggest a poorer prognosis. These findings provide key insights into the genetic landscape of 12;21-positive ALL.

P1039 - Genomic Landscape of Pediatric AML in Ukraine

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Acute myeloid leukemia (AML) is a group of hematological diseases, genetically and phenotypically heterogeneous. AML is a very complex heterogeneous and intricate hematological malignancy in which classification is based on genetic and cytogenetic abnormalities as assigned to the current ICC and WHO classification systems. The introduction of NGS techniques into diagnostics and increased awareness of the genetic complexity of AML has allowed us to make the transition from studying individual genes to evaluating a comprehensive panel of genomic loci.

The aim of our study was to use the capabilities of NGS technology to describe the genetic landscape of pediatric AML in children from Ukraine.

We have detected gene alterations and fusions. In all patients, a total of 72 pathogenic variants were identified in genes included in the myeloid disease panel. The most common genetic variants were: NRAS (16; 22%), FLT3-ITD (9; 12.5%), PTPN11 (9; 12.5%), KRAS (7; 9.7%), KIT (5; 6.9%), WT1 (5; 6.9%), IDH1 (3; 4.1%) variants of the CEBPA, EZH2, FLT3-TKD, NPM1, STAG2 genes were found with a frequency of 2.77% (2 individuals) and the remaining genes: BRAF, CSF3R, ETV6, IDH2, IKZF1, MPL, PHF6, RUNX1 were found with a frequency of 1.38% (1 person).

We identified 14 different types of fusions in 50 patients (57.5%). The most frequently encountered chimeric oncogene transcripts were: RUNX1::RUNX1T1 (11; 22%), KMT2A::MLL T3 and PML::RARA (7; 14%), CBFB::MYH11 and KMT2A::MLLT10 (6; 12%), KMT2A: :SEPT6 (3; 6%), KMT2A::MLLT1 and PICA LM::MLLT10 (2; 4%), and other fusions, such as KMT2A::SEPT5, KMT2A::MLLT11, KMT2A: :ELL, DEK::NUP214, KAT6A::NCOA2 and SND1::BRAF met once (2%).

As follows, the study of the spectrum of genetic changes in a cohort of pediatric patients with AML is a tool that allows doctors to stratify patients by risk groups and make a prognosis.

P1042 - Unusual Cytogenetic Profile in Myelodysplastic Neoplasm. A Case Report of Hyperdiploidy with TRB Gene Involvement

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Introduction:
Myelodysplastic neoplasms (MDS) are clonal hematopoietic stem cell neoplasms characterized by cytopenia, morphological dysplasia, ineffective hematopoiesis and increased risk of progression to acute myeloid leukemia. The WHO classifies MDS based on distinct morphological and genetic features, with a median diagnosis age of 77 years, with an increased incidence in patients with ages between 60 and 90 and in patients previously exposed to chemotherapy or radiation therapy.
Cytogenetic abnormalities play a crucial role in MDS prognosis and treatment, with complex karyotypes generally associated with poor outcomes. Common chromosomal alterations include monosomy/deletion of chromosomes 5, 7, and 20, and hyperdiploidy remains a rare finding associated with poor prognosis. Identifying the specific alterations in complex karyotypes may be important for prognosis and treatment decision.
Case Report:
A 79-year-old man with a history of prostate cancer presented with pancytopenia and was referred to hematology consultation for differential diagnosis between MDS and bone marrow infiltration by metastatic prostate cancer cells. Morphological evaluation supported the diagnosis of MDS. Classical cytogenetic analysis revealed a complex karyotype 77~91,XY,t(5;7)(q1?3;q3?4),-6,+mar,inc[cp13]/45~48,XY,t(5;7)(q1?3;q3?4)[cp2].
Discussion and Conclusion:
This case highlights a rare cytogenetic profile in MDS, marked by hyperdiploidy with a t(5;7)(q1?3;q3?4). Hyperdiploidy is a rare finding in MDS associated with poor prognosis. The translocation t(5;7) disrupts the 7q34 locus, a region harboring the TRB gene. TRB rearrangements are classically linked to clonal T-cell expansions in lymphoid malignancies, but emerging evidence suggests that dysregulated TRB expression may also modulate immune surveillance and apoptotic pathways in myeloid neoplasms.
This case demonstrates the importance of comprehensive cytogenetic analysis in MDS diagnosis and risk stratification, especially in patients with complex abnormalities. Further studies are needed to elucidate the prognostic and therapeutic implications of TRB gene and hyperdiploidy involvement in MDS.

P1047 - Oligosecretory Multiple Myeloma with Low Plasma Cell Count. A Case Study with Detection of Prognostic Genomic Abnormalities in Metaphase Cells

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Multiple myeloma (MM) is a plasma cell dyscrasia (PCD) that can evolve from a premalignant monoclonal gammopathy. Prognosis depends on specific genetic markers. Karyotyping and fluorescence in situ hybridization (FISH) are routinely performed for chromosomal investigations to aid in diagnosis and risk stratification of MM patients. While karyotyping remains the gold standard, FISH on CD138+ enriched cells is crucial for detecting prognosis-specific genomic abnormalities.
We present an intriguing case of newly diagnosed oligosecretory multiple myeloma. Bone marrow

aspirate (BMA) showed normocellular marrow with no increase in plasma cells (PCs). Flow cytometry revealed a small subset of aberrant PCs (0.0007%), suspicious for monoclonal gammopathy. Notably, chromosomal abnormalities were only detected in dividing metaphases in both karyotyping and FISH.

Karyotyping reported 30% abnormality. Due to insufficient enriched PCs, interphase FISH was performed on non-enriched cultured cells which was negative for FGFR3/IGH (t(4;14)), CCND1/IGH (t(11;14)), IGH/MAF (t(14;16)), del(13q)/monosomy 13, and TP53 (17p). Although low-level abnormalities were present, they fell below laboratory cut-off values, resulting in a negative FISH report. Subsequent interphase FISH on limited enriched PCs confirmed three copies of CKS1B/1q (19%), corroborating the metaphase FISH findings in CD138+ cells. Metaphase FISH showed 3 signals of IGH and 3 signals of CKS1B while remaining negative in interphase cultured cells.

This rare observation of metaphase abnormalities in both karyotyping and FISH, coupled with a negative interphase FISH result, highlights the complexities in MM diagnosis. We discuss the variables influencing these findings and emphasize the importance of a multidisciplinary laboratory approach for precise diagnosis and management of MM.

P1055 - Mapping Cancer Risk in Constitutional Chromosomal Deletions. A Cytogenetic Analysis

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Chromosomal deletions are common in cancers and significantly contribute to tumorigenesis. However, systematic studies linking constitutional deletions to cancer risk across the entire chromosome complement are scarce. This study investigates how the size and location of deletions influence cancer susceptibility.

We conducted a molecular cytogenetic analysis of 17 Tunisian patients with constitutional chromosomal deletions using array comparative genomic hybridization (CGH) and fluorescence in situ hybridization (FISH).

We have identified cancer risks associated with various constitutional chromosomal deletions of different sizes: Colorectal cancer is linked to a 1.7 Mb deletion at 1p32, encompassing the proto-oncogene JUN. Bladder cancer is associated with a 5.8 Mb deletion at 4p, involving FGFR3 and eight cancer-related genes. A 17 Mb deletion at 4q13 harbors twelve genes related to pancreatic cancer. A 21 Mb deletion at 5p14, tied to elevated melanoma risk, includes SDHA and TERT, while a 14.5 Mb deletion at 7p14.1 affects POU6F2 and is linked to Wilms'tumor and lungadenocarcinoma. Deletions at 7 q11.2 and7q32.2 involve BCL7B and BRAF, respectively, increasing the risk for non-Hodgkin lymphoma and developmental disorders. Smaller deletions at 9p24 and 10q26.1 impact genes like KANK1 and MKI67, associated with leukemia, while an 11.7 Mb deletion at 11q24 affects CHEK1 and other tumor suppressors, elevating hepatocellular carcinoma risk. Lastly, a 21.4 Mb deletion at 16p involves PALB2, linked to breast cancer.

Since the phenotypic consequences of such deletions are highly dependent on the specific genes affected in the deleted region, our results suggest that these deletions, beyond their implication in specific phenotype-genotype correlations belonging to known or unknown genetic syndromes, may contribute to the development of cancers. Taken together, here we underscore the need for detailed genetic analysis to guide clinical management within actionable genes.

P1062 - Intra and Intertumoral Heterogeneity in Glioblastomas Revealed by Optical Genome Mapping

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Glioblastomas (GBMs) are the most common primary brain tumors, characterized by extensive genetic complexity and an extremely poor prognosis. A hallmark of GBMs is their pronounced inter- and intra-tumoral heterogeneity, which drives the evolution of genetically distinct subclones, contributing to treatment resistance and disease recurrence.

To investigate this heterogeneity, we analyzed spatially distinct tumor samples (center, margin 1, margin 2) obtained from three GBM patients using Optical Genome Mapping (OGM).

Standard diagnostic tests, including I-FISH, MLPA, and MS-MLPA, confirmed GBM-specific aberrations (+7/-10, TERT mutations, MGMT promoter methylation) in the diagnostic samples of all three patients. Subsequent high-resolution OGM analysis of three different samples from each tumor revealed additional complex intra- and interchromosomal rearrangements.

In two patients, significant genetic divergence was observed between the tumor margins and the central region. In the first case, the differences were primarily associated with copy number variations (CNVs), including deletions and duplications. In the second case, the tumor exhibited extensive CNVs and various inter-chromosomal rearrangements across all three regions. In contrast, in the third patient, abnormalities (including GBM-specific aberrations) present in the tumor center were absent in the marginal samples, suggesting the possible sampling of non-tumorous tissue. All additional aberrations detected by OGM were unique to each tumor.

These findings demonstrate that, despite shared diagnostic markers, GBMs exhibit substantial genomic variability both between tumors and within individual tumors. OGM enables high-resolution characterization of this complexity and reveals region-specific alterations that may drive clonal evolution and treatment resistance. Understanding both inter- and intra-tumoral heterogeneity is crucial for developing effective, adaptive treatment strategies to overcome resistance and improve patient outcomes.

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P1067 - Neocentromeres in Complex AML Karyotypes as an Indicator of Chromosomal Instability and Disease Progression

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Neocentromeres are newly formed chromosomal regions that can replace the function of traditional centromeres. They are well-known from human clinical studies. However, a few have also been reported in different malignancies. Their presence suggests a potential mechanism by which

tumor cells may bypass conventional chromosomal segregation control pathways. Although they contribute to genomic instability, a hallmark of cancer cells, their occurrence in neoplasia, including acute myeloid leukemia (AML), appears to be rare.
We investigated complex karyotypes in bone marrow cells from 114 AML patients using centromeric/multicentromeric FISH and identified four cases (3.5%) with derivative chromosomes exhibiting newly formed constrictions. The complex karyotypes were analyzed using G-banding, FISH, mFISH, mBAND, and aCGH/SNP. In all four cases, neocentromeres were detected on derivative chromosome 11. In two patients, marker chromosomes were identified as inv dup(11)(q13.3qter), with neocentromeres located at 11q13.3 in one case and in its distal region in the other. In a third case, the neocentromere was detected on a marker chromosome composed of chromosomal material from chromosomes 1 and 11, localized to 11q23.3. In the fourth case, the derivative chromosome resulted from an amplification of the 11q23.3–11qter region.
In conclusion, we identified neocentromeres in the highly complex karyotypes of four AML patients, indicating advanced disease. In two of them, neocentromeres arose due to inverted duplications, a mechanism frequently associated with neocentromere formation. Nevertheless, chromosome 11 as a target of this phenomenon has been described sporadically. Neocentromeres can influence cell division, increase chromosomal instability, and drive clonal evolution that supports unrestricted tumor growth and resistance to treatment. Thus, they may serve as biomarkers for aggressive malignant processes and disease progression.

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P1071 - Optical Genome Mapping Improves Detection of Cryptic Aberrations in Acute Myeloid Leukemia

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A comprehensive genomic analysis of leukemic cells and the detection of specific genetic aberrations in acute myeloid leukemia (AML) are essential for accurate subtype classification, prognosis assessment, and treatment management.
We performed optical genome mapping (OGM) in 10 selected AML patients who had previously undergone standard cytogenomic methods (G-banding, FISH, mFISH, mBAND) and NGS. Three patients had a normal karyotype, two had the PML::RARA fusion gene, one patient had a complex karyotype, and the remaining patients showed one to three non-random chromosomal aberrations.
In all cases OGM successfully identified clinically relevant alterations detected by standard methods. Additionally, OGM revealed cryptic genomic variants in five patients, including one with a normal karyotype. In case of PML::RARA-positive acute promyelocytic leukemia (APL), OGM detected a cryptic 11p13 deletion, leading to the loss of the WT1 gene. Furthermore, a partial tandem duplication (PTD) of the KMT2A gene was identified in one patient with normal karyotype. Neutral copy loss of heterozygosity (cnLOH) was observed in three cases (6p25p21, 18q21 and 2q24).
The key advantage of OGM over standard cytogenomic techniques is its ability to detect

cryptic copy number variants (CNVs), including PTDs, cnLOH, and structural variants (SVs). In our study, we revealed the deletion of the WT1 gene, which can significantly impact the prognosis of patients with APL with the PML::RARA fusion and contribute to disease progression. Moreover, AML patients with the presence of KMT2A-PTD generally have a poor prognosis, with a higher risk of relapse and shorter survival. As an effective tool for detecting fusion genes and cryptic aberrations, OGM identified previously undetectable genomic alterations in five of our patients (50%), demonstrating its potential to improve AML risk stratification and disease monitoring.

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P1083 - What is Wrong in the Deletion of Chromosome Region 5q in Myelodysplastic Syndrome. Identification of a Novel Actor of the Sensitivity to Lenalidomide of MDS with del(5q)

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Myelodysplastic Neoplasm (MDS) is a clonal disease of bone marrow cells, characterized by cytopenia, dysplasia and inefficient hematopoiesis. MDS presents an increased risk of progression to acute myeloid leukemia. Complete deletion of chromosome 5 or partial deletion of 5q [del(5q)] is the most common chromosomal abnormality.

Our goal was to investigate genes lost in del(5q) and clarify whether their haploinsufficiency could be implicated in MDS pathogenesis. The RNA-Binding Motif 22 (RBM22) gene is located on 5q and is deleted in 92% of del(5q) MDS patients in our cohort. We hypothesize that haploinsufficiency of RBM22, due to loss of 5q, plays a major role in the pathogenesis of del(5q) MDS and in the response to standard treatment, lenalidomide.

We investigated the role of RBM22 in cell cycle progression, myeloid differentiation and sensitivity to lenalidomide. We worked on normal human hematopoietic stem and progenitor cells (HSPC), and myeloid cell lines (MDS-L, HL-60). We demonstrated that RBM22 depletion reduces proliferation by delaying the progression of the G1-phase, S-phase and G2/M phase. RBM22 depletion alters mitosis, generating endomitosis, and leads to an increase of polyploid cells. These alterations mimic the phenotype of del(5q) MDS blasts. We demonstrated that depletion for RBM22 alters megakaryocytic and erythroid differentiation. We showed that, in human HSPC, RBM22 haploinsufficiency deregulates gene expression and pre-mRNA splicing, particularly in genes involved in response to the standard treatment for low-risk del(5q) MDS lenalidomide. We demonstrated that, in MDS-L cells depleted for RBM22 and exposed to lenalidomide, megakaryocytic differentiation and apoptosis are accentuated.

Altogether, we demonstrated that RBM22 haploinsufficiency contributes to the phenotype of cytopenia and sensitivity to lenalidomide of myeloid cell lineages in MDS-del5q.

P1085 - Multiple Variable Chromosomal Aberrations in Primary Fibroblasts Further Hints to Chromosomal Instability as a Long Term Effect Even Years After Irradiation

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Total body irradiation (TBI) has been part of standard conditioning regimens prior to allogenic stem cell transplantation for many years. The most concerning long-term effect after successful therapy is the increased risk of secondary tumors. In general, ionizing radiation possesses the capacity to induce a multitude of chromosomal aberrations in diverse tissues. A wide spectrum of chromosomal aberrations has been described in fibroblasts of single patients after accidental irradiation or in patients who have undergone radiotherapy. Despite these observations, systematic in vivo cytogenetic analyses of fibroblasts of such patients are lacking.
We will present data from a 45-year-old female patient who was referred to our genetics clinic with cognitive deficits. At 26, she was diagnosed with Pre-B-Cell Acute Lymphoblastic Leukemia (ALL) and treated with allogeneic stem cell transplantation requiring radiotherapy. Therefore, genome analysis was performed on skin fibroblasts. Interestingly, chromosome analysis of skin fibroblasts showed severe chromosomal damage even 2 decades after irradiation. This finding was corroborated by two additional skin biopsies, which revealed multiple different structural chromosomal aberrations. Genome analysis did not show causative variants for chromosomal breakage or hereditary cancer predisposition syndromes.
Two other cases will be presented.
Our current findings give further hints that complex variable chromosomal aberrations in primary fibroblasts may potentially emerge as a long-term effect years after irradiation. Further research is warranted to investigate this phenomenon.

P1086 - Morphological Features and Mutational Status of the FGFR Gene in Urothelial Carcinoma

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Background & objectives.
Urothelial Bladder cancer (UBC)is a heterogeneous group of malignant tumors(MT) with a frequency of 50-70% among the genitourinary MT.The main causes of death are relapses, distant metastases. The FGFR gene determines the characteristics of oncogenesis and clinical manifestations of UBC in each specific case and is considered a prognostic and predictive factor.
Methods
Biopsy material of the primary tumor from55 patients with progression after chemotherapy (cisplatin+gemcitabine) was examined.The age of patients ranged from 35 to 78years, among them:men -4 (80%), women -11 (20%). Distribution by stages: pT1-20 (36.4%), pT2-22(40%), pT3-11 (20%), pT4-2 (3.6%). Distribution of patients by degree of tumor differentiation was as follows: G1-9 (16.4%), G2-20 (36.4%), G3-18 (32.7%); Gx-8 (14.5%). A commercial PCR kit was used to perform FGFR tests. The results of PCR tests were processed by software.
Results.
Of the 55 samples studied, mutation was detected in 13 samples. Detected mutation types:
FGFR3 exon7 p.S249C(c.746C>G)-7/13(53%); p.R248C(c.742C>T)-1/13(7.7%);
exon10 p.Y373C(c.1118A>G)-3/13(23%);
FGFR3 exon10 p.G370C(c.1108G>T)-1/13(7.7%); Fusion FGFR2:BICC1 exon17-1/13(7.7%);
UBC with muscle-invasive structure was detected in 18(32.7%)cases, sarcoma-like structure with muscle invasion was detected in-2(3.6%); non-invasive UBC-17(30.9%).Samples

in which the degree of invasion cannot be determined since the material contains only tumor-11(20%);
Samples with heterogeneous morphology or degree of differentiation-7(12.7%)
Samples with double FGFR mutations were detected-2/55 (3.6%);2samples with tumors of different degrees of invasion and FGFR gene status; 1 case with tumor heterogeneous differentiation: G1 and G3 with focal squamous cell differentiation (biopsies were obtained from 2 parts of the same tumor).

Conclusion
UBC may contain varying degrees of differentiation, morphology, and degree of invasion in muscle;
UBC may contain different status of the FGFR gene depending on the morphology and degree of invasion;
FGFR mutations are more common in non-invasive UB cancers;
FGFR mutations at UBC are associated with a favorable prognosis;
When morphological and histological heterogeneity of UBC is detected, it is advisable to perform FGFR testing from each different tumor site separately to avoid missing genetic heterogeneity.

P1087 - Distribution of Gene Aberrations in Chronic Lymphocytic Leukemia by NGS Testing in a Serbian Patients Cohort

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Different molecular and genomic techniques are employed in chronic lymphocytic leukemia (CLL) to detect molecular biomarkers. By applying next-generation sequencing (NGS) analysis, a high number of recurrently mutated genes were identified to be altered in CLL patients, most of which are associated with poor clinical outcome. The aim of this study was to evaluate the incidence of recurrent molecular abnormalities in CLL patients before first therapy and to associate them with other clinical and genetic markers.
Our study involves a two-year period, from January 2023. to January 2025., during which the NGS analysis was performed in 304 CLL patients before first treatment. The SOPHIA GENETICS capture-based NGS panel including 23 genes was used. Libraries were performed according to manufacturer's recommendations using as input 200 ng of genomic DNA and were sequenced on a NextSeq 550 DX instrument. FISH panel probes included 17p13.1/TP53, 11q22.3/ATM, 13q14.3, and trisomy 12.
Mutations and copy number variations (CNVs) were recorded in 94% of cases, with 78,7% of mutated patients presenting 2 or more mutations. The incidence was highest in ATM (28,9%), followed by TP53 (22%) and NOTCH1 (14%), while among CNVs, the most prominent was the deletion of DLEU1 (42,9%), followed by RB1 (15,4%) and ATM (10,7%). TP53 mutations were identified in 33 cases negative for deletion of 17p13. High concordance was recorded between the presence of trisomy 12 and amplifications of the KRAS, ATF1 and CDK4 genes. Other results will be discussed subsequently.
Comprehensive biological characterization in CLL using NGS may offer new perspectives for a better refinement of risk stratification that could be of help in the clinical management of CLL patient, assessment of relapse after therapy initiation and detection of minimal residual disease.

P1096 - Telomere Dysfunction DNA Breaks Chromosomal Aberration Formation and the Dark Side of the Centromere

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The centromere and telomere are two essential chromosomal structures that maintain genome stability. While telomeres safeguard chromosome ends, centromeres ensure accurate chromosome segregation during cell division. Traditionally considered a highly stable genomic region, the centromere has recently been identified as a hotspot for structural alterations, contributing to the "dark side" of genomic instability. In this study, we investigate the impact of telomere dysfunction on peri-centromeric and centromeric fragility, chromatin decondensation, and ongoing genomic instability.
Materials and Methods
Fifty patients with hematological disorders were included in the study. Circulating lymphocytes from eight healthy donors were exposed to genotoxic stress (4 Gy of ionizing radiation) to induce chromosomal aberrations. Circulating lymphocytes from 200 healthy donors were used as controls. Telomere analysis, centromere configuration, and chromosomal aberrations were assessed using Next-Generation Cytogenetics (NGC), followed by the M-FISH technique.
Results
Significant telomere shortening was observed in hematological patients with complex karyotypes compared to patients without complex karyotypes and healthy donors. A distinct centromere configuration was identified in patients with complex karyotypes. Notably, over 80% of chromosomal breakpoints involved in aberration formation were localized in peri-centromeric (60%) and telomeric (20%) regions. In vitro experiments using circulating lymphocytes from healthy donors confirmed that 60% of induced chromosomal aberrations were localized in the peri-centromeric region.
Conclusion
This study provides, for the first time, evidence of a correlation between telomere dysfunction and centromere involvement in chromosomal aberration formation. The specific centromeric sequence configuration observed in patient nuclei could serve as a novel biomarker for genomic instability. Understanding this "dark side" of the centromere opens new avenues for targeted therapeutic strategies to mitigate genomic instability in aging and cancer.

P1099 - Optimization of the Routine Diagnostic Workflow for Myeloid Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions (MLN-TK) by Optical Genome Mapping

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Myeloid/Lymphoid Neoplasms with eosinophilia and Tyrosine Kinase gene fusions (MLN-TK) is a diverse group of malignancies characterized by recurrent genetic rearrangements in genes such as PDGFRA, PDGFRB, FGFR1, JAK2, ETV6 and FLT3. Identification of the genomic rearrangements is important for accurate diagnosis and the use of targeted therapies such as tyrosine kinase inhibition.
Optical genome mapping (OGM) is a novel technology that can detect genome-wide structural and numerical aberrations, in one single test, by mapping ultra-long linear DNA molecules, enzymatically labeled at a specific sequence motif, to the reference genome. Here, we evaluated the use of OGM for the retrospective genomic analysis of ten patients

with suspected or confirmed MLN-TK, previously analyzed by current standard of care (SOC) methodologies, i.e. chromosome banding analysis (CBA), fluorescence in situ hybridization (FISH) and/or PCR-based techniques. We selected one case with a FIP1L1::PDGFRA rearrangement (both at diagnosis and relapse), cases with rearrangements in PDGFRB (n=3), FGFR1 (n=1), JAK2 (n=1) and ETV6 (n=1); and three cases with hypereosinophilia where no MLN-TK-related abnormality could be demonstrated.

In six abnormal cases, OGM confirmed the presence of gene rearrangements previously determined by SOC methods, identified the fusion partner in the PDGFRB-, JAK2- and ETV6-rearranged cases and elucidated the precise mechanism leading to a BCR::FGFR1 rearrangement. In addition, OGM detected two cryptic rearrangements in two cases, while no abnormalities were observed in the remaining two cases.

Here, we illustrated that OGM is a valid technique in the routine genetic diagnostics of MLN-TK to detect new recurrent structural aberrations and identify unknown fusion partners, optimizing individual patient treatment.

P1104 - Dynamic Follow Up of Tumor Burden in Multiple Myeloma Through Analysis of ccfDNA Markers

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Chromosomal abnormalities are important for prognostic risk-stratification in multiple myeloma (MM). Markers from ccfDNA may offer a minimally invasive alternative for prognosis and follow-up. We evaluated tumor fraction (TF), CNAs, RAS mutations and IGH-FR1/IGK clonotype as alternative markers. Concordance between ccfDNA and BM-PLCs was high: 84% for gain or amp(1q21), 96% for del(17)(p13.1)/-17; 91% for del(1)(p32.3), 73% for del(13q)/-13 and 87% for hyperdiploidy. As marker of disease burden, TF correlated with R-ISS stage, β2-microglobulin and %PCs in trephine biopsy. By the end of induction treatment, five cases presented TF above 3%LOD with negative impact in PFS. No correlation was found between %TF and type of response suggesting a potential use of TF as prognostic biomarker but not for depth of response. In BM we detected 33/43 IGH-FR1 and 25/43 IGK patients with clones. In ccfDNA the same clone was detected in 16/33 IGH-FR1 and in 15/25 IGK. In nine patients IGH-FR1 clones were still detectable at D8 and in six at D15 to completely normalize at cycle 2-D1. For IGK five cases at D8 and in two at D5, all normalized at C2D1 showing an early response to treatment. 9/43 cases showed a NRAS Q61 mutation and 6/43 a KRAS Q61 mutation in BM. ccfDNA showed 6/9 cases NRAS Q61 and 3/6 KRAS Q61. Five cases had persistent mutations during follow-up. We validated the detection of CNAs in ccfDNA and successfully characterized clonotypes and RAS mutations in this substrate. This suggests that ccfDNA can be used for risk stratification in MM, which is of particular interest when BM-PC purification fails. Furthermore, we showed that ccfDNA markers can be used to characterize the dynamics of the response and are more sensitive than BM-marker-based techniques for earlier detection.

P1106 - What Does Atypical Philadelphia FISH Signal Pattern Indicate in CML

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Chronic myeloid leukemia (CML) is characterized by the Philadelphia chromosome (Ph), occurs as a result of a t(9;22). In 5-10% of CML cases, variant t(9;22)s (vPh) are observed. Additionally, while t(9;22) is formed, deletions can be observed on chromosomes 9 and 22. These deletions are observed more frequently in vPh.

There is conflicting information in the literature about the prognostic effects of vPh and deletions of 9q and 22q. There is also limited information about the frequency and breakpoints of other chromosomes included in the variant t(9;22). Atypical BCR::ABL1 FISH signal pattern indicates deletions and variant translocations. In this study, we aimed to investigate the clinical significance of atypical FISH signal patterns and determine the frequency of variant translocations. Bone marrow samples of 231 newly diagnosed CML patients were analyzed by conventional cytogenetics and FISH.

As a result of FISH analysis, atypical FISH signal patterns were detected in 49/231 cases and vPh was detected in 7 cases with conventional cytogenetics. It was determined that chromosomes 1, 3, 5, 7, 8, and 21 were included in vPh. When cases with classical and non-classical signal patterns were compared in terms of 6th and 12th month treatment responses, survival times and treatment changes, it was found that cases with classical signal patterns had significantly higher treatment responses at 6th month ($p<0,001$).

Because variant translocations are extremely rare and involve many different chromosome breaks, a large number of cases are needed to clearly understand their prognostic implications. Due to the limitations of conventional cytogenetic analyses, it should be taken into account in patient follow-up that atypical Philadelphia FISH signal patterns indicating deletions and/or variant translocations may cause a delay in obtaining a complete cytogenetic response at 6th month.

P1113 - Complex Karyotype Prognosis of Acute Myeloid Leukemia in Tunisian Patients

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Acute myeloid leukemia is a rare hematological malignancy with poor prognosis high mortality and relapse rates. Cytogenetic analysis appears to be the most important prognostic factor. The aim of our study is to determine the impact of complex karyotypes (CK) on the prognosis of AML. We conducted a retrospective study including AML patients treated between 2013 and 2021. Data were collected from medical records. We analyzed karyotypes as well as overall survival (OS) and relapse-free survival (RFS).

We included 202 patients. The median age was 42 years and the gender ratio was 1.03 (104 M/98 F). According to their karyotype : 15.3% had low risk, 61.9% had intermediate risk, and 18.8% had unfavorable risk. The percentage of patients with a CK among those in the unfavorable risk group was 8.8%. The post-induction cytological remission (CR) rate was 12.1%, 38%, and 20% for the unfavorable, intermediate, and low-risk groups, respectively. Among patients with a CK, the CR rate was only 4.9%. The death rate during induction therapy was higher for the high-risk group, estimated at 20.9%, or 1.7 times that of the intermediate-risk group (11.9%) and 8 times that of the low-risk group (2.5%). The death rate during induction therapy for the CK group was 1%. The relapse rate was 3.8%, 23%, and 6.9% in the favorable, intermediate, and unfavorable-risk groups, respectively. Among these, the subgroup of patients with CK had a relapse rate of 3%. The 36-month OS for the unfavorable-risk group was 35%, and it was 40% for patients with CK. The 2-year RFS in the unfavorable-risk group was 24%, while it was estimated at 35% for patients with CK.

CK appears to be a very poor prognostic factor. Thus, cytogenetic results must be integrated into treatment protocols to improve clinical outcomes.

P1116 - Immunofluorescent Visualization of H3K27ac and H3K27me3 Histone Modifications in Normal and Cancer Chromosomes

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Epigenome, the general epigenetic state of an organism, is as important as the genome in normal development. Epigenetics is the study of heritable changes in gene expression that occur through changes in chromatin structure and organization rather than in the DNA sequence. Cancer epigenetics studies today are almost exclusively at the molecular level. There is currently no field of "cancer cytoepigenetics" that corresponds to cancer cytogenetics, which is a very important branch of cancer genetics. If epigenetic changes can be demonstrated on chromosomes, it may be possible to monitor changes in epigenetic regulation, just as it is possible to monitor karyotype changes in cells during disease progression. The introduction of such a technique would be of great benefit in clinical applications. Chemical modifications in histone proteins can induce the formation of a permissive euchromatin or a repressive heterochromatin state. The aim of this study was to examine histone modifications that form permissive and repressive chromatin states regarding gene expression in normal and cancer chromosomes by immunofluorescence methods and to determine whether there is a difference between them in this respect. The study included healthy individuals to obtain normal chromosomes and K562 cell-line for cancer chromosomes. Immunofluorescent staining was performed using specific antibodies for permissive chromatin marker H3K27ac and repressive chromatin marker H3K27me3 to chromosome preparations from healthy subjects and K562 cell-line. The band patterns obtained in both sample types showed that both modifications were concentrated in gene-rich regions which roughly corresponds to light G bands. For both histone modifications examined, no significant difference was observed in immunofluorescent band patterns of chromosomes (chromosomes 1, 12 and 19) that could be evaluated in both normal and cancer samples.

P1133 - Linking Genetic Predisposition to Telomere Disfunction in Familial Non-Medullary Thyroid Cancer

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Familial non-medullary thyroid carcinoma (FNMTC) accounts for 3% to 9% of all thyroid cancer cases. Familial thyroid tumors are typically papillary thyroid carcinoma (fPTC), which tends to be more aggressive and recurrent than sporadic PTC (sPTC), though its genetic mechanisms are still unclear. Although an imbalance of the telomere-telomerase complex has also been reported in fPTC, there are conflicting observations regarding telomere length (TL) between affected and unaffected fPTC and sPTC (Cappezzone et al., 2021). In this study, we aim to elucidate the role of telomere dysfunction and identify potentially causative

rare deleterious variants in fPTC. We analyzed five Sardinian families, collecting blood samples from 42 individuals: 18 fPTC, 8 unaffected family members (UFM), and 16 sPTC. TL was measured using quantitative fluorescence in situ hybridization (Q-FISH), and Whole exome sequencing (WES) was performed to identify predisposing genes. The comparison between fPTC to UFM displayed a reduction in telomere fluorescence (Q-FISH value: 86,4±11 versus 110,2±14), whereas sPTC have longer telomeres (Q-FISH value: 115.3±15) compared to fPTC patients ($p<0.001$). WES, performed on 8 fPTC, 4 UFM (belong to 4 families) and 7 sPTC, identified a PAK6 gene variant in three affected family members. The PAK6 (p21-activated kinase 6) gene belongs to the PAK gene family, which encodes serine/threonine kinase involved in various cellular processes. In thyroid cancer, the role of PAK family genes is poorly investigated, but PAK4 has been described as a potential susceptibility gene for fPTC, and it is associated with an aggressive phenotype (Jiang Y, et al., 2024). Our findings suggest that telomere shortening is a distinguishing feature of fPTC and implicates PAK6 as a potential predisposing factor, similar to PAK4. Further studies are needed to clarify its functional role and possible link with telomere shortening.

P1135 - Evaluation of the Utility of TERT Promoter Mutations in the Early Detection of Urothelial Cancer

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Bladder cancer is a significant public health concern due to its high incidence, frequent recurrence, and exceptionally high cost of treatment in advanced stages. Urothelial carcinoma is the predominant histological form of bladder and upper urinary tract cancers, accounting for approximately 90% of all cases. Various urinary biomarkers targeting different molecular mechanisms have been developed and are currently under clinical evaluation; however, none have yet achieved the status of a reliable population-based screening tool, primarily due to limitations in cost-effectiveness, sensitivity, and specificity. We present a novel, non-invasive method for the early detection of urothelial carcinoma based on the identification of TERT promoter mutations (C228T and C250T) in DNA extracted from urine sediment. The method combines a specifically designed patient preparation protocol, optimized column-based DNA isolation, and highly sensitive detection using QuantStudio Absolute Q Digital PCR. A total of 195 patients were enrolled in the study, including 58 individuals with histopathologically confirmed urothelial bladder cancer, 55 asymptomatic individuals from the general population (control group), and 82 high-risk individuals with known environmental exposure. Based on cancer and control groups, the method achieved 89.66% sensitivity and 100% specificity. Among the high-risk group, 8 out of 82 individuals (9.75%) tested positive; of those, three were subsequently diagnosed with upper tract urothelial carcinoma, 1 with low-grade urothelial bladder cancer, and 4 with chronic inflammation, which could not be excluded as a potential precancerous condition. Given these findings, the presented method may serve as an economically viable screening tool in appropriately selected populations.

P1139 - Occurence of Myeloid and Lymphoid Disorders in a Hungarian Family

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Authors present the occurrence of polycythaemia vera in a father, daughter and father's brother together with the presence of chronic lymphocytic leukemia in the mother and monoclonal B-lymphocytosis in another daughter in the same family. Several rare types of familial polycythemia or erhrocytosis are known. These are characterized by isolated erythrocytosis with different gene mutations (including EGLN1, EPAS1, VHL or EPOR). Our patients had JAK2 V617F mutation, which is typical in polycythemia vera and other chronic myeloproliferative neoplasms. This mutation leads to constitutive activation of Janus kinase 2, which is responsible for increased proliferation, differentiation, signal transduction in myeloid cells. The authors present the clinical course of each patient. The authors highlight the role of molecular methods in achieving accurate diagnosis.

5. Genomics

P1014 - Genetic and Environmental Factors in Hashimoto's Thyroiditis Study on the Association of MTNR1B Gene Polymorphisms with Body Mass Index in a Croatian Population

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Hashimoto's thyroiditis is an autoimmune disease of the thyroid gland that causes chronic inflammation and can lead to hypothyroidism. Melatonin, the hormone that regulates the sleep-wake cycle, also influences the immune system. Its receptor, MTNR1B, modulates immune responses and is sporadically expressed in the thyroid gland. Alterations in the melatonin-MTNR1B receptor signaling pathway may play a role in the development and/or various clinical manifestations of autoimmune diseases. Obesity exacerbates the severity of some autoimmune diseases, reduces the efficacy of treatment, and may accelerate the progression of these diseases. This study aims to investigate the association of MTNR1B gene polymorphisms (rs10830963, rs1387153, and rs4753426) with Hashimoto's thyroiditis, taking into account the body mass index (BMI) of patients. Patients with Hashimoto's thyroiditis were included in the study and categorized into groups based on BMI (normal weight BMI≤25kg/m2 and overweight/obese BMI>25kg/m2). The polymorphisms of the MTNR1B gene were analyzed using the TaqMan method. The study included 115 patients with a clinical, ultrasound, and laboratory-confirmed diagnosis of Hashimoto's thyroiditis (64 normal-weight and 51 overweight/obese patients) with a mean age of 4312 years. The present study showed that specific MTNR1B polymorphisms may increase the risk of disease in patients with a higher BMI. The BMI was found to be associated with the rs10830963 polymorphism of the MTNR1B gene, and the G allele and GG genotype of the rs10830963 polymorphism were more common in patients with Hashimoto's thyroiditis with a higher BMI. The results suggest that genetic factors related to body mass play a role in the development of Hashimoto's thyroiditis and open up new possibilities for personalized treatment approaches.

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P1032 - A Rare and Complex Case of a Male Patient with Digeorge – Like Phenotype Carrying Three Different Mosaic Copy Number Variants on Chromosome 22

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Background: 22q11.2 microdeletions cause various phenotypes, including DiGeorge Syndrome (DGS; OMIM#188400). However, some patients with clinical phenotypes suggestive of DGS, require additional investigation to delineate the exact genetic cause of their symptoms. We present a patient with DGS-like phenotype, carrying a rare combination of mosaic aberrations encompassing the Velocardiofacial/ DiGeorge region.
Material and Methods:A 17-year old male patient along with his non-affected parents was referred for DGS genetic testing, with developmental delay, hypotonia, joint laxity, hypospadias, intellectual disability and dysmorphic features. Genetic testing included Fluorescence in situ Hybridization (FISH)(DGS-LSI DiGeorge/ VCFS Region-VYSIS Inc), karyotype and array-CGH (SurePrint ISCA array V2, Agilent). For confirmation and further investigation, multiplex ligation-dependent probe amplification (MLPA), targeted FISH and trio-based whole-exome sequencing (trio-WES) were used.
Results: Normal results were obtained from DGS-FISH and karyotype. Array-CGH, however, revealed a 6Mb mosaic duplication and two mosaic deletions of 1.7Mb and 1.9Mb. All aberrations were de novo and no balanced rearrangements were detected in the parents. Targeted FISH and MLPA confirmed all aberrations and their mosaic state. No causative single-nucleotide variants were identified by trio-WES, although the structural variants described above were detectable. Thus, the final result for the patient is [arr 22q11.21q12.1(18035777_25903543)x3[0.6]dn,22q12.1(27320031_29029992)x1[0.6]dn,22q12.3(33681958_35630078)x1[0.6]dn].
Conclusion:We described a patient carrying a causative rare and complex aberration delineated by a combination of different genetic tests that complement each-other in terms of resolution and accuracy.
We emphasize the importance of a combined targeted and non-targeted approaches to successfully resolve such rare cases.

P1033 - HRAS Related Costello Syndrome Caused by HRAS c.34G>A p.Gly12Ser Variation in Child Suspected with Achondroplasia

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Background: HRAS related Costello syndrome is a rare multiple congenital anomaly syndrome associated with a coarse facies, short stature, distinctive hand posture and appearance, severe feeding diculty, and failure to thrive. Other features include cardiac anomalies and developmental disability.
Methods: Whole genome sequencing – Centogenome Solo was performed. Parental targeted testing is pending
Results: Autosomal dominant HRAS c.34G>A p.(Gly12Ser) variation was detected. This variant causes an amino acid change from Gly to Ser at position 12 in exon(s) no. 2 (of 5). The patient was 5 months old, primarily suspected with achondroplasia or other type of dwarfism. Detailed pediatric developmental assessment showed dysmorphic appearance. The head is dolichocephalic, the forehead is prominent, there is a hypertelorism. The anterior fontanelle is at the level of the surrounding bones, it is open 2x2

cm. The heart's action is rhythmic, the tones are clear, and a discreet systolic murmur is heard. The abdomen is soft and painless to palpation.The patient is conscious, occasionally in opisthotonos position, there is muscle hypotonia especially of the body axis and pronounced neck laxity. The shoulder girdle is tight and the extrentities are somewhat shorter in relation to the body. A certain level of developmental delay is present.

Conclusion: HRAS related Costello syndrome has wide phenotypic spectrum, ranging from a mild to a severe phenotype. The child is monitored in our hospital, has showed signs of huge improvement in physical and cognitive development. Prenatal genetic counseling for future pregnancies is issued once the parental target testing is performed.

P1119 - Baracuda (B Allele Ratio Chromosomal Uniparental Disomy and Aneuploidies) A Visual Tool to Improve the Detection and Interpretation of Mosaic CNVs and Uniparental Disomies in Rare Disease Genomics

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AURAGEN is one of two French clinical genomics laboratories participating in the French Genomic Medicine plan, including a large-scale genome sequencing program for rare diseases Our mission is to end diagnostic odysseys for patients with suspected genetic diseases. While copy number variants (CNVs), mosaic CNVs and uniparental disomies (UPDs) play a critical role in diagnosis, they remain challenging to detect and interpret using short-read sequencing technologies.

To address this, we developed BARACUDA (B-Allele RAtio Chromosomal Uniparental Disomy and Aneuploidies), a visualization tool designed to highlight abnormal patterns of inheritance from genome sequencing data. Disomies are highlighted using a SNP-array-like approach using unambiguous inheritance pattern for SNVs in probands. Chromosomal events, including large gain, loss as mosaic events are detected by deviation from normal B-allele frequency distribution. Monosomies and trisomies are distinguished using read depth information from the proband. For each chromosome, mirrored histograms of B-allele ratios for both parents offers a comprehensive visualization of inheritance patterns.

This approach complete CNV tools, it enables the detection mosaic chromosomal anomalies and UPDs. Among 13,273 analyzed cases, we identified 35 dysgonosomies, 29 UPD profiles, and 80 abnormal profiles – including mosaic, long CNVs and complete monosomies and trisomy. Notably, a mosaic trisomy 8 (<10%) of maternal origin was confirmed via blood analysis (7%). A maternal isodisomy of chromosome 14 (UPD(14)mat) was also confirmed by methylation analysis and explained a clinical suspicion of Temple syndrome.

This original visualization strategy significantly improves the detection of variants traditionally difficult to resolve with genomic technologies. We believe BARACUDA can be useful to other genomics laboratories and contribute to improving diagnostic yield in rare disease genomics.

P1130 - Investigating X Chromosome Inactivation Patterns in X Autosome Translocations Using Long Read Sequencing and the T2T Genome Assembly

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X chromosome inactivation (XCI) is a critical mechanism in female mammals that ensures dosage compensation by silencing one of the two X chromosomes. While XCI is typically random, certain genomic alterations, such as X-autosome translocations, can lead to skewed inactivation patterns, potentially unmasking deleterious alleles and contributing to phenotypic abnormalities. In this study, we utilised long-read genome sequencing (LRS) with the PacBio Revio platform and the telomere-to-telomere (T2T) genome assembly to investigate the effects of X-autosome translocations on XCI patterns and associated genomic architecture.
By combining the unique ability of LRS to span complex and repetitive genomic regions with the completeness of the T2T assembly, we accurately mapped translocation breakpoints. We phased the derivative and structurally healthy X chromosomes in nine carriers of X-autosome translocations. Using the epigenetic signatures (5mC) from the LRS data, we (i) measured XCI, (ii) determined which X chromosome was active or inactive, and (iii) examined methylation patterns across the derivative chromosomes and translocation breakpoints into the autosome.
All individuals exhibited skewed XCI, as indicated by methylation levels on the AR (androgen receptor) gene promoter (differential methylation 40–60%), confirmed by similar patterns on the RP2 promoter (differential methylation 30–70%). Furthermore, our results suggest that the structurally unaffected X is preferentially inactivated. Detailed analysis of methylation patterns across the breakpoints is ongoing and will be presented at the meeting.
This study highlights the power of long-read sequencing and the T2T genome in resolving complex structural rearrangements and their effects on epigenetic regulation. Our findings provide novel insights into the interplay between structural variants and XCI, offering a deeper understanding of their implications for female phenotypic diversity and rare disease mechanisms.

6. Other Cytogenomic Topics

P1013 - The DEB Test Beyond Fanconi Anemia. A New Look Into Chromosome Instability

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Background: Fanconi anemia (FA) is a rare genetic disorder characterized by chromosome instability (CI), particularly upon exposure to 1,2:3,4-Diepoxybutane (DEB), a DNA cross-linking agent. The DEB test is the gold standard for FA diagnosis due to its high sensitivity, specificity, and non-overlapping separation between positive and negative values. However, some patients referred to our laboratory for this test exhibit intermediate CI levels—values between FA and control ranges—suggesting a potential deficiency or reduction in DNA repair mechanisms/capacity.
Materials and Methods: We conducted a retrospective study of CI levels in patients referred for the DEB test between 1993 and 2025.

The study included three groups: FA patients (n=83), healthy controls (n=244), and non-FA individuals with molecular exclusion of FA (n=813). CI was assessed using non-treated and two DEB-induced lymphocyte cultures. Statistical analysis compared CI parameters across the groups, including the percentage of aberrant cells, the mean number of breaks per cell, and the frequencies of specific chromosomal aberrations (breaks, triradial and tetraradial figures, dicentric and ring chromosomes).
Results: Among non-FA individuals, a subset of patients exhibiting intermediate CI levels was identified. This group included patients diagnosed with inherited bone marrow failure syndromes (IBMFS), particularly Shwachman-Diamond syndrome, as well as individuals without a definitive diagnosis.
Conclusion: The spectrum of CI levels in individuals without FA found in our study highlights the clinical significance of precise CI analysis beyond FA diagnosis. Patients with IBMFS and intermediate CI may have compromised DNA repair, which could influence treatment strategies, particularly in hematopoietic stem cell transplantation (HSCT). Adapting conditioning regimens to account for their compromised DNA repair capacity could help minimize treatment-related toxicity. Further investigation is crucial to understand the underlying mechanisms of CI and its clinical implications.

P1026 - Impact of Sperm Fractioning on Chromosome Positioning Chromatin Integrity and DNA Methylation Level

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Sperm chromosomes are non-randomly organized in three-dimensional nuclear space. The sperm cell nucleus architecture plays an important role in the regulation of early embryo development via the first contact with ooplasm of the chromosomal regions carrying specific genes, which expression is crucial at the first stages of embryo development.
The aim of this study was to determine whether selection of spermatozoa with good motility and/or morphology or high fertilization potential, is related to specific positioning of chromosomes, supported by assesment of DNA protamination, its fragmentation, methylation (5mC) or hydroxymethylation (5hmC) levels.
Semen samples from 5 normozoospermic males were collected and processed for fractionation via swim up (to select viable and motile spermatozoa), Percoll gradient (90/47%; (good motility and morphology) or hyaluronan binding assay (HBA; motile spermatozoa capable to bind to hyaluronan). Sperm chromatin protamination was assessed by aniline blue (AB) staining, while DNA fragmentation by acridine orange (AO) or TUNEL assay. Fluorescence in situ hybridization (FISH) was applied to analyse the positioning of chromosomes 4/7/8/9/18/X/Y. Then, second round of staining for the same spermatozoa with fixed positions on slides were performed for global 5mC/5hmC of sperm DNA (immune-fluorescence).
Our study demonstrated that high-quality sperm selection significantly increased chromatin protamination (+24-26%) and 5mC and 5hmC levels (+7-12%), and reduced ssDNA fragmentation (-60-70%). Motile and morphologically normal spermatozoa showed distinct chromosome repositioning, with sex chromosomes shifted to the nuclear periphery, a key chromosomal region of the initial interaction with the ooplasm during fertilization process, while evaluated autosomes revealed various patterns of repositioning. These findings underscore the importance of sperm fractionation for sepraration of sperm with optimal characteristics for assisted reproductive technologies (ART) and suggest that targeted selection based on chromatin dynamics may refine ART protocols.
Funding: National Science Centre Poland 2020/38/E/NZ2/00134 (MO)

P1053 - Preliminary Experience with AI Based Karyotyping in Peripheral Blood Specimens

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Introduction: Artificial intelligence (AI) has recently been integrated into chromosome analysis and karyotyping. The goal of the present evaluation was to assess the turnaround time and determine possible impact of band resolution.
Methods: G-banded slides of peripheral blood samples were prepared by standard methods and scanned using the HiBand system (Applied Spectral Imaging). For each slide, thirty metaphases, automatically selected by the system at 10X, were captured at 100X. Computer-aided karyograms were generated for each analyzable metaphase. Cells were classified according to their band resolution (high: >550 and low: <500). Three cytogeneticists reviewed the suggested karyograms. Time required to correct each karyogram was recorded. Statistical significance was assessed using the Mann Whitney U test. A p-value < 0.05 was considered significant.
Results: Thirty G-banded blood cases were included in this analysis for a total of 62 slides. Thirty metaphases were scanned at high magnification for each slide, resulting in a total of 1,860 metaphases. Computer-aided karyograms were automatically generated for 1,749 of the scanned metaphases (94%). Hundred-fifty cells (5 per case) were selected by the users for analysis. Among these cells, 68 had high band resolution (45%) and 82 had low band resolution (55%). Across all users, the average time spent on each case was.24±9 minutes (range 9-35 minutes). For the user most experienced with the system, significantly shorter average analysis time was reported for cells with lower band resolution than for cells with higher band resolution (2.2±0.7 versus 2.7±0.8, p=0.01).
Conclusion: While the turnaround time observed in this evaluation is comparable to earlier reports using AI-based chromosome analysis on peripheral blood specimens, band resolution was found to potentially impact the time spent on each metaphase. Additional studies are needed in order to further assess the impact of band resolution on analysis.

P1056 - Developing Artificial Intelligence Supported Karyotyping Software Kayra

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Aim: This study aimed to develop karyotyping software capable of identifying normal and abnormal chromosomes with minimal human intervention. Deep learning neural networks were trained on annotated metaphase images to segment, classify, and orient chromosomes, even when overlapping. The cloud-based software allows image upload and karyogram correction in a browser. Its performance was tested against a widely used European reference software on 10 normal metaphases, totaling 459 chromosomes, from both PHA-stimulated blood cultures and spontaneous bone marrow cultures.
Results: The software automatically optimizes image parameters, which users can adjust. KAYRA achieved 98.91% segmentation efficiency for solitary, contiguous, or intersecting chromosomes, compared to 40.52% for the reference software. Chromosome identification rates were 89.1% vs. 54.5%, with the highest accuracy for large and medium-sized chromosomes ($p<0.0001$). Correct vertical orientation was 89.76% vs. 78.43% ($p<0.0001$). Notably, 93.5% of chromosomes from spontaneous bone marrow cultures—requiring more expertise—were correctly positioned by KAYRA, compared to 86.5% for easier PHA-stimulated cultures

($p<0.0001$). Statistical analyses used Fisher's exact test.
Conclusion: KAYRA shows great potential for cytogenetic laboratories, but further research is needed for application in abnormal karyotype analysis.
Acknowledgment: We express our gratitude to the National Research, Development, and Innovation Office for supporting the project titled "AI-Assisted Karyotyping-Based Medical Diagnostics", implemented by Jedlik Innováció Ltd. (Project ID: 2021-1.1.4-GYORSÍTÓSÁV-2022-00054).

P1092 - Nijmegen Syndrome from a Founder Mutation: A Genetic Convergence Across Generations

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The founder effect is an important concept in population genetics being defined as the presence of genes in a current population with origin in a narrow, well-defined ancestral group. There are many diseases caused by the founder mutations, having as practical effect the necessity of targeted testing of the mutation / mutations in the respective population. One such example is Nijmegen Syndrome - a rare syndrome of chromosomal instability, caused by mutations in the NBN gene. It is characterized by severe progressive microcephaly, intrauterine growth retardation and short stature, facial dysmorphia, premature ovarian failure in females and increased risk of hematologic malignancies.
We present the case of a 17-year-old girl with severe progressive microcephaly, facial dysmorphia, intellectual disability, hypergonadotropic hypogonadism, vitiligo. The patient comes from a geographically isolated area. The patient present in vitro sensitivity to damaging agents. We used Mitomycin C cultures and in this way we identified various anomalies, but the most frequent were radials chromosomes. Sanger sequencing identified the NBN gene mutation in exon 6: c.657_661delACAAA (K219Nfs*16) in homozygous state and established the diagnosis. Since the transmission of the disease is autosomal recessive, the genetic studies have also been extended to the family members at risk (brother, parents). In the proband, we note the chronic infection with viruses with lymphotropic capacity (EBV, CMV). Early diagnosis is especially important because it is associated with an increased risk of malignancies, especially lymphomas, and heterozygotes which also have an increased risk of certain cancers.
In conclusion, monogenic diseases with founder mutations represent a special category because of the possibility of an easier diagnosis than in the case of diseases with multiple mutations and early diagnosis is always equivalent to better management.

P1114 - Immunofluorescent Visualization of H3K79me2 and H3K27me3 Histone Modifications in Metaphase and PCC Obtained Interphase Chromosomes

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Epigenetic alterations, heritable through cell divisions without DNA sequence changes, are mediated by DNA methylation, post-translational histone modifications, and non-coding RNAs. Immunofluorescence techniques, utilizing antibodies specific to histone modifications, allow the labeling of these modifications on chromosomes, yielding distinct banding patterns. There are a limited number of studies on metaphase chromosomes with these methods, which combine cytogenetic techniques with epigenetic studies and can therefore be called "Cytoepigenetics". However, no such studies have yet been reported on interphase chromosomes obtained using the PCC (Premature Chromosome Condensation) method. PCC, employing phosphatase inhibitors like calyculin A, enables chromosome retrieval from interphase. In this study, H3K79me2 and H3K27me3 histone modifications were visualized on both metaphase and PCC-derived interphase chromosomes using specific antibodies. The research was conducted on isolated lymphocytes obtained from healthy adult volunteers. To prepare chromosome spreads for immunofluorescence experiments, a method that does not contain acidic fixatives and preserves histone proteins was used while harvesting both cultures for interphase and metaphase chromosomes. The slides were then stained with antibodies specific to the selected histone modifications, and the preparations were examined under a fluorescence microscope. The results showed that both interphase and metaphase chromosomes displayed specific band patterns for the H3K79me2 and H3K27me3 modifications. This study represents the first attempt to visualize histone modifications in interphase chromatin at the single-cell level and in chromosome images, providing new insights into the epigenetic mechanisms underlying cell cycle and differentiation processes.

P1118 - The Bancco+ Project. A National Initiative to Improve Clinical Interpretation and Epidemiological Knowledge of CNVs in Neurodevelopmental Disorders and Fetal Anomalies

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Copy number variants (CNVs) contribute to 10-15% of neurodevelopmental disorders (NDDs). Since 2007, over 200,000 chromosomal microarray analyses (CMA) have been performed in France, mainly in patients with isolated or syndromic NDD. The BANCCO+ project, funded by the French ANR under France 2030 initiative to create a high-resolution CNV resource, including CNV identified by NGS.

BANCCO+ involves three academic partners (HCL, AMU, CHU Poitiers), five national networks (AChroPuce, ACLF, ANPGM, NGS-Diag, SOFFOET), two rare disease networks (AnDDI-Rares, Defiscience), the CLAD reference center, the ITHACA European Reference Network (ITHACA), and the DEFIDIAG

program (French Genomics Medecine Initiative 2025).
Clinical objectives include:
• Expanding patient inclusion into BANCCO+, targeting 100,000 patients by 2028 (currently 40 800 vs 50,208 for DECIPHER).
• Incorporating CNVs identified through exome/genome sequencing from molecular and cytogenetic diagnostic labs
• Integrating CNVs from DEFIDIAG (trio-based WGS).
• Creating a CNV catalog for fetuses with structural malformations (in collaboration with French fetopathologist society).
• Providing advanced annotation tools to support clinical interpretation.
Scientific goals include:
• Describing CNV epidemiology, mainly in large NDD and fetal anomaly cohorts, including small-sized CNVs.
• Discovering novel genes involved in NDDs.
• Improving understanding of human genome organization.
• Enhace collaborative research between geneticians.
Conclusions:
- Nineteen centers from the AchroPuce network actively contribute to enhancing data sharing. Nearly 57 500 CNVs documented, strengthening knowledges on genotype and phenotype correlations.
- Currently BANCCO+ focused on legal and organizational groundwork, including consortium agreements, ethical oversight, and the creation of a curation working group.
- BANCCO+ aims to support medical geneticists in CNV interpretation, including those derived from whole genome sequencing in French Genomics Medicine Initiative and to interface with the future national Data Collector and Analyzer (CAD).

Abstracts Read by Title

P1058 - Chromosomal Abnormalities and Polymorphisms in Infertile Armenian Couples. A Cytogenetic Analysis+

Irina Puppo [1], Alla Vardanyan [1], Susanna Petrosyan [2], Narek Pepanyan [2], Inassa Nazaryan [2]
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P1059 - Additional Y chromosome in 47,XYY implications for male infertility

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Literature on Social Media

E.C.A. is also present on Social Media. Here are announcements of interesting articles that we have posted on Facebook. The articles and news items are related to cytogenomics or to biology in general. If you have relevant articles that you would like to share, please contact mariano.rocchi@uniba.it.

FUNCTIONAL MICROPROTEINS

Advances in DNA sequencing technologies, particularly long-read sequencing, have revolutionized the study of the transcriptome, revealing thousands of small transcripts previously categorized as noncoding. This reclassification is partly due to the presence of noncanonical open reading frames (ORFs) within these transcripts.
A major challenge of uncovering the functions of these small transcripts remains. In a recent paper published in Trends in Genetics, Azam et al. (1) leveraged CRISPRCas9 to knock out microproteins in cell culture systems. Their approach uncovered the involvement of over 1,000 microproteins in regulating cell proliferation.

[1] https://www.cell.com/trends/genetics/abstract/S0168-9525(24)00298-1?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0168952524002981%3Fshowall%3Dtrue

HAPLOINSUFFICIENCY AND DOMINANCE

Haploinsufficiency is a mechanism where the loss of one functional allele results in insufficient protein levels to maintain normal function, leading to a dominant phenotype. The intro-ductory section of the paper by Veitia (1), summarizes various ways haploinsufficiency can arise.
Dominant diseases are caused by single-allele mutations such as nonsense, frameshift, missense mutations, trinucleotide expansions, regulatory region mutations, or gain-of-function mutations. Juvik et al. (2) examine how mutants causing mRNA decay trigger transcriptional adaptation, where the decay products upregulate “adaptive genes” which compensate for the loss of function. However, in some cases, these genes exacerbate the pathological phenotype via gain-of-function effects. The mutation itself is not inherently deleterious but becomes harmful because it triggers mRNA decay, which can have deleterious effects through adaptive genes.

[1] https://www.cell.com/trends/genetics/abstract/S0168-9525(24)00235-X?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS016895252400235X%3Fshowall%3Dtrue
[2] https://www.cell.com/trends/genetics/fulltext/S0168-9525(24)00291-9?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0168952524002919%3Fshowall%3Dtrue

UNDERSTANDING PROTEIN LANGUAGE THROUGH NATURAL LANGUAGE MODELS

ESM3 is an advanced language model that simulates protein evolution on a timescale equivalent to 500 million years (1). This model, based on artificial intelligence technologies, generates innovative protein sequences and structures far removed from those found in nature.
The model was used to design a variant of the green fluorescent protein (GFP) with 58% similarity to known natural proteins.
ESM3 can accelerate evolutionary discoveries by creating new and functional proteins more quickly than natural processes.

[1] https://www.science.org/doi/10.1126/science.ads0018

GENETICS OF MALE INFERTILITY: ADDING A NEW PIECE TO THE PUZZLE

A recent study published in PNAS (1) has revealed new insights into male fertility by investigating a gene cluster essential for sperm development. This cluster comprises 11 genes in humans and 13 similar genes in mice. The close genetic link between these genes suggests they

have co-evolved to perform crucial functions within the mammalian reproductive system.
Using mice model and CRISPR/Cas9 gene-editing technology, researchers demonstrated that specific genes within the cluster are vital for the progression of sperm cells from round spermatids to elongated spermatids. Deleting various genes in different combinations resulted in distinct forms of sterility, underscoring their key role in sperm differentiation and motility.
The puzzle of the genetic basis of male infertility is gradually coming together, offering promising prospects beyond basic research. The authors highlight one key application: non-hormonal male contraception. Understanding the critical genes involved in sperm function paves the way for this future possibility.

[1] https://doi.org/10.1073/pnas.2413195121

GENE DUPLICATION AND ADAPTATION

Gene duplication plays a crucial role in evolution by providing raw material for new functions and enhancing gene expression. Increased gene expression can be essential for developing resistance to toxins.
A study published in PNAS (1) demonstrates that gene duplication helped woodrats (Neotoma, rodent) boost the expression of biotransformation genes, allowing them to adapt to a diet of the toxic creosote bush (*Larrea tridentata*).

[1] https://www.science.org/doi/10.1126/science.adp7978

FUEGIANS AND THEIR ADAPTATION TO COLD

Darwin day, 12 February, commemorates the birth of Darwin in 1809. In his book, The Voyage of the Beagle, Darwin describes his encounter with Fuegians, the inhabitants of the Tierra del Fuego (South America). Fuegians were “naked and scarcely protected from the wind and rain of this tempestuous climate [and] sleep on the wet ground…”. Tierra del Fuego, closely facing the South Pole, has a very cold climate.
How did Fuegians adapt to such a cold climate? A paper by Watanabe et al. (1) has identified specific gene variants involved in the brown adipose tissue accumulation.

[1] https://www.nature.com/articles/s41598-021-02783-1

OBESITY GENES IN DOGS AND HUMANS

Labrador Retrievers are widely used as assistance dogs, and their training often involves food rewards. This means that the most obedient dogs tend to be those that are highly food-motivated. Over time, this selection process favored dogs that had lost the sensation of satiety.
This condition has been linked to mutations in specific genes, as demonstrated by Raffan et al. (2016)[1], who identified a deletion in the POMC gene associated with increased appetite and weight in Labrador Retrievers
More recently, a study published in Science (2025)[2] by a research team led by E. Raffan provided a more comprehensive analysis of the genetic connection between obesity in dogs and humans. This research highlights the shared genetic mechanisms influencing appetite regulation in both species.

[1] https://www.cell.com/cell-metabolism/fulltext/S1550-4131(16)30163-2?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1550413116301632%3Fshowall%3Dtrue
[2] https://www.science.org/doi/10.1126/science.ads2145

WHY WOMEN TEND TO LIVE LONGER AND BE MORE RESILIENT TO COGNITIVE DECLINE THAN MEN

A recent study published in Science Advances (2025)[1] by Gadek et al. investigates how aging affects gene expression on the silent X chromosome (Xi) in the female mouse hippocampus. Using allele-specific single-nucleus RNA sequencing, the researchers found that aging alters transcription on both the active (Xa) and inactive (Xi) X chromosomes, with specific genes escaping inactivation as mice age.

One key finding is the increased expression of Plp1, a gene involved in myelination, which was also observed in the parahippocampus of aging women. The study suggests that reactivation of genes on Xi may contribute to cognitive resilience in aging females. The results highlight potential genetic mechanisms underlying sex differences in brain aging and open new avenues for therapeutic targets against cognitive decline. The paper warranted a comment in Nature[2].

[1] https://www.science.org/doi/10.1126/sciadv.ads8169
[2] https://www.nature.com/articles/d41586-025-00723-x

SOMATIC LOSS OF SEX CHROMOSOMES AND IMMUNITY

Many studies have linked immune response to genetic background. Sonehara et al.[1] investigate the role of somatic mutations, particularly acquired chromosomal alterations, in shaping the immune response to COVID-19 infection. Notably, they highlight the impact of somatic loss of sex chromosomes, a phenomenon increasingly observed with aging.

[1] https://www.cell.com/cell-genomics/fulltext/S2666-979X(25)00039-4?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS2666979X25000394%3Fshowall%3Dtrue

MANIPULATING THE GENETIC CODE IN BACTERIA

The genetic code is degenerate, meaning multiple codons can encode the same amino acid. For example, CCU, CCC, CCA, and CCG all code for proline. This redundancy has inspired researchers to systematically reassign codons in bacterial genomes, a process that opens new possibilities in synthetic biology and biotechnology.
Imagine modifying a bacterium by replacing all CCU codons with CCC. Since both encode proline, this change has no effect on bacterial function. Then, the gene encoding the CCU-specific tRNA is deleted, again without consequences for the bacterium. However, when a phage infects the bacterium, it encounters CCU codons in its genes but finds no corresponding tRNA. As a result, its proteins cannot be synthesized, rendering the phage harmless[1].
This concept of genetic firewalling is a promising strategy to protect industrially valuable bacterial strains from viral infections. For example, a bacterial culture producing human insulin could be immune to phage attacks, ensuring stable and uninterrupted production.
The study by Grome et al.[2] in Nature takes this approach further by constructing a genomically recoded organism (GRO) named “Ochre”, which compresses all stop codons into a single functional stop codon (UAA) while liberating and manipulating other codons for synthetic amino acid incorporation. Additionally, Release Factor 2 was manipulated so that it exclusively recognized UAA stop codons while losing affinity for UGA. In this way they prevented efficient translation termination at UGA, rendering viral transcripts containing UGA non-functional.

[1]https://www.science.org/doi/10.1126/science.abg3029?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed
[2] https://www.nature.com/articles/s41586-024-08501-x

RARE GENETC DISEASES

Steyaert et al.[1] used HiFi long-read genome sequencing on 293 individuals from 114 previously undiagnosed rare disease families. It identified definitive genetic causes in 11.8% of cases and potential candidates in another 5.4%, showing that long-read sequencing can uncover disease-causing variants missed by traditional methods, especially structural variants and repeat expansions.
These are promising results, but the diagnostic yield remains relatively low, highlighting how limited our understanding of the human genome still is.

[1]https://genome.cshlp.org/content/early/2025/03/26/gr.279414.124

TRANSPOSON AND GENOME

Genomes adapt not only to the external environment, but also to internal challenges — such as the activity of transposable elements.
Transposable elements (TEs), once considered "junk DNA", are now recognized as major drivers of genome evolution, contributing to genetic innovation but also threatening genomic stability. To counteract this, organisms have evolved a variety of defense mechanisms, including KRAB-ZFPs, piRNAs, the HUSH complex, and 4.5SH RNA, leading to a continuous evolutionary arms race. This dynamic interplay not only preserves genome integrity but also fosters the development of novel gene regulatory systems and species-specific adaptations.
The paper is by Iwasaki et al.[1].

[1] https://www.cell.com/trends/genetics/abstract/S0168-9525(25)00009-5?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0168952525000095%3Fshowall%3Dtrue

EUGENICS

Mark Peifer, in an article in TIG1, argues that eugenics should be explicitly included in genetics education, not to promote it, but to understand its historical and ongoing influence. Eugenics, rooted in racism and scientific misuse, shaped early genetics and justified discriminatory policies like forced sterilizations and immigration restrictions. The author describes integrating this topic into a genetics course, showing students how science has been distorted for political purposes. The piece stresses that scientists have a responsibility to speak out when science is misused, as eugenic ideas still echo at the present time.

[1] https://www.cell.com/trends/genetics/fulltext/S0168-9525(25)00028-9?dgcid=raven_jbs_aip_email

UNDERSTANDING THE ROLE OF THE Y CHROMOSOME IN SPERMATOGENESIS: NEW INSIGHTS FROM GENE DELETIONS

A recent study explored the connection between Y chromosome and male fertility by using CRISPR-Cas9 technology to create mice with specific Y chromosome gene deletions[1]. This approach enabled researchers to assess the role of specific genes in sperm production. While some genes were essential for normal sperm development, others had more subtle effects, leading to minor disruptions in sperm functionality.
An interesting aspect of the study was the discovery that deleting multiple Y chromosome genes at once led to more pronounced fertility issues. This suggests that while individual genes may have minimal effects, their interactions when deleted together can significantly disrupt sperm development. These findings underscore the complexity of the Y chromosome's genetic landscape, highlighting the importance of gene interactions in male fertility.
The research provides valuable insights into human infertility and points to the potential health risks linked to Y chromosome gene loss and its broader implications in reproductive genetics.Final del formulari

[1] https://www.science.org/doi/10.1126/science.ads6495

THE EVOLUTION OF ENDURANCE RUNNING IN HORSES

Castiglione et al.[1] published a paper describing how horses evolved exceptional endurance due to a surprising genetic twist.
A mutation in the KEAP1 gene, which would normally stop the production of a crucial protein, instead gets recoded into a functional version with an extra cysteine residue. This rare genetic "read-through" boosts the horse's NRF2 antioxidant response, helping cells resist damage from reactive oxygen species (ROS) generated during intense exercise. As a result, horses can produce ATP faster and more efficiently, powering their muscles and enhancing their ability to perform sustained, high-intensity activi-

ties. This molecular advantage allowed horses to thrive as endurance animals, evolving from small, dog-sized ancestors into the powerful runners.
Similarly, humans evolved to be excellent endurance runners, a trait crucial to early survival strategies like persistence hunting. This evolutionary pressure triggered a cascade of changes:
Loss of body fur to allow better cooling through sweating,
followed by darkening of the skin to protect against UV radiation, effectively replacing the protective role of fur.
These changes not only enabled efficient heat regulation during long-distance running but also had profound effects on human physiology, skin biology, and even social behaviors.

[1] https://www.science.org/doi/10.1126/science.adr8589

SOMATIC MUTATIONS AND MOSAICISM

Somatic mosaicism, driven by persistent DNA lesions, is gaining attention thanks to a recent Nature study by Spencer Chapman et al.[1] The paper demonstrates that certain DNA lesions in human somatic cells, especially haematopoietic stem and progenitor cells (HSPCs), can persist for years, sometimes originating in utero, and lead to multiallelic variation and phylogeny-violating mutations.
Building on this, the Trends in Genetics (TIG) commentary by Arnedo-Pac and Aitken[2] spotlights the study, placing it in the broader context of lesion segregation and mutational asymmetry. TIG emphasizes how this research resolves previously "impossible" phylogenetic trees and confirms that both endogenous and exogenous DNA damage can leave a long-lasting mark on our genomes.

[1] https://www.nature.com/articles/s41586-024-08423-8
[2] https://www.cell.com/trends/genetics/fulltext/S0168-9525(25)00049-6?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0168952525000496%3Fshowall%3Dtrue

THE OBSTETRICAL DILEMMA: A CLASSIC EVOLUTIONARY TRADE-OFF, REVISITED

The dilemma was well described by Mitteroecker and Fischer[1].
Taking advantage of the vast genetic and imaging resources of the UK Biobank, Xu et al.[2] used deep learning and genome-wide association studies (GWAS) on over 31,000 pelvic scans to revisit the long-standing obstetrical dilemma—the idea that human evolution faced a trade-off between narrow pelvises for bipedal locomotion and larger infant heads due to increased brain size.
Key findings:

- Pelvic shape is highly heritable: between 32% and 48% of pelvic variation is due to genetics. The study identified 180 genetic loci associated with pelvic proportions.
- Sex-specific genetic architecture: birth canal–related traits, such as the subpubic angle, showed different genetic patterns in men and women, highlighting reproductive specialization.
- Childbirth trade-offs: narrower birth canals were linked to a higher risk of obstructed labor and emergency C-sections.
- Locomotion effects: narrower pelvises correlated with faster walking speeds, but also an increased risk of back pain and knee disorders.
- Pelvic floor consequences: wider pelvises (more favorable for childbirth) were associated with increased risks of incontinence and genital prolapse, adding a new dimension to the evolutionary trade-offs.
- No support for shortened gestation as a solution: the study found no genetic evidence linking pelvic dimensions to gestation length, contradicting the long-standing idea that human evolution addressed the childbirth challenge by having babies earlier (with smaller heads). This hypothesis, once thought to help resolve the dilemma, lacks empirical support.

Conclusion:
Rather than being resolved by shortened pregnancy, the obstetrical dilemma appears to reflect coevolution between the shape of the pelvis and the size of the human head, with additional

constraints from pelvic floor health and locomotor demands. This large-scale, data-rich study offers a modern, more complex view of a foundational hypothesis in human evolutionary biology.

[1] https://www.ajog.org/article/S0002-9378(22)00733-5/fulltext
[2] https://www.science.org/doi/10.1126/science.adq1521?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

MUTATION RATE IN HUMANS

Recent advances in sequencing technologies have dramatically improved our ability to measure human de novo mutation (DNM) rates. Historically, most studies relied on the analysis of parent-offspring trios using short-read sequencing (SRS) technologies, which mainly captured single-nucleotide variants (SNVs) and small indels, while leaving large repetitive regions, such as centromeres and segmental duplications, largely unexplored.

One of the earliest direct estimates of the human mutation rate, as reported in 2009[1], was based on the sequencing of approximately 10 Mb of euchromatic Y chromosome DNA across a deep-rooting pedigree. This landmark study, based on short-read data, primarily captured point mutations and did not account for larger structural variations or highly repetitive DNA regions.

In contrast, the present study[2] (by the group of E.E.Eichler) represents a major step forward. By sequencing a four-generation, 28-member human pedigree using five complementary sequencing platforms (short-read and multiple long-read technologies), researchers assembled near-complete, telomere-to-telomere genomes for most individuals. This comprehensive strategy allowed the detection not only of SNVs and small indels but also of larger and more complex variants - including tandem repeat expansions/contractions, large de novo structural variants, and mutations in centromeric and other heterochromatic regions previously inaccessible to short-read sequencing.

Main results of the study include:

- A total of 1,037 de novo SNVs were detected across 20 offspring, refining the per-generation mutation rate estimate, to 51.9/generation.
- A clear paternal age effect was confirmed for SNVs (with about 1.28 additional mutations per year of paternal age).
- Tandem repeat mutations were more frequent than previously thought, occurring at approximately 3.3 mutations per genome per generation.
- Large-scale de novo structural variants were identified, including mutations within centromeric satellite DNA.
- The contribution of postzygotic mutations was characterized in detail, revealing a significant but minor proportion of all DNMs.
- No significant association was observed between recombination hotspots and the formation of large de novo structural variants.
- Rates of mutation varied substantially between different genomic regions and repeat classes.

Altogether, this study provides the most comprehensive direct measurement of the spectrum and rate of de novo mutations in humans to date, overcoming the limitations of previous trio-based, short-read studies. These results refine our understanding of human genetic variation, mutation processes, and inheritance patterns at a genome-wide level.

[1] https://www.cell.com/current-biology/fulltext/S0960-9822(09)01454-7?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0960982209014547%3Fshowall%3Dtrue
[2] https://www.nature.com/articles/s41586-025-08922-2

MENDEL'S PEAS

Gregor Mendel’s seven pea plant traits, which laid the foundation of genetics, were long understood only at the phenotypic level. Over recent decades, researchers identified the molecular basis for four of these traits. In a major milestone, this new study, which appeared in Nature[1] (see also the comment in Science[2]),

finally reveals the genetic basis of all seven of Mendel's original traits.

Using a massive genomic analysis involving nearly 700 pea varieties, researchers created a detailed variation map with 155 million SNPs. They confirmed and extended the knowledge about the known genes for: seed shape, seed color, flower color, and plant height, and, crucially, identified the genetic causes of the three previously unresolved traits:

- Pod color (Gp): Linked to a large deletion (~100 kb) near the ChlG gene, affecting chlorophyll synthesis and leading to yellow pods.
- Pod shape (P and V loci): Two genes were found (PsCLE41 and PsMYB26) which affect secondary cell wall development and pod "parchment" formation, critical for edible versus inedible pods.
- Flower position / Fasciation (Fa): A 5-bp deletion in a CIK-like receptor kinase gene (PsCIK2/3) explains the fasciated stem phenotype, modulated by an additional modifier locus (Mfa).

The work used a combination of Genome-wide association studies (GWAS), genetic mapping, RNA sequencing, and functional tests like mutant analysis to pinpoint these genes. Notably, this research highlights how Mendel intelligently chose simple, easily trackable traits (what we now call "simple Mendelian traits") after carefully testing many other pea characteristics. His focus on traits controlled by major, easily segregating alleles was key to the clarity of his discoveries.

Beyond solving the historical mysteries, the study also opens new breeding possibilities by identifying many genes affecting agriculturally important traits (like seed size, pod width, and plant architecture).

[1] https://www.nature.com/articles/s41586-025-08891-6
[2] https://www.science.org/content/article/massive-pea-study-solves-last-genetic-riddles-famed-friar

VACCINATIONS ON THE SAME ARM

You know those ideas that are so simple and obvious that you immediately say, "Why didn't I think of that?" This is one of them. And yet, behind the simplicity is a tour-de-force Cell-level study.

Dhenni et al.[1] reveal that where you get your vaccine booster actually matters - specifically, getting it in the same arm as the first dose leads to a faster and stronger immune response. In mice and humans, they show that memory B cells residing in the draining lymph node (dLN) re-enter germinal centers and mount a more potent response when the booster is given in the same location. This is driven by subcapsular sinus macrophages (SSMs), which "remember" the initial antigen encounter and help re-activate memory B cells more efficiently.

The study combines elegant mouse models, intravital imaging, single-cell transcriptomics, and human data from BNT162b2 (Pfizer) vaccine recipients. In humans, same-arm boosting led to an earlier peak in neutralizing antibodies and broader B cell clonal expansion—within 5–7 days instead of 4 weeks.

It's not just about the idea. It's about doing the work to prove it.

Comment in Nature[2]

[1] https://www.cell.com/cell/fulltext/S0092-8674(25)00407-6
[2] https://www.nature.com/articles/d41586-025-01326-2

REVISITING HUMAN KNOCKOUTS IN A NEW LIGHT

Consanguinity is a major force shaping the human genome in certain populations. In Pakistan, an estimated 60% of marriages occur between first cousins, leading to widespread homozygosity. This creates unique opportunities to discover recessive genetic effects, not only for rare Mendelian diseases, but also for common complex conditions.

The 2017 Nature study by Saleheen et al.[1] pioneered this approach, analyzing over 10,000 individuals from a Pakistani cohort. They

identified more than 1,300 genes "knocked out" in humans, some with clear biological effects, like dramatically reduced triglyceride responses in APOC3 knockouts.

In 2025, Heng et al.[2] followed through. Using the Genes & Health cohort of 44,000 British Pakistanis and Bangladeshis, similarly characterized by high consanguinity, they tested for recessive associations across 898 diseases. The study identified 185 genetic regions strongly linked to disease, many of which would have gone unnoticed using the usual methods that only look for effects from a single mutated copy of a gene. Highlights include:

- A protective missense variant in SGLT4 against hypertension.
- A recessive risk variant in PNPLA3 for fatty liver disease.
- Several new hits for thalassemia and bilirubin metabolism.

The two studies - eight years apart - tell a coherent story. What was first a bold idea has now become a proven method for mapping human gene function through autozygosity.

[1] https://www.nature.com/articles/nature22034
[2] https://www.cell.com/ajhg/fulltext/S0002-9297(25)00141-7

WOUND HEALING IN HUMANS

It was widely believed that wound healing in humans takes significantly longer than in other mammals, but there was no solid scientific evidence to support this idea. Now, there is finally a dedicated and well-documented study on the subject. The work by Matsumoto-Oda et al.[1] shows that human wound healing is significantly slower, more than twice as slow, than in other mammals, including primates like baboons, vervet monkeys, and even one of our closest relatives, the chimpanzees. This suggests that slower healing may be a relatively recent and unique trait in human evolution.

A commentary from the Smithsonian2 highlights a possible explanation: humans have fewer hair follicles, which in other mammals contain stem cells that help regenerate skin. In exchange, humans evolved more sweat glands, which improve thermoregulation but may compromise skin repair. This appears to be another evolutionary trade-off in the story of Homo sapiens.

On this topic, a BBC documentary narrated by David Attenborough, part of the Dynasties series, follows the power struggle within a chimpanzee troop over the course of more than a year. In one striking episode, the alpha male is found severely injured, apparently left for dead, after a nighttime attack by rival males. His wounds are deep and dramatic, and the expectation is that he will die at any moment. And yet, he manages to heal and, in an incredibly short time, returns to the group and reclaims his position as alpha.

[1] https://royalsocietypublishing.org/doi/10.1098/rspb.2025.0233
[2] https://www.smithsonianmag.com/smart-news/human-evolution-traded-fur-for-sweat-glands-and-now-our-wounds-take-longer-to-heal-than-those-of-other-mammals-180986533/

SPERM CENTROMERES AND CENP-A

A review published by Štiavnická et al.[1] discusses the unique role and persistence of the centromeric histone variant CENP-A in mature sperm cells across different species, including humans, mice, cattle, and flies, and its implications for fertility and early embryonic development.

Importance of centromeres

Centromeres are critical chromosomal regions that ensure accurate chromosome segregation during cell division. While composed of repetitive DNA sequences, their functional identity is defined epigenetically by the presence of CENP-A, a variant of histone H3. CENP-A is central to kinetochore formation and chromosome stability.

Spermiogenesis and the histone-to-protamine transition

During spermiogenesis, most histones are replaced by protamines to tightly compact DNA. Despite this massive chromatin reorganization, CENP-A is retained at centromeres in mature sperm. This persistence is unusual, since histones are almost completely absent in sperm chromatin,

raising important questions about biological function of CENP-A.

Historical insights and discovery

The first clues to centromeric proteins in sperm came from autoimmune sera (CREST) used to stain cells from patients with CREST syndrome. These sera identified CENP-A, -B, and -C. Later, bovine sperm was used to purify CENP-A due to its low histone content, facilitating the first cloning of the human CENP-A gene.

Retention of CENP-A in sperm

Initially, studies failed to detect centromere proteins in mature sperm, likely due to technical limitations imposed by extreme chromatin compaction. With the development of sperm decondensation protocols, researchers confirmed that CENP-A is indeed retained, whereas CENP-B and CENP-C are absent, at least in mouse and bovine sperm.

Comparative Species Data

- In flies, only CENP-A persists in sperm and its presence is essential for early embryonic development. Depleting sperm CENP-A results in embryonic lethality.
- In mice, more recent studies using genetic tagging and western blotting confirm CENP-A's exclusive presence in sperm. Its absence or reduction impairs centromere strength in embryos and compromises fertility.
- In humans and cattle, centromeric foci are observed, but comprehensive molecular confirmation of exclusive CENP-A retention is still under investigation.

Mechanisms of inheritance and function

In Drosophila, paternal CENP-A persists after fertilization and is gradually replaced by maternal CENP-A. It is essential for the correct incorporation of paternal chromosomes into the embryonic spindle. Moreover, insufficient paternal CENP-A cannot be rescued by maternal supply, highlighting a self-templating inheritance mechanism.

In mice, inheritance is more nuanced. Paternal CENP-A deficits can be partially compensated by maternal CENP-A, but asymmetries in parental CENP-A levels exist and are resolved post-fertilization. This suggests an epigenetic memory and a need for balancing centromere strength between parental chromosomes.

Future directions and open questions

The review emphasizes the need to understand:

- Why and how CENP-A is maintained in sperm despite global chromatin changes.
- The molecular structure of centromeric chromatin in protamine-bound sperm nuclei.
- The role of centromeric proteins in fertility and embryo development, especially in humans.
- How centromeres are spatially organized in the sperm nucleus and how this affects function.

The authors propose combining genome editing, super-resolution imaging, and long-read sequencing to map CENP-A positions and better understand centromere biology in reproduction.

[1] https://link.springer.com/article/10.1007/s10577-025-09766-2

CENTROMERE FISSION AND WHOLE-ARM ANEUPLOIDIES IN CANCER

Whole-arm aneuploidies, resulting from the loss or gain of entire chromosome arms, are among the most frequent chromosomal alterations in human cancers. While these have often been attributed to mitotic missegregation, Zheng et al.[1] show that centromere breakage, a structural form of chromosomal instability, plays a dominant role in driving such alterations. Across 17 tumor types, whole-arm losses occur more frequently than gains, and their distribution patterns strongly suggest structural origins. The authors demonstrate that, mechanistically, the centromeres become prone to breakage during S phase due to replication stress, in part linked to histone overexpression. These breaks lead to the loss of entire chromosome arms and are strongly associated with poor patient outcomes. Importantly, the prevalence of centromere break-induced arm aneuploidy highlights a mechanism distinct from classical mitotic errors.

Beyond cancer biology, this phenomenon recalls similar processes in evolutionary cytogenetics, where centromeric fissions have contributed to karyotype diversification in various species,

including reptiles. Such parallels underscore the broader biological impact of centromere instability as a driver of both somatic genome remodeling and long-term evolutionary change.

[1] https://doi.org/10.1073/pnas.2505385122

HUMAN DE NOVO MUTATIONS

A Nature paper, by E. Eichler's group[1], presents the most complete and detailed analysis to date of human de novo mutations (DNMs) by sequencing and assembling the genomes of 28 individuals across four generations (CEPH 1463 pedigree) using five complementary sequencing technologies (PacBio HiFi, ONT, Illumina, Strand-seq, Element AVITI).

Key Results:

- 98–206 de novo mutations per transmission, with:
- 74.5 SNVs
- 7.4 non-TR indels
- 65.3 TR-related DNMs (including STRs and VNTRs)
- 4.4 centromeric DNMs
- Y chromosome: 12.4 DNMs/generation, largely in repetitive satellite DNA.
- Strong paternal bias for germline mutations (75–81%), while postzygotic mutations (PZMs) show no parental bias.
- TR DNMs affect more base pairs per generation than SNVs, and 32 TR loci show recurrent mutations, a novel observation in healthy pedigrees.
- Centromeric SVs: 18 de novo SVs were identified in centromeres, all validated with long reads.
- Y chromosome satellite regions show a >20-fold higher DNM rate than euchromatic regions.

Thanks to high-quality telomere-to-telomere assemblies, this study accesses and analyzes repetitive genomic regions, including centromeres and Y-chromosome satellites, that were previously inaccessible with short-read technologies.
This landmark pedigree study demonstrates that mutation rates and mechanisms vary drastically by genomic context, especially in repeats and centromeres, and underscores the necessity of long-read, multigenerational sequencing for accurate measurement.

[1] https://www.nature.com/articles/s41586-025-08922-2

ARTIFICIAL INTELLIGENCE IN MEDICINE

Google Research and DeepMind have developed and evaluated an advanced version of their medical AI system, AMIE (Articulate Medical Intelligence Explorer), capable of conducting rich, clinically effective diagnostic dialogues with patients. The original model focused on text-only interactions, but the most recent version integrates multimodal capabilities—enabling AMIE to process and reason over images (e.g., rashes, ECGs) and documents (e.g., lab results, PDFs)—thus aligning more closely with real-world remote care practices[1].

Key Advances

- • Multimodal understanding: AMIE can now request and interpret images and clinical documents, improving diagnostic accuracy especially in domains like dermatology and cardiology.
- Structured, phase-based dialogue: A novel state-aware framework guides AMIE through clinical phases (history-taking, diagnosis, management, follow-up), emulating how experienced clinicians think and act.
- Superior performance: In a randomized, blinded study using 105 scenarios, AMIE outperformed or matched primary care physicians (PCPs) across 29 of 32 clinically relevant evaluation axes, and on 7 of 9 multimodal reasoning axes.
- Robust evaluation: Performance was evaluated by 18 clinical specialists and validated through automated scoring pipelines, confirming improvements in information gathering, management reasoning, and patient communication.

A comment on this paper appeared in "Nature News"[2] highlights the experimental yet promising nature of AMIE. It stresses the innovation of using synthetic dialogues for training and evaluation, but notes limitations in generali-

zability and transparency (e.g., lack of access to full prompts or source code). Still, experts view this as a step toward AI systems that "mirror how clinicians actually think".

While still experimental, AMIE's multimodal version represents a concrete move toward deployable AI assistants in telehealth, with broad implications for scalability, accessibility, and quality of care.

[1] https://arxiv.org/abs/2505.04653
[2]https://www.nature.com/articles/d41586-025-01437-w

"SIMPLE MENDELIAN DISEASE" IS SIMPLISTIC: THE CASE OF SICKLE CELL DISEASE

Although sickle cell disease (SCD) results from a single mutation in the HBB gene, its clinical expression is highly variable. In a recent commentary[1], A. Starlard-Davenport uses SCD as a case study to challenge the notion that monogenic disorders are inherently simple.
Genetic modifiers such as BCL11A, HBS1L-MYB, and HBG2, which influence fetal hemoglobin (HbF) levels, along with epigenetic mechanisms and environmental factors, contribute to the disease's complexity.
Social determinants, healthcare disparities, and limited access to advanced therapies further exacerbate outcomes, particularly in underserved populations.
SCD highlights the inadequacy of labeling monogenic conditions as "simple" and underscores the need for personalized, multidisciplinary care.

[1] https://www.cell.com/ajhg/abstract/S0002-9297(25)00189-2?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0002929725001892%3Fshowall%3Dtrue

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LOSS OF CHROMOSOME Y

A review article by Bruhn-Olszewska et al.[1] explores how mosaic loss of the Y chromosome (LOY), the most common post-zygotic mutation in aging men, affects male health. Besides age, LOY is associated with lifestyle factors such as smoking and genetic susceptibility (e.g., CHEK2 mutations). LOY, which occurs in a proportion of cells, especially in blood cells, is associated with a range of diseases:

- Immune system dysfunction, likely due to altered gene expression in leukocytes
- Increased risk of diseases, including cancer, cardiovascular conditions, and Alzheimer's disease
- Higher all-cause mortality

Recent studies also suggest that LOY could influence fibrosis, inflammation, and impaired tissue repair beyond hematopoietic cells.

[1] https://www.nature.com/articles/s41576-024-00805-y

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COMMITTEE

ECC SCIENTIFIC PROGRAMME COMMITTEE

E.C.A. News

- The 2025 General Assembly of the E.C.A. with Board elections will take place during the 15th European Cytogenomics Conference on Monday, 30 June 2025, at 6:00 pm at the conference venue in Katholieke Universiteit Leuven, Leuven, Belgium
- Elections 2025 – renewal or re-election of five board members: J.S. Heslop-Harrison, K. Madan, T. Lavabre-Bertrand, M.R. Pinto Leite, H. Rieder.
- Only one list has been received by the President, with the following candidates: J.S. Heslop-Harrison (United Kingdom), K. Madan (the Netherlands), M.R. Pinto Leite (Portugal), C. Haferlach (Germany), J. Drabova (Czech Republic)

E.C.A. Fellowships

- The **E.C.A.** offers two **Fellowships** for each of the following courses:

  European Diploma in Classical and Molecular Cytogenetics
  to be held in Nîmes (France) 23-29 March 2026 (see page 110)

  Goldrain Course in Clinical Cytogenetics
  to be held in Goldrain Castle (South Tyrol, Italy) August 2026
  (The course for this year is fully booked, an early application for 2026 is recommended)

- The fellowships **include the course fees and the accommodation** during the lectures in Nîmes or in Goldrain but **do not include travel expenses** for either of the courses or for accommodation during the practical training for the Nîmes course. Applications with CV, list of publications and a letter of support should be addressed to the appropriate course organizer. The Educational Advisory Council of the E.C.A. will select the successful candidates.

For details see http://ww.biologia.uniba.it/SEC/

MINUTES OF THE E.C.A. BOARD MEETING MARCH 2025

The E.C.A. Board held a meeting in Hotel Vatel, Nîmes, on Saturday 25 March 2025, 6pm CET to 8pm. The following 12 board members were present in person:
Mariano Rocchi
Jean-Michel Dupont
Thierry Lavabre-Bertrand
Kamlesh Madan
Konstantin Miller
Jose-Miguel Garcia-Sagredo
Anna Lindstrand
Roberta Vanni
Joan Blanco Rodríguez
Pat Heslop-Harrison
Franck Pellestor
Elisabeth Syk Lundberg

Present on-line:
Rosario Pinto Leite
Joris Veermeesch (by invitation, as the organizer of the 2025 conference in Leuven)
Apologies:
Harald Rieder
Meral Yirmbies Karaoguz

Opening
The President opened the meeting at 18.25.
Board members were welcomed, attending both in person and remotely.

The Minutes of the E.C.A. Board meeting held on 23 March 2024 Hotel Vatel,
Nîmes, France, published in Newsletter, were taken as accepted.

Report from General Secretary
The General Secretary reviewed the state of the Membership with 1300 members in the database including ordinary members, honorary members, associate members and technologists. Among them, only 263 are Active members with paid fee (197 Members including 10 technologists, 47 Associate members and 19 companies). Only 10 new members registered in 2024.

The list of new members in 2024 was approved. As previously, new members are welcomed immediately after first approval by the General Secretary, and their membership is activated on paying and is formally approved at the subsequent board meeting.

The Website renewal is working but there may be a problem with not sending renewal reminders.

Report from the Treasurer
The Treasurer and former Treasurer reported the financial status of the Association.

The overall financial position and balance of the Society was satisfactory.

Fellowships were given for Nimes and Goldrain courses, totalling 7,200€.

Despite approximately 50% decline from the pre-covid period, the financial balance is still satisfactory. The reserve balance was maintained to cover *force majeur*.
Although it is not expected that there would be exceptional costs, the deficit of the conferences is not sustainable, so efforts must continue with Dekon to ensure they are financially successful, or at least make no deficit.

There is also the possibility of increasing the membership fee which has been the same for more than 15 years. This should be discussed and voted during the next General Assembly.

The Accounts were unanimously approved by the Board.

Leuven conference 15th ECC 29 June to 1 July 2025
The Scientific Programme is almost complete and will be formally placed on the website imminently. The activities of Sunday morning must be emphasized to enable people to make appropriate travel arrangements.

Joris Veermeesch reported the workshop organization on Sunday. BioNano and Illumina and UCSC will give workshops, and another company is still reaching a decision. Bionano will hold two sessions; the others one session. Rooms still have to be booked. There was some discussion about needing benchmarks for charges to companies.

There was discussion about charges for attending the Workshops; people will pay on arrival. Having a small charge will help ensure people are committed to attend, and cover costs of room plus coffee breaks, although this will need extra administrative effort. A fee of 50€ seems reasonnable to cover these expenses and compares favorably to other conferences.

There was also discussion of lunch arrangements; there will be the opportunity for participants to buy lunches at the Hospital and other options locally.

The Permanent Working Groups (PWGs) will meet on Sunday afternoon. Prenatal; Tumor; Animal, Plant and Comparative Cytogenomics (double slot) are planned. Marker chromosome, Quality and Mutagenesis & Instability PWGs will probably also hold meetings.

The number of posters in Montpellier was156: Clinical 66; Tumor 43; Prenatal 15; Animal/plant 12; Accreditation 3; Genomics 9; Other cytogenetics 8. As in previous years, abstract submissions will be evaluated. It was noted that most abstracts are acceptable but it is important that non-scientific topics/results are excluded.
Overall, the number of abstract submissions is 115 at the moment for Leuven conference, and more are expected before the deadline.

The number of companies attending is still low despite greater efforts to attract more companies.

Support of attendees was discussed but will be limited given the need to ensure financial sustainability for the conference. Poster prizes will be awarded at the conference.

Future Association organization
Partnerships and organization of the Association for the future were discussed, particularly in the light of the pandemic crisis. Small organizational matters need improvement, including timeliness. The board considered that the Association was meeting its objectives as a not-for-profit, professional association:the newsletter is a useful service to members; reviews of important publications, also in the social media, are well received; the Goldrain and Nimes courses are extremely well received (see below); the biennial ECC Conferences are most successful and appreciated by the membership.

Goldrain and Nimes courses
The President reported that both Nimes and Goldrain courses are most successful. The number of applications is extremely good and all slots for the next Goldrain courses are full. The financial balance of the course is positive, thus facilitating organisation of next year's course.
Nîmes course is also well attended with a balanced financial result.
Strategy to differenciate both courses seems efficient with several students attending (or willing to attend) both courses.

Re-election of the Board
The reelection of board members was discussed. Two members have resigned and three members, being eligible for re-election, are willing to stand. The election will be held as specified in the constitution and ballot papers will be distributed in advance of the Annual General Assembly.

Dates of next Meeting
The Annual General Assembly and Board Meeting will be held in Leuven.

There being no further business, the President closed the Board Meeting at 20.10.

Kind reminder

Dear E.C.A. member, please renew your membership: http://www.e-c-a.eu/



Nîmes – France, March 23-29, 2026

EUROPEAN CYTOGENETICISTS ASSOCIATION (E.C.A.)

European Diploma

in Classical and Molecular Cytogenetics

Director: Professor Jean-Michel Dupont, Paris - France

http://www.biologia.uniba.it/SEC/

The Course is designed to provide advanced training in constitutional, haematological, and oncological cytogenetics to medical graduates, pharmacists, pathologists, biologists, health professionals and researchers, with an academic qualification. It is taught by about 20 leaders from major cytogenomics groups involved in research and applications across Europe who will train the students to identify genetic abnormalities for diagnosis and prognosis, and for fundamental and applied research using both classical and molecular cytogenetic techniques. The course, co- organized by E.C.A. and two French Universities, was started by Professor Jean Paul Bureau in 1997, and has been held in Nîmes under his directorship until 2017.

Registration

You can select either (September 2025 – January 31st, 2026)

- Basic diploma: only the lectures and a final online examination (no previous experience required)
- Advanced diploma: lectures + 2 months training in a cytogenetic laboratory (6 months experience in cytogenetics required), and onsite final examination (written and oral) in Paris

For registration, please send a letter of application with your CV to the organizers, Prof. Jean-Michel DUPONT (jean-michel.dupont@aphp.fr) or to Prof. Franck PELLESTOR (f-pellestor@chu-montpellier.fr).

2025 Registration fee may be adjusted: €1034 if paid by the participant, 2034€ if paid by an institution

Beware: the fee does not include accommodation during the lectures or the training

Accommodation

A **special** price is available for participants in the 4* Vatel hotel close to the course venue (https://www.hotelvatel.fr/en/nimes) . We highly recommend that all participants stay in this hotel where all the lecturers will be hosted in order to promote interactions during the course.

Scholarships

E.C.A. will award two scholarships covering the registration and accommodation fees. The Education Committee of the E.C.A. will select the suitable candidate.

Students whose registration is paid by a third party institution are not eligible for a scholarship

Topics

Technical Aspects: *Classical Cytogenetics:* Cell culture techniques; Chromosome staining methods (Q-, G-, C-, R-banding); *Molecular Cytogenetics:* Methods and principles of Fluorescence In Situ Hybridization (FISH); CGHarray and SNParray; Application of Massively Parallel Sequencing to Cytogenetics; Optical Genome Mapping ; Databases in Cytogenetics; *Laboratory quality assessment*.

Clinical cytogenetics: *Basics:* Frequency of chromosome disorders; Cell cycle, mitosis and meiosis, gametogenesis; Heterochromatic and euchromatic variants; Numerical chromosome abnormalities; Structural abnormalities: translocations, inversions, insertions, deletions, rings, markers; Risk assessment for balanced abnormalities; X inactivation; numerical and structural abnormalities of the X and the Y; Mosaicism; Chimaeras; ISCN 2024; *Clinical:* Phenotype of common autosomal and sex chromosome aneuploidies; Chromosome abnormalities in recurrent abortions; Cytogenetics and infertility; Microdeletion syndromes; Uniparental disomy and its consequences; Genomic imprinting; Genetic counselling and ethical issues in cytogenetics; *Prenatal diagnosis:* Indications, methods and interpretation; Risk assessment for chromosomal abnormalities; Non-invasive methods using foetal nucleic acids in maternal blood; Pre-implantation diagnosis; *Cancer* Cytogenetics: Molecular approach to cancer cytogenetics; Predisposition to cancer, Chromosome instability syndromes; Chromosome mutagenesis; Solid tumors; Clinical application in onco-haematology.

Other topics: Genome architecture; Structure of chromatin; Structure of metaphase chromosomes; Mechanisms of chromosome aberrations; Origin of aneuploidy; Evolution and plasticity of the human genome; Animal cytogenetics; Plant cytogenetics.