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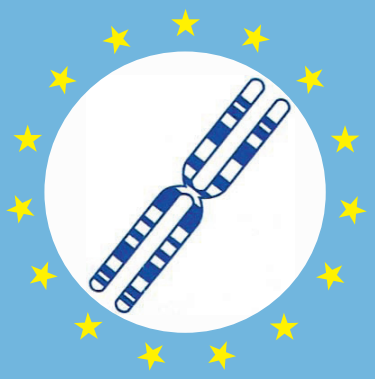

E.C.A. NEWS LETTER

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E.C.A. Newsletter

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V.i.S.d.P.: Jean Michel Dupont, President of the E.C.A.
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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. Our E.C.A. conferences will also 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 **.
Please contact us (mariano.rocchi@uniba.it) if you wish to share an interesting news item or a pertinent article.

President's Address

Dear Members of ECA, Colleagues and Friends

I would like to reach out to all of you as the new President of ECA, elected following the last General Assembly and first meeting of the new Board of Directors. I shall devote my full energy and commitment to fulfilling the E.C.A. objectives and to meet your expectations. First of all, I would like to thank the members who have just left the Board for all their contributions to the functioning of the association and to welcome the newly elected members: Claudia Haferlach from Germany and Jana Drabova from The Czech Republic.

On behalf of all the members of the Board of ECA, I send you, your families and friends my warmest greetings for the Newyear.

2025 was a very successful year for our community with a fascinating conference in Leuven. This conference was special in several ways. First, we chose a university as a venue and we shortened the program by one day. This new setup was highly appreciated according to the feed-back from the participants. Leuven University provided all the facilities expected for a high-level scientific conference, in a modern building with perfect spaces of the right size for networking and exhibition. Second, we introduced pre-conference workshops, which were well attended and were a great success. We hope to expand the idea for our next conference.

Of course, the main reason for the success of the conference was the scientific program prepared by the Scientific Committee under the leadership of Prof. Joris Vermeesch from Leuven. The program covered all the usual aspects in our field, from chromosome biology to diagnostic strategies, human cytogenetics in medicine to animal and plant cytogenetics.

With the 2025 conference behind us, the E.C.A. board is now working on plans for the next conference in 2027. The first step is selecting a venue, which includes visiting potential locations. The final decision about the venue will be published early in 2026 on the ECA website (https://e-c-a.eu/EN/).

As is customary after a conference, the coordinators of the Permanent Working Groups and the chairs of the Conference Plenary and Parallel sessions provide a summary of all the presentations and discussion. You will find these in the following pages.

In this Newsletter You will also find updates of the Facebook posts highlighting the most relevant scientific papers for our community.

Among the main activities of E.C.A., cytogenetic / cytogenomic courses are of utmost importance to maintain the "chromosome knowledge" in the genetic community at a time when emphasis on genome-wide sequencing methods may result in overlooking the complexity of genome architecture. Large attendance for both the Nîmes course in March (European Diploma in Classical and Molecular Cytogenetics) and the Goldrain course in August (Goldrain course in Clinical Cytogenetic) confirms the need for ongoing education in the field. As a part of our education effort, E.C.A. offers several scholarships for both courses. Registrations are still available for both (see flyers at the end of the Newsletter and updated information in the dedicated website: http://www.biologia.uniba.it/SEC/).

I wish you all a fascinating and fruitful year 2025.

Jean-Michel Dupont

E.C.A. President

In Memory of Albert Schinzel (1944 - 2025)

Albert Schinzel, a former president of the E.C.A., passed away in September 2025. Albert was the president from 2000 to 2006 and he oversaw three successful early E.C.A. conferences in Paris, Bologna and Madrid. Albert will be most remembered by E.C.A. members and students from all over the world for the annual Goldrain course which he founded two decades ago.

Albert Schinzel was a distinguished clinical geneticist and an expert in dysmorphology. He was a pioneer in the field of clinical cytogenetics and his name is associated with several genetic syndromes. Albert had a special talent for detecting associations between chromosomal errors and phenotype. This together with his vast knowledge and rigorous analysis resulted in his "Catalogue of Unbalanced Chromosome Aberrations in Man" (first published in 1983, updated in 2001 and reprinted in 2020); it remains a fundamental reference book.

He set up the Goldrain course in Clinical Cytogenetics in 2006. After his retirement in 2009 from the University of Zurich where he was the Director of the Institute of Medical Genetics, he fully devoted himself to this course, his passionate project. For two decades the course has been a tremendous success. Students from all over the world hear about this course by word of mouth and there is often a waiting list for the following year. There are several reasons for its success. Albert carefully chose Goldrain Castle as the venue. It has a peaceful inspiring atmosphere with a view of mountains all around and the students and lecturers spend a lot of time together, also during meals. The castle is situated in the mountains in South Tyrol, Italy. The midweek half-day excursion has always been very relaxing and inspiring, especially under the guidance of Albert, who had extensive knowledge of the geography, history and culture of the area.

Albert had organized the course in such a way that lectures on laboratory methods and interpretation were closely linked to those on clinical diagnosis. A number of workshops on both clinical and laboratory topics were a part of the program. In this way both types of students, laboratory specialists and clinical geneticists, could get the real essence of 'clinical cytogenetics'. They could understand the nature and challenges of each other's work.

Professor Albert Schinzel was first and foremost a teacher and a mentor. He had the knack of involving the students in discussions, making individual and group photos and creating an atmosphere of togetherness; many students kept in touch with each other and with some teachers for years afterwards.

Albert, who was always fully involved in the organization, teaching and guiding discussions, was very sorry that he was unable to be present at the 2025 course. A Goldrain course without Albert Schinzel is difficult to imagine. However, those of us who have been a part of the faculty, will continue the course in honour of Albert's legacy.

On the website of the Goldrain course you can find a personal note 'Remembering Albert' by Mariano Rocchi, the new director of the Goldrain course, who worked closely with Albert Schinzel in recent years, at http://www.biologia.uniba.it/SEC/

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

Permanent Working Group Reports

Animal, plant, and comparative cytogenetics
Co-ordinator **Pat Heslop-Harrison**

The PWG session on Animal, Plant, and Comparative Cytogenomics showcased the remarkable power of integrating classical chromosome studies with cutting-edge genomic and bioinformatic analyses to address fundamental questions across a wide range of organisms. The speakers presented diverse work, from the mechanisms of genome expression to the resolution of complex evolutionary histories and the application of cytogenetics in livestock.

The first speaker, **Alla Krasikova** from Saint-Petersburg State University, presented a technical tour-de-force on the transcriptional activity of tandem repeats, entitled "Retrotransposable elements drive transcription of tandem repeats". Using the elegant model of lampbrush chromosomes from chicken oocytes, her work addressed how the transcription of these repetitive sequences is initiated. By combining strand-specific RNA-seq on T2T genome assemblies with stunning DNA-RNA FISH visualisations, she demonstrated that transcription is not random. The data strongly support the hypothesis that retrotransposable elements, including Long Terminal Repeats (LTRs) of retrotransposons, act as promoters, that drive transcription of adjacent tandem repeat arrays. In contrast, chromosome-specific centromeric repeats lacking these elements remained transcriptionally silent. This research provides crucial insights into the regulation of the non-coding genome and the functional roles of RNAs derived from tandem repeats.

This was followed by a presentation from **Ioana Nicolae** of the R&D Institute for Bovine, Romania, on "Cytogenetic investigations in Romanian Black and White Spotted cattle". Her talk highlighted the continued importance of cytogenetic screening in animal breeding and health. An investigation of 78 females from the Romanian Black and White Spotted breed revealed that a significant number (27) exhibited chromosomal instability, including breakages and gaps. These chromosomal abnormalities were phenotypically linked to a range of reproductive problems, such as repeated inseminations, pregnancy loss, and congenital malformations. The findings underscore the value of cytogenetics as a diagnostic tool for improving livestock health and productivity, with potential links between genetic instability and environmental factors.

Next, **Alessia Daponte** from the University of Bari “Aldo Moro” presented a powerful new bioinformatic tool in her talk, "Unraveling the genetic architecture of centromeres with CENdetectHOR". Addressing the challenge of analysing highly repetitive centromeric DNA, even in the era of complete telomere-to-telomere (T2T) assemblies, her group developed CENdetectHOR. This computational pipeline can identify and annotate Higher-Order Repeat (HOR) arrays without prior genomic information. Validated on the human T2T genome and then applied to great apes, the tool successfully uncovered complex evolutionary dynamics, such as the massive homogenisation of centromeric repeats in the orangutan and allowed for the detailed modelling of HOR array origins, demonstrating its utility for closing critical gaps in our understanding of chromosome structure and evolution.

Tony Heitkam from the Leibniz Institute of Plant Genetics and Crop Plant Research then took the audience through "The Crocus Chronicles," unravelling the century-old enigma of saffron's origin. Saffron (*Crocus sativus*) is a sterile triploid, propagated clonally for 4,000 years. Using comparative multi-colour FISH,

Heitkam's team demonstrated conclusively that saffron is an autotriploid, originating from a hybridisation event between heterogeneous cytotypes of its wild progenitor, *Crocus cartwrightianus*. The talk highlighted why a chromosomal perspective is essential, as the chromosome-specific haplotype diversity in the progenitors is not visible with molecular markers alone. The presentation also bridged to modern genomics, discussing an ongoing project to assemble the saffron genome and investigate how somaclonal and epigenetic variation has accumulated across different accessions of this ancient clone.

The final talk of the session, "Repetitive DNA sequences mark genome boundaries in the terrestrial orchid *Epipactis*," was presented by **Paulina Tomaszewska** from the University of Wroclaw. This work tackled the taxonomically challenging *Epipactis* genus, where phenotypic plasticity makes species identification difficult. By integrating survey sequencing, Repeat-Explorer analysis, and chromosome in-situ hybridization, the study revealed that the repetitive DNA landscape provides clear evolutionary insights. Two major evolutionary branches within the genus could be distinguished by the presence or absence of specific repetitive elements, such as the Tekay retrotransposon and a striking amplification of telomere-like repeats on several chromosome pairs. The talk was a superb example of how detailed cytogenomic analysis of the repeatome can resolve complex phylogenetic relationships where other methods fall short.

Overall, the session demonstrated how chromosome-level analysis, when combined with advanced sequencing and bioinformatics, is central to advancing modern research.

Chromosomes' integrity, stability, and dynamics

Co-ordinators **José Garcia-Sagredo, Emanuela Volpi**

Exploring new chromosomal paradigms for precision medicine and early disease detection.

The meeting was convened and chaired by the PWG Coordinators, José Garcia-Sagredo and Emanuela Volpi. The meeting had a strong turn-out, indicating a renewed interest within the ECA in foundational, cross-sectional topics that have been consolidated under this expanded group following its rebranding in 2023.

This year's meeting theme was "Exploring New Chromosomal Paradigms for Precision Medicine and Early Disease Detection." The central question addressed by the invited talks was whether disruptions in chromosomal functions, beyond their mechanistic significance in pathobiology, could provide valuable insights for expanding the range of molecular biomarkers used in disease management, especially for early diagnosis. The talks explored this question from various perspectives and with different approaches.

The first presentation was given by **Ulrike Mau-Holzmann** from the University of Tübingen, Germany (P1085), and focused on long-term radiation-induced genomic instability. Ulrike presented several case studies involving leukaemia patients in remission who showed persistent evidence of chromosomal damage in their skin fibroblasts, even twenty years after undergoing allogeneic stem cell transplantation following total body irradiation. These findings support the clinical value of systematically monitoring cytogenetic changes in patients who have undergone such treatment regimens.

The second presentation was delivered by **Claudia Oliveira** from the Unit for Multidisciplinary Research in Biomedicine in Porto, Portugal (P1013). Claudia reported on the applicability of the DEB test, which is considered the gold standard for diagnosing Fanconi Anaemia, in identifying cases of intermediate chromosomal instability. This category includes individuals who do not have a specific diagnosis.

The evidence of compromised DNA repair could have implications for treatment strategies. This highlights the need for further investigation into the causes of intermediate chromosomal instability and its clinical consequences.

The third presentation was given by **Zuzanna Graczik** from the Institute of Human Genetics PAS in Poznan, Poland (P1026). Zuzanna shared the results of her research, which aimed to determine whether the positioning of chromosomes within the nucleus of spermatozoa is associated with improved motility, morphology, or higher fertilisation potential. Her findings indicated that high-quality sperm, selected through fractionation, exhibited specific chromatin characteristics and chromosomal positioning. This suggests that targeted selection based on chromatin dynamics could enhance assisted reproductive technologies (ART).

Radhia M'kacher, a scientist and entrepreneur, and the founder of Cell Environment in Evry-France, gave the fourth and final presentation (P1096). Radhia reported the outcomes of her interesting study on the impact of telomere dysfunction on peri-centromeric and centromeric fragility, chromatin decondensation, and genomic instability. Radhia's research provides novel evidence of a correlation between telomere dysfunction and centromere involvement in chromosomal aberration formation, also suggesting that centromeric sequence configuration in nuclei might serve as a biomarker of genomic instability.

As always at the ECA conferences, the PWG satellite meetings serve as valuable networking opportunities, fostering informal encounters and catalysing scientific exchanges that persist throughout the conference and beyond. The PWG Coordinators would like to thank the speakers for their excellent contributions, as well as everyone who attended and asked questions and contributed to the general discussion. We look forward to seeing everyone again in 2027.

Clinical and molecular approaches to cytogenetic syndromes & cytogenomics

Co-ordinators **Joris Vermeesch, Anna Lindstrand, Damien Sanlaville**

The PWG session brought together a diverse range of presentations highlighting recent advances in cytogenomic technologies and their application to clinical diagnostics of rare and complex disorders. The presentations illustrated how novel methods, from high-resolution array analyses to short- and long-read genome sequencing and epigenomic profiling, are expanding our ability to detect and interpret structural variation underlying human disease.

The session began with **Paola Evangelidou**, describing a particularly complex case of a male patient with a DiGeorge-like phenotype carrying three distinct mosaic copy number variants on chromosome 22. Building on this theme of structural complexity, **Caroline Schluth-Bolard** presented an unusual mechanism of disease : *FGF14* disruption through chromoanagenesis, leading to spinocerebellar ataxia.

Martine Doco-Fenzy revisited inv-dup-del and dup-trp rearrangements using array-CGH and optical genome mapping. Her talk emphasized how complementary approaches can refine breakpoint characterization and better delineate genomic architecture.

Continuing with methodological perspectives, **Lusine Nazaryan-Petersen** demonstrated the capacity of short-read whole genome sequencing to detect structural variants for genetic diagnosis, while **Marlene Ek** showed how long-read genome sequencing can further improve diagnostic yield in pediatric neurological disorders.

The final two talks focused on the X chromosome: **Igor Lebedev** proposed integrating X inactivation status for improved CNV classification, and **Esmee ten Berk de Boer** presented the use of long-read sequencing and the T2T reference to investigate X-inactivation patterns in X-autosome translocations.

Prenatal diagnosis

Co-ordinators

Rosario Pinto Leite, Jean-Michel Dupont

NIPT survey in Europe

Ten years after the wide spread use of Non-Invasive Prenatal Testing (NIPT) in clinical settings, the PWG decided to hold a survey on the implementation of this technology in European health services. The results of the survey were presented during the PWG meeting. These results will be published in the next newsletter in July.

Apart from the results of the survey on NIPT, there were four presentations that had been selected from the submitted abstracts.

Alla Vardanyan from EcoSense laboratory in Yerevan, Armenia, reported on the 8-year experience with NIPT in her country, mainly performed in various private laboratories abroad. She presented a cohort of 1,604 women tested because of increased risk after first trimester fetal screening, with an overall positive rate of 3%. The laboratory offers sex aneuploidy testing as well as microdeletion testing. There was one case of a derivative chromosome 4, arising from a paternal t(4;13)(p15.1;q32) reciprocal translocation, responsible for Wolf Hirschhorn. They also report on an unexpected significant increase in T21 findings in 2021 that they claim is associated with stress induced by COVID-19 pandemic and war in Armenia.

Maria Antonia Caro Miró (first author: Maria Rosa Martorell Riera is) from Palma de Mallorca University hospital reported on the implementation of NIPT services in Balearic Islands public hospitals starting in 2018. Main reason for referral is again positive first trimester screening, with cut-offs for high risk and intermediate risk set at 1/51 and 1/1200 respectively. The service relying on whole genome sequencing offers screening for rare autosomal trisomies and large segmental imbalances with an assessment on a case-by-case basis of the appropriateness of confirmatory invasive testing.

Kevin Cassinari from Rouen University hospital in France presented an interesting case of jumping-like translocation in prenatal setting. This rare chromosome rearrangement is associated with one breakpoint on one receptor chromosome and three different donor chromosomes in different cell lines, leading to different imbalances in each clone: duplication 2q, 3p or 15q associated with the same 15q deletion. The authors presented the different strategies and tools used to decipher this complex case and the limitation of each of them.

The last presentation by **Nicolas Chatron** from Lyon University Hospital in France (first author: Vanessa Del Vitto) addressed the performance of shallow sequencing of cell free DNA compared to arrayCGH for chromosomal analysis in cases of miscarriage. The main issue of standard of care procedure is the complexity of getting access to biological material; using cell free DNA would enable this obstacle to be circumvented. The authors claim that cf DNA reduces the failure rate while most of the results are fully concordant between the two techniques. More work on the bioinformatic pipeline is nevertheless needed to improve the accuracy and reduce the error rate.

Plenary Sessions

Plenary session 1 - Structural variation in health and disease
Chaired by Joris Vermeesch and Anna Lindstrand

The opening plenary session brought together four leading researchers exploring the complexity, diversity, and clinical relevance of structural variation in the human genome. The talks highlighted how the integration of long-read sequencing, optical genome mapping, and population-scale datasets is transforming our understanding of how genomic architecture shapes human diversity and disease susceptibility.

Alexandre Reymond opened the session with a presentation on "*The pleiotropic spectrum of proximal 16p11.2 CNVs*." He described the diverse types of rearrangements occurring in this hotspot region, driven by its complex genomic architecture. Using the UK Biobank, his group has delineated mirror phenotypes—autism versus autism spectrum features, macrocephaly versus microcephaly, and obesity versus underweight—associated with reciprocal 16p11.2 deletions and duplications. The CNV acts both as a direct disease cause and a phenotypic modifier, with 46 significant genotype–phenotype associations identified for the BP4–BP5 rearrangements. Reymond emphasized that while deletions are enriched in clinical cohorts, they are not absent in population samples, reflecting variable expressivity and incomplete penetrance across carriers.

David Porubsky followed with a talk on "*Structural variation of the 22q11.2 region in normal and diseased human populations.*" Leveraging the T2T reference genome and the Human Pangenome, he and his team have mapped 135 distinct haplotypes across this complex region. His analysis revealed striking population diversity, with larger and more structurally variable haplotypes particularly frequent among African genomes. The results demonstrate how pangenomic representations can capture genomic diversity invisible to single-reference analyses, providing new insight into the mechanisms underlying recurrent rearrangements at 22q11.2 and their role in disease.

In the third presentation, **Tobias Marschall** introduced the *Verso Assemble* pipeline, a novel approach for mapping structural variation in the context of the human pangenome. His work focuses on genes and genomic loci that are poorly resolved by conventional reference-based pipelines. The method allows more accurate assembly and comparison of structurally variable regions, enabling precise identification of allelic variation that may impact gene function and disease risk. Marschall's work illustrates the importance of computational innovation in leveraging the power of pangenomic data for SV discovery.

Finally, **Nivin Moustafa-Hawash** presented a clinical perspective with "*Optical genome mapping in the clinic reveals germline and somatic findings.*" Drawing on results from 700 analyzed cases, she demonstrated how optical genome mapping (OGM) can detect a wide range of clinically relevant rearrangements in both constitutional and somatic settings. Overall, this plenary session underscored the convergence of technological, computational, and population-based advances in unraveling structural variation. Together, the talks painted a vivid picture of how emerging pangenomic and optical approaches are reshaping our understanding of the genomic underpinnings of human health and disease.

Plenary session 2 - Complexity of cancer genomes
Chaired by Roberta Vanni and Barbara Dewaele

This year's ECC conference featured a thought-provoking plenary session on the *Complexity of Cancer Genomes*. The session brought together experts who presented cutting-edge research on the genomic intricacies underlying cancer, with a particular focus on sarcomas, chromosome

segregation errors, and lymphoid malignancies. Discussions underscored the potential of emerging technologies in dissecting complex karyotypes and their role in diagnosis, prognosis, and treatment stratification.

Jonas Demeulemeester (University Hospitals Leuven, Belgium) opened the session with a presentation entitled *"Comprehensive multi-modal profiling to advance sarcoma precision oncology and clinical care."* He emphasized the limitations of current sarcoma diagnostics, which rely on sequential tests, including NGS panels, FISH, arrays, and karyotyping. To overcome these barriers, his group developed an innovative, multimodal approach that integrates fiber sequencing genotyping, nanopore direct RNA sequencing, and mass spectrometry. This strategy leverages the strengths of each technology: fiber sequencing enables the detection of mutations, epigenetic, and chromatin modifications; nanopore RNA sequencing captures full-length transcripts; and mass spectrometry provides complementary proteomic data. Compared with an Optical Genome Mapping (OGM) validation cohort, this platform outperformed existing methods, including accurate sarcoma classification based on epigenetic signatures. By significantly reducing diagnostic turnaround time to under 10 days, this multi-omics approach not only enhances diagnostic resolution but also paves the way for the discovery of novel biomarkers and more precise therapeutic targeting.

Stefano Santaguida (European Institute of Oncology and University of Milan, Italy) followed with an outstanding presentation entitled *"Mechanistic insights into the consequences of chromosome segregation errors on cell physiology."* Aneuploidy induces significant chromosomal changes and plays a critical role in cancer by affecting the expression of hundreds of genes, thereby disrupting the homeostasis of untransformed cells. While the consequences of aneuploidy are well established, its underlying mechanisms remain incompletely understood. To further investigate this phenomenon, Santaguida and colleagues induced random aneuploidies by transiently inhibiting the mitotic checkpoint protein MPS1. This interference led to the formation of micronuclei, small, extranuclear bodies that act as hubs for cellular signaling. The researchers hypothesized that the rupture and repair dynamics of micronuclei membranes might differ from those of the primary nuclear envelope. Their study revealed that components of the autophagy machinery, particularly the autophagic receptor p62, localize to micronuclei, where they exert localized control over micronuclear activity. They observed that approximately 50% of micronuclei exhibited enrichment of p62, along with signs of DNA damage and membrane rupture. Specifically, these micronuclei displayed partial loss of their outer membrane and disruption in the inner membrane, suggesting that p62 plays a role in regulating micronuclear membrane integrity. Furthermore, the researchers found that the proximity of micronuclei to mitochondria influenced the oxidation of p62, promoting micronuclear rupture. This supported their hypothesis that p62 drives micronuclear collapse and chromosomal rearrangements by inhibiting membrane repair.

Amber Verhasselt (Catholic University of Leuven, Belgium) then presented her selected oral abstract entitled *"Optical Genome Mapping is a powerful diagnostic tool in non-Hodgkin lymphoma."* She demonstrated that OGM offers a high-resolution, genome-wide view of structural variants and copy number alterations, enabling detection of clinically actionable Tier I and II aberrations in over 90% of cases—including 98.3% of class-defining aberrations. Moreover, OGM increased diagnostic yield by identifying additional aberrations in 40 cases and rescuing 27 cases that had failed chromosome banding analysis, with a detection limit of 10–15% aberrant cells. Her data reinforce the value of OGM as a robust diagnostic adjunct in the evaluation of aggressive B-cell lymphomas.

The session concluded with a selected abstract presentation by **Şule Altiner** (Turkey), entitled *"Cytogenetic profile of hematological malignancies with complex karyotype: a single-center study from Turkey."* This large-scale

cytogenetic study analyzed over 16,400 patients, identifying complex karyotypes—strong predictors of poor outcome—in 2.35% of cases. Recurrent abnormalities were highlighted in acute myeloid leukemia and myelodysplastic syndromes, providing insights from a regional perspective and emphasizing the need for standardized cytogenetic assessment in hematologic cancers with complex karyotypes.

In summary, this plenary session highlighted the growing need for integrative genomic approaches to decipher the complexity of cancer genomes. The combination of cytogenetics, long-read sequencing, OGM, single-cell analyses, and proteomic profiling is poised to transform cancer diagnostics and therapeutics, enabling faster, more accurate, and clinically actionable insights.

Plenary Session 3 - Clinical Cytogenomics
Chaired by Damien Sanlaville and Orsetta Zuffardi

The session provided a deep insight into how new genomic technological approaches help in clarifying genotype-phenotype correlations.

Thomas Bourgeron highlighted the relationship between neuroanatomical variations, such as cortical thickness, and differences in autism-related symptoms and traits, where possible, with molecular correlations.

Jesper Eisfeldt illustrated the advantages of long-read genome sequencing in deciphering complex rearrangements, illustrating his talk with fantastic figures that made it easier to understand the rearrangements and emphasizing how frequently their complexity remains hidden by other approaches.

Andrea Ciolfi demonstrated how DNA methylation profiling can be a valuable tool for achieving a definitive clinical diagnosis. He also emphasized that some Mendelian disorders, that are associated with variants in multiple genes, exhibit overlapping genome-wide DNA methylation profiles, regardless of which gene is responsible for the disease**.**

Dominik Rezny, whose abstract was selected for oral presentation, showcased his laboratory's expertise in optical genome mapping and long-read sequencing to improve the clinical understanding of disorders caused by structural variants.

Plenary Session 4 - Animal, Plant and Comparative Cytogenomics
Chaired by Pat Heslop-Harrison and Mariano Rocchi

The plenary session on Animal, Plant, and Comparative Cytogenomics provided a sweeping overview of the field's current frontiers, demonstrating how integrating chromosome biology with advanced genomics is resolving long-standing questions in evolution, agriculture, and biomedicine. The talks spanned from the fundamental principles of 3D genome architecture to the practical applications of cytogenomics in conserving crop diversity and understanding disease resistance.

The session was opened by **Aurora Ruiz-Herrera** from the Universitat Autònoma de Barcelona, who presented on the "Evolution and function of 3D chromatin folding". Her talk explored the evolutionary plasticity of genomes, from species with over 100 small chromosomes to those with only a few large ones. Using genome-wide Chromosome Conformation Capture (Hi-C) across a wide range of mammals, her group has shown how genome and chromosome size directly modulate the patterns of chromatin folding. She presented powerful data from natural mouse mutants with chromosomal fusions, using them as a model to study evolution in action. Stunning Hi-C heatmaps revealed how these

fusions completely reorganize chromosome territories and interaction patterns, providing a mechanistic link between large-scale structural variation and the 3D organization of the genome in the germline.

Next, **Julie Sardos** from the Alliance of Bioversity International and CIAT in Montpellier discussed the vast genetic diversity of a globally important crop in her talk, "Diversity and diversification in banana: how in silico chromosome painting opens new perspectives for the conservation and use of an iconic fruit". In contrast to other clonal crops that show little variation, banana cultivars are genetically complex. Sardos introduced *in silico* chromosome painting, a powerful SNP-based approach to provide a fine-scale identity to cultivars by identifying their ancestral genomic contributors. This method is a game-changer for managing the world's largest banana collection (housed in Leuven), allowing for the identification of clonal diversification events, filling gaps in collections, and enabling a much wiser use of banana genetic resources for future breeding and food security.

The broad impact of the field was summarized by **Pat Heslop-Harrison** from the University of Leicester in his talk, "What cytogenomics has done, and is doing, for agriculture in our world". He highlighted that genetics has driven about half of all improvements in crop yields. Using examples from cereals, forage grasses, and livestock, he illustrated how chromosome biology has been fundamental to genetic improvement. Techniques like in situ hybridization have been invaluable for tracking the introgression of alien chromosomes in breeding programs and for understanding the nature of hybrids. The talk also emphasized the role of rapidly evolving repetitive DNA, such as transposons, not only as markers but as drivers of diversity and modulators of gene expression, underscoring the central role of cytogenomics in solving real-world agricultural challenges.

The session then moved to comparative animal biology with a talk by **Simon Mallet** from Lienss, Evry-France, titled "Interstitial telomeric sequences and accumulation of DNA damage hallmarks of genomic instability in cancer resistant wild vertebrates". In a fascinating study, his team investigated the basis of cancer resistance in ten different wild animal species. Counter-intuitively, they discovered that the genomes of cancer-resistant species harboured significant hallmarks of genomic instability. Specifically, they found a strong correlation between the presence of large blocks of interstitial telomeric sequences (ITS) and an increased frequency of DNA damage markers like micronuclei. This work highlights a novel and unexpected paradigm, linking a surprising degree of underlying genomic instability to the evolution of cancer resistance in the wild.

The final presentation was given by **Fengtang Yang** of Shandong University of Technology, who spoke on the "Genomic complexity and evolutionary plasticity ın *Dugesia japonica* revealed by multi ploidy chromosome level assemblies". The planarian *D. japonica* is a key model for regeneration, but its complex, repeat-dense, and variably polyploid genome has been a major challenge to assemble. His team generated four high-quality, chromosome-level assemblies using a combination of long- and short-read sequencing technologies. The 1.9 Gb haploid genome was found to be 75-79% repetitive, with Maverick DNA transposons dominating the landscape. These elements were found to be preferentially located in promoter regions, suggesting a key

role in gene regulation. This work provides an exceptional resource for the field and offers new insights into genome plasticity and the evolutionary role of repetitive elements.

The session powerfully demonstrated that cytogenomics continues to be a fundamental discipline, offering profound insights into genome evolution, agricultural innovation, and biological complexity across diverse organisms.

Plenary Session 5 - Prenatal Diagnosis and Preimplantation
Chaired by Elisabeth Syk Lundberg and Rosario Pinto Leite

The last Plenary session of the Conference was dedicated to different aspects of prenatal testing and possible prenatal treatment. The session included two invited speakers and one selected oral presentation.

The first invited speaker was **Alan Handyside** from University of Kent, UK. He could not attend the meeting in person but was fortunately able to give his presentation on-line after some technical problems. He gave a talk on preimplantation genetic testing for aneuploidy (PGT-A). This method is 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, 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 develop¬mental 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.

The next talk was presented by **Nathalie Janel** from Université Paris Cité, France. She used a mouse model to investigate the possibility to treat some of the symptoms caused by trisomy 21. Neuroinflammation and microglial activation have been reported in fetuses and children with Down syndrome (DS) and may cause defects in neurodevelopmental processes. 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. They therefore investigated the potential effect of sPIF on 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. Treatment with sPIF has no negative effect on vital functions and enhanced the Dp(16)1Yey pups' social com¬munication. Moreover, it rescued the impairment in hippocampal-dependent working memory in adult Dp(16)1Yey mice. At the cellular level, treatment with sPIF restored 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. In conclusion, sPIF treatment had neuropro-

tective effects in a mouse model. The present results further strengthen the hypothesis that cognitive dysfunction linked to gene deregulation may be corrected.

The last talk was a selected oral presentation by **Charlotte Tardy** from the Genetics department, Lyon University Hospital, France, who addressed the problem of balanced chromosomal rearrangements detected during prenatal karyotyping. Forty percent of de novo balanced rearrangements carried by symptomatic patients may be considered pathogenic after breakpoint characterization in a postnatal setting. Their project ARPAGON (Analysis of Rearrangements in Prenatal Assessment using Genomic Oxford Nanopore Sequencing) aims at demonstrating the feasibility of such characterization in a time window compatible with pregnancy management. So far, three fetuses harbouring a reciprocal translocation identified via fetal karyotyping, prompted by ultrasound anomalies and confirmed balanced after CMA, have been studied. In all cases nanopore sequencing outperformed conventional methods in terms of resolving balanced chromosomal rearrangements and was compatible with prenatal testing.

Concurrent Sessions

Concurrent session 1 - Meiosis and Mitosis
Chaired by Elisabeth Syk Lundberg and Jean-Michel Dupont

The first concurrent session was dedicated to cell division and mechanisms leading to aneuploidy which is a prominent cause of genomic imbalance with a huge impact in medical genetics.

Two speakers were invited to present their research focused on the meiotic to mitotic transition and the mechanism of Mosaic Variegated Aneuploidy.

Marta de Ruijter-Villani from Utrecht University in the Netherlands addressed the question of the control of correct segregation of chromosomes during the first cell division after fecundation. Because bovine oocytes are similar to human oocytes in terms of size and duration of the first division, with a similar rate of aneuploidy in embryos, they were selected as a model for imaging the successive steps of the first mitotic division. During its maturation, the oocyte loses its centrosome and the zygote relies on the paternal centrosomes brought in by the sperm. Real-time imaging showed that the distal sperm centrosome which has a v-shaped morphology was associated with the paternal pronucleus while the proximal sperm centriole was always associated with the maternal pronucleus. Both have a different composition compared to the canonical centrosome and although the usual microtubule nucleation role is mainly driven by the chromosome in the zygote, centrosome maturation is a critical step leading to blockage at the two-cell stage when impaired. Imaging of embryos showed a 50% dysfunction rate of centrosomes (altered position or impaired microtubule nucleation), similar for both, associated with a delayed alignment of chromosomes and increased mis-segregation at anaphase.

In line with previous papers, these results highlight critical aspects of the control of the first mitotic cell division and new pathways to aneuploidy.

Also from Utrecht University, the second speaker, **Carolina Villarroya-Beltri** used Mosaic Variegated Aneuploidy (MVA) as a model to understand the effect of aneuploidy on the whole body. MVA is a rare condition where dysfunction of the Spindle Assembly Checkpoint (SAC) results in a high rate of aneuploid cells (up to 40% of all patient's cells), with different chromosomes involved in different cells but almost exclusively chromosome gains (no monosomies). This high rate of aneuploidy is associated with developmental defects and a high risk of cancer. In a patient affected by MVA, compound heterozygous mutations in MAD1L1 leading to reduced BUBR1 protein was responsible for SAC

dysfunction and nuclear anomalies. But they could also show that the 40% rate of peripheral blood cells with different aneuploidies was associated with an abnormal immune system expression and increased inflammation. The inflammatory response against aneuploid cells was mediated by the expansion of non-canonical T-cell clones.

In mouse models, they could more precisely show that aneuploidy can affect the T-cell repertoire against lamina propria of intra epithelial cells. These results highlight how affected cells that have a tumoral evolution will first compensate for the negative effects of aneuploidy before they start neoplastic transformation. Heterozygous individuals for mutations in critical SAC proteins face a high risk for aneuploidy as well as increased susceptibility to cancer and premature aging.

Concurrent Session 2 - Automation and AI in Clinical Genetics
Chaired by Barbara Dewaele and Franck Pellestor

This session highlighted the growing impact of digital technologies and artificial intelligence in modern clinical cytogenetics and genomics. Two experts presented how computational tools are revolutionizing diagnostic workflows, data interpretation, and the accessibility of genomic information.

Claudia Haferlach (MLL – Munich Leukemia Laboratory, Germany) opened the session with her presentation entitled “Application of AI in Hematological Diagnosis.” She detailed the integration of machine learning algorithms into routine laboratory practices to improve the accuracy and efficiency of diagnosing hematological malignancies. Through machine learning (ML) and deep learning (DL) algorithms, Artificial Intelligence is widely used to automate complex diagnostic processes. These include blood sample analysis, chromosome sorting for karyotyping, and predicting disease progression and treatment outcomes. Haferlach presented real-life examples where AI-assisted image analysis and pattern recognition have significantly improved cytogenetic analysis, including automated karyotyping. Her talk highlighted the potential of AI not only as an automation tool, but also as a partner in diagnostic decision-making. This AI-powered predictive technology promises to revolutionize the management of hematological diseases by predicting their progression and individual responses to treatments. By analyzing trends in historical clinical data, AI can suggest personalized treatment strategies and improve patient outcomes.

The second presentation, titled "Online Resources at UCSC," was given by **Robert Kuhn** (UCSC Genome Browser, Santa Cruz, USA). As a key figure in the UCSC Genome Browser project, Kuhn provided an update on the platform's latest features, highlighting its usefulness for clinical and research cytogeneticists. The UCSC Genome Browser offers an intuitive graphical interface for visualizing and analyzing clinical copy number variation (CNV) data and other genomic information. In this highly informative and didactic talk, Kuhn demonstrated how the browser enables intuitive visualization. He also shared numerous practical tips and lesser-known features of the browser—tricks that have proven so useful that many Participants wished they had known about them much sooner! His presentation reaffirmed the indispensable and evolving role of the UCSC Genome Browser in genomic medicine.

This session clearly demonstrated that AI and digital platforms are not future trends, but current tools reshaping the landscape of clinical genetics. These presentations made it clear that the combination of AI-derived insights and comprehensive genomic platforms clearly improves diagnostic accuracy, streamlines laboratory workflows, and facilitates the personalization of patient care. As the field evolves, the synergy between automation, human expertise, and open-access resources will be essential to deliver accurate and rapid genomic diagnostics.

Concurrent Session 3 - Nuclear organisation and disease
Chaired by Emanuela Volpi and Pat Heslop-Harrison

The third concurrent session focused on the role of nuclear organisation in the context of disease, with three presentations on the molecular and epigenetic underpinnings of rare genetic disorders. Chaired by Emanuela Volpi and Pat Heslop-Harrison, the session discussed many aspects of nucleolar dysfunction, epigenetic reprogramming, and the detection of structural variants in whole genome sequencing.

Martin Mensah began the session with his talk, "Nucleolar Dysfunction in Rare Genetic Diseases." Martin presented research on Brachyphalangy, Polydactyly, and Tibial Aplasia Syndrome (BPTAS), an ultra-rare multiorgan malformation disorder. The study identified a novel de novo frameshift mutation in the HMGB1 protein, specifically affecting its C-terminal acidic intrinsically disordered region (IDR). This mutation replaces the IDR with an arginine-rich basic tail, altering HMGB1's phase separation properties and increasing its nucleolar partitioning, ultimately causing nucleolar dysfunction. The research highlighted that frameshift-induced IDR swapping could be a novel disease mechanism and may explain other unidentified pathogenic variants in IDRs.

Next, **Cristina Cardoso** presented "Epigenetic Reprogramming and Disease", discussing the role of a DNA methylation reader (MeCP2) in heterochromatin organisation. Mutations in the MECP2 gene are linked to Rett syndrome, a severe neurological disorder. The presentation explained how MeCP2 forms liquid-like droplets through multivalent electrostatic interactions, a process enhanced by crowded environments and DNA but restricted by DNA methylation. The study demonstrated that MeCP2's self-interaction is vital for its liquid-liquid phase separation (LLPS) and is disrupted by Rett syndrome mutations. These findings advance our understanding of heterochromatin dynamics and its regulation.

Finally, **Lusine Nazaryan-Petersen** discussed "Detection of Structural Variants by Short Read Whole Genome Sequencing and Interpretation for Genetic Diagnosis" and outlined the use of whole genome sequencing as a diagnostic test. Their comprehensive pipeline detects a wide array of structural variants (SVs), from copy number variations and insertions to complex rearrangements like chromothripsis to provide genetic diagnoses. The diagnostic yield for likely pathogenic SVs varies by patient group, reaching approximately 5% in critically ill children.

Collectively, these talks highlighted how nuclear architecture, from nucleolar structures to chromatin dynamics and SV detection, impacts disease mechanisms and diagnostics. Using interdisciplinary molecular, cytogenetic and bioinformatic approaches, along with phenotypic characterization, genetic diagnoses.

Concurrent Session 4 - Clonal correction of constitutional chromosome imbalances
Chaired by Damien Sanlaville and Orsetta Zuffardi

This session illustrated those mosaic situations, whether overt or hidden, confined to a single tissue or expanded to multiple tissues, that are created within each of us and that can have either positive or negative effects on an individual's health. If the cell that acquires a new DNA conformation has a good survival ability, or a higher survival ability than the original one, a clone will form. Many studies have explored and are exploring the links between ageing and clonal hematopoiesis. The phenotypic effects of clonality are less well understood in individuals with constitutional genomic and/or chromosomal alterations.

Diane van Opstal emphasized the complexity of trisomic rescue by demonstrating that the entire

process can involve multiple events during early embryogenesis, leading to various types of mosaicism. Cell lines with uniparental disomy for an entire chromosome or with structural abnormalities involving a chromosome different from the original in trisomy may, when present in critical fetal tissues, account for the abnormal phenotype in undiagnosed cases.

Alfredo Brusco showed that constitutional variants, whether single-nucleotide or structural, are often accompanied, at least in blood, by two or more cell lines, where somatic recombination has replaced the original variant. The result is a normal genome, except for the presence of a chromosomal region with copy-neutral loss of heterozygosity (CN-LOH), which typically involves a segment much larger than that affected by the single-nucleotide mutation or the structural variant. A common finding is the presence of segmental uniparental disomy regions of various sizes, all of them encompassing the original variant. The phenotypic outcomes of this type of mosaicism, secondary to somatic recombination events, are more pronounced in certain conditions affecting single tissues and less so in others, where the genes involved in deletion or duplication are expressed across multiple tissues.

Anikó Ujfalusi presented the selected abstract, demonstrating the potential of new technological approaches in clarifying several rearrangements involving the X chromosome.

Concurrent Session 5 - Accreditation and workshop on ISCN
Chaired by Franck Pellestor and Harald Rieder

The concurrent session 5 focused on 2 very important aspects of cytogenetics laboratory practice: the accreditation process and the latest recommendations of the International System for Human Cytogenomic Nomenclature (ISCN). Two speakers were invited for this session.

The first speaker, **Konstantin Miller**, from the Hannover Medical School, gave a very clear, informative, and well-researched presentation on the ISO 15189 standard and its application in cytogenetics laboratories. This presentation greatly interested the participants who came to learn about the implementation of the new edition of ISO 15189 and the key points to remember for cytogenetics laboratories. The new edition of ISO 15189 :2022 establishes an updated international framework for the quality and competence of medical laboratories, serving as an essential basis for their accreditation. The revision closely aligns with ISO/IEC 17025, as well as the general quality management principles outlined in ISO 9001. Miller presented significant updates related to ensuring impartiality and confidentiality within medical laboratories, strengthening requirements for patient-related procedures, and establishing measurable objectives. Other key aspects include comprehensive risk management strategies, process requirements, and internal quality controls for review procedures. The standard also addresses participation in external quality assessments, reporting requirements, and rigorous data and information management practices, including cybersecurity measures and emergency risk management. Practical examples illustrating how to avoid nonconformities when implementing these new requirements were provided and discussed, giving attendees a clearer understanding of the standard's implementation.

In the second presentation, given by **Jean Michel Dupont** from Paris Cité University, the latest version of the ISCN 2024 standard was extensively discussed and commented on. Jean Michel Dupont perfectly described the recent essential revisions to the ISCN, reflecting the rapid evolution of cytogenetics. The updated ISCN incorporates major technical advances in molecular cytogenetics and improved rules for representing complex results, while resolving redundancies and inconsistencies between the different chapters. Key additions include a new chapter on optical genome mapping techniques and an expanded chapter on sequencing, featuring many new examples. Chapter 10, on

region-specific analyses, has been expanded to include region-specific analyses using any technique, as well as a new section on the nomenclature of methylation analyses. Each change to the standard was illustrated with examples. Following his presentation, Dupont engaged the entire audience through an interactive presentation of examples to help participants deepen their understanding and effectively apply the revised nomenclature rules. These two presentations, and the updates they included, provided participants with a better understanding of laboratory quality management and the use of cytogenetic nomenclature.

Concurrent Session 6 - Applied Cytogenotoxicity
Chaired by José Garcia Sagredo and Joan Blanco

This session was dedicated to exploring two distinct applications of cytogenotoxicity methodologies: the assessment of the carcinogenic potential of long-term exposure to micro- and nanoplastics (MNPLs), and the detection of radiosensitivity in individuals with inborn errors of immunity (IEI).

Alba Hernández Bonilla, from the Autonomous University of Barcelona, opened the session with a compelling presentation on the potential carcinogenic effects of plastic particles, based on in vitro studies using various cell lines. She began by emphasizing that MNPLs are emerging environmental pollutants now found across all ecosystems. Due to their small size, MNPLs are easily absorbed by the human body, can be distributed systemically, and tend to bioaccumulate in tissues. Hernández Bonilla presented key findings from the EU-funded PlasticHeal project (www.plasticheal.eu/en), which aims to develop innovative methodologies to investigate the health impacts and mechanisms of action of micro- and nanoplastics. Her research focused on the long-term effects of chronic MNPL exposure in cultured cells. The results presented in the session suggest a cause for concern, particularly with stem cells, which showed the most significant adverse responses among the cell types tested. These findings highlight the potential for lasting cellular damage from MNPLs—even after exposure has ceased—and underline the need for further investigation into their carcinogenic risk.

The second presentation, delivered by **Ans Baeyens** from the University of Gent, addressed the clinical importance of evaluating chromosomal radiosensitivity in patients with inborn errors of immunity (IEI). She explained that some forms of IEI are associated with defects in DNA repair mechanisms, making affected individuals highly sensitive to ionizing radiation. This radiosensitivity (RS) can significantly impact the safety and efficacy of radiation-based therapies, emphasizing the need for personalized treatment strategies. Baeyens presented data from a cohort study in which chromosomal radiosensitivity was assessed using the micronucleus (MN) assay. The results revealed considerable variability in radiosensitivity levels across different genetic subtypes. Additionally, age was identified as a factor influencing both spontaneous and radiation-induced micronucleus (MN) formation. Baeyens' findings underscore the importance of implementing targeted radiosensitivity screening in patients with suspected DNA repair defects, to support safer and more personalized therapeutic strategies.

The session concluded with a selected oral presentation by **Marlene EK** from the Karolinska Institute, who highlighted the potential of long-read genome sequencing to enhance the diagnosis of pediatric neurological disorders.

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.

TRIO ANALYSIS IN PREGNANCY LOSS

Aneuploidies are the well-known reason for most of the spontaneous fetal losses in early pregnancy.
In a genomic study of early pregnancy loss, Annadottir et al.1 compared the parental genomes to the that of the aborted fetus in 467 cases. This trio-based whole-genome sequencing showed a high proportion of aneuploidies (206 fetal losses) and triploidies (14 losses). Via the parental genome sequences the authors were able to determine in which parent the genetic error occurred. As expected, 80 percent of the aneuploidies were due to maternal meiotic error (mostly MI). Almost 7 percent of these maternal events occurred before sister chromatid formation in fetal oocytes. Triploidies were of paternal origin in 11 cases due to dispermy and in 19 cases of maternal orgin (mostly by meiotic error). In addition, several cases of large duplications or deletions were found. Compared to adult trios, there was a threefold enrichment of pathogenic small sequence variants (SSVs) in trios of pregnancy loss. The authors suggest that this indicates SSVs are causative in about two thirds of euploid losses. Although this new research approach may not be suitable at present for routine clinical diagnostics, it does allow identification of essential genes and their function in early fetal development. The editorial in Nature by Gao2 gives a handy overview of the different genetic causes of early pregnancy loss. One has to bear in mind, as this editorial points out, that fetal development depends not only on the fetus's own genetic viability but also on several other factors, for example, the maternal genetic variation and the interplay between maternal and fetal genotypes.

[1] https://doi.org/10.1038/s41586-025-09031-w
[2] https://doi.org/10.1038/d41586-025-01706-8

HORSE DOMESTICATION

The domestication of horses illustrates how evolutionary change can be facilitated when key traits are controlled by very few genes.
Liu et al., in a paper which appeared in Science (1), report that a single variant at the GSDMC locus, affecting spinal anatomy, strength, and coordination, had a profound effect on horse rideability.
Because only one (or a few) loci were involved, selective breeding rapidly increased its frequency, demonstrating that domestication is more likely to succeed when a useful trait depends on simple rather than highly polygenic genetic architecture. The paper was accompanied by an insightful commentary (same Science issue).

[1] https://www.science.org/doi/10.1126/science.adp4581

MICRO SEQUENCES WITH RELEVANT FUNCTIONS

Although often overlooked, "micro" elements in the genome can hide crucial biological functions.
Microproteins: Very small proteins encoded by short open reading frames (<100 amino acids) were long dismissed as noise by gene-finding algorithms. Recent ribosome profiling and CRISPR screening, however, have revealed that many are translated and play essential roles in cell growth and regulation (1).
Short tandem repeats (STRs): These repetitive DNA elements, especially those with sequence variability, have been underestimated because short-read sequencing technologies fail to capture them reliably. With long-read sequencing, their impact on gene regulation and phenotypic diversity has become clear (2).
Together, these cases illustrate that the "micro" fraction of the genome, once ignored, can encode key functional elements with significant roles in physiology and disease.

[1] https://www.cell.com/trends/genetics/fulltext/S0168-9525(24)00298-1?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0168952524002981%3Fshowall%3Dtrue
[2] https://genomebiology.biomedcentral.com/articles/10.1186/s13059-025-03754-9

SHOULD CYTOGENETICS BE REPLACED BY MOLECULAR TECHNOLOGIES?

A debate titled "Cytogenetics is a Dinosaur and Should Be Replaced by Molecular Technologies" was held at the 28th International Conference on Prenatal Diagnosis and Fetal Therapy, organized by the International Society for Prenatal Diagnosis (ISPD). It took place in Boston, Massachusetts, in July 2024, and featured a lively exchange between Michael Talkowski and Yassmine Akkari, moderated by Amy Breman.
The debate was summarized in Prenatal Diagnosis (1).
One of the most compelling arguments, in support of cytogenetic, was that cytogenetics is not merely a technique but a science—the science of chromosome organization and behavior. Without this knowledge, new technologies risk remaining sterile tools.
Yassmine Akkari recalled a cartoon in which, in 1997, a renowned scientist stands at a podium declaring "cytogenetics is dead." The same scientist repeats the statement in 2007 and again in 2017. In the final frame, however, it is the scientist who is dead.

[1] https://obgyn.onlinelibrary.wiley.com/doi/10.1002/pd.6847

DECODING ROBERTSONIAN TRANSLOCATIONS

Robertsonian translocations, present in about 1 in 800 humans, are fusions between two acrocentric chromosomes that can cause infertility, miscarriages and trisomies such as Down syndrome. For over a century their origins remained unclear. In 2023, a study in Nature (1) showed that the short arms of human acrocentric chromosomes (13, 14, 15, 21 and 22) share large pseudohomologous regions, including the macrosatellite SST1, and undergo continuous recombination. This discovery provided the first strong evidence that sequence homology between different acrocentrics could facilitate chromosomal exchanges. Now, in a follow-up study by largely the same group of authors, Nature (2) reports the first complete assemblies of three Robertsonian chromosomes. They uncovered a common breakpoint within the SST1 arrays on chromosomes 13, 14 and 21. An inversion on chromosome 14 brings these repeats into the correct orientation to allow a meiotic crossover, fusing the long arms of two chromosomes and eliminating the ribosomal DNA arrays.
The resulting chromosomes carry two centromeric arrays, but usually only one is epigenetically active, ensuring stable segregation during cell division. This combination of sequence homology, structural inversion and epigenetic adaptation explains how Robertsonian chromosomes form and persist.
Taken together, these studies — conducted by essentially the same team — not only resolve a long-standing puzzle in human cytogenetics, but also provide a framework for understanding how structural variants arise and shape genome evolution.

[1] https://www.nature.com/articles/s41586-023-05976-y
[2] https://www.nature.com/articles/s41586-025-09540-8

CHROMOSOMES IN HUMAN EMBRYOS a review

The paper by Ivanova et al. (1) discusses why human embryos frequently carry chromosome abnormalities. Whole-chromosome aneuploidies usually originate during maternal meiosis, with risk increasing markedly with age, whereas mosaicism arises from errors in the first embryonic divisions. In humans, the oocyte meiotic spindle forms without centrosomes. This combined with less stringent checkpoint control, increases the chance of incorrect kinetochore-microtubule attachments, especially merotelic ones, where a single kinetochore attaches to microtubules from both spindle poles, leading to chromosome missegregation. Early embryonic mitoses rely on centrosomes of paternal origin; defects in sperm centrosomes increase the likelihood of mosaicism. Mutations in maternal genes such as TUBB8, MEI1, and PLK4 compromise spindle stability and cohesion, whereas aging reduces cohesion levels and the protection provided by protein shugoshin, resulting to errors at meiosis I. Estimates of mosaicism from preimplantation genetic testing for aneuploidy remain uncertain, underlining the need for closer integration between basic research and clinical practice.

[1] https://www.cell.com/hgg-advances/fulltext/S2666-2477(25)00040-5?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS2666247725000405%3Fshowall%3Dtrue

OVEREXPRESSION STRATEGIES FOR IMPROVED PLANT TRAITS

Scientific publications often tend to overstate the potential impact of their findings. It is only rarely that such claims prove to be truly transformative—classic examples include PCR, CRISPR-Cas9, and RNA editing for vaccines.
A recent paper in Science (1) presents an elegant approach that enables (i) overexpression of a gene in plants and (ii) rapid testing of numerous variants.
How does it work

- A gene of interest is inserted into a geminivirus-based replicon.
- Once inside the plant cell, the replicon self-amplifies: many DNA copies are made, leading to strong expression of that gene (G) but only if G is functional!

That is:

- Replicon replication is engineered to depend on the activity of G:
- If G is expressed, it activates Rep leading to massive replication.
- If G is non-functional, Rep is not activated, leading to no replication.

Parallel testing in one leaf

- Through agroinfiltration, thousands of replicons carrying different variants are introduced into millions of leaf cells.
- Each cell becomes a micro-test chamber.
- Selection and readout
- Functional variants replicate abundantly and dominate.
- Non-functional variants disappear.
- Deep sequencing reveals which variants have been enriched.

In this way, hundreds or thousands of variants of a resistance gene—or of a gene involved in protein, enzyme, or metabolite production—can be tested within just a few days in a single leaf.
Will this work really have a major impact on crop production? Let's wait and see.

[1] https://www.science.org/doi/10.1126/science.ady2167

ON THE "NORMALIZATION" OF MOSAIC EMBRYOS

Since the foundational paper by Vermeesch's group in 2009 (1), it has been well established that chromosome mosaicism arising during the first cell divisions of an embryo is quite common. A second important finding was that mosaic embryos can develop into healthy newborns. The key question then became: how does this "normalization" occur?
A recent paper published on BioRxiv (2), which also involves Vermeesch's group, provides the answers.
The study uses single-cell genome-and-transcriptome sequencing (G&T-seq) on 756 cells from 112 human preimplantation embryos to investigate how chromosomal instability (CIN) affects early development.

- Widespread aneuploidy: About 50% of cells carried numerical or structural chromosomal abnormalities, observed across all developmental stages and lineages.
- Gene dosage effects: Gains and losses of DNA segments caused measurable but stage-dependent changes in gene expression. Gains typically had stronger effect than losses, indicating partial dosage compensation.
- Regulatory network perturbation: Aneuploidy in transcription factor genes altered the expression of their target genes, disrupting gene regulatory networks.
- Developmental delay: Aneuploid cells generally showed slower developmental progression compared to euploid cells within the same embryo.
- Cell competition and fitness: Aneuploid cells displayed stress signatures, reduced metabolic and ribosomal activity, and impaired proteostasis. This unfit cellular phenotype likely triggers cell competition, leading to the preferential survival of euploid cells.

Conclusion: Chromosome instability in early human embryos affects gene regulation, delays development in aneuploid cells, and activates mechanisms that may eliminate these cells, explaining how mosaic embryos can still give rise to healthy offspring.

[1] https://pubmed.ncbi.nlm.nih.gov/19396175/
[2] https://www.biorxiv.org/content/10.1101/2023.03.08.530586v1

LONG-LIVED RATS REVEAL A SECRET: BETTER DNA REPAIR.

Although many factors have been identified as contributing to aging and death—including cellular senescence, genomic instability, telomere attrition, and metabolic decline—a comprehensive and unified theory of aging is still lacking. Among the hallmarks of aging, DNA damage and the gradual accumulation of mutations over time have long been recognized as central mechanisms. Understanding how some species can mitigate these effects provides important insight into the biology of longevity.
In a study by Chen et al. (1), the authors investigated why the naked mole-rat (Heterocephalus glaber), an exceptionally long-lived rodent, shows remarkable resistance to aging. They discovered that, unlike in humans and mice, the cyclic GMP–AMP synthase (cGAS) protein in naked mole-rats is more stable and remains bound to chromatin for a longer time after DNA damage, enhancing the recruitment of key repair factors such as FANCI and RAD50. As a consequence, homologous recombination repair efficiency is boosted, cellular senescence is limited, and tissue aging is delayed. Remarkably, introducing naked mole-rat cGAS into fruit flies and aged mice improved health span and reduced aging markers, whereas reverting the four amino acid substitutions abolished these effects.
If, as this work suggests, improving DNA repair mechanisms is crucial for a longer and healthier life—a finding consistent with the mutation accumulation theory of aging—an obvious question arises: why did such efficient DNA repair systems not evolve in humans?

[1] https://www.ncbi.nlm.nih.gov/pubmed/41066557

A MALE-SPECIFIC microRNA IS ESSENTIAL FOR AVIAN SEX CHROMOSOME DOSAGE COMPENSATION

Fallahshahroudi et al. (1) have uncovered a unique sex chromosome dosage compensation mechanism in birds, where male-essential microRNA (miR-2954) plays a critical role in male survival. Avian sex determination differs from mammals, with females being heterogametic (ZW) and males homogametic (ZZ). The W chromosome has undergone significant gene loss during evolution, raising questions about how birds balance gene dosage between sexes. This study reveals that miR-2954, which exhibits strong male-biased expression, counteracts the effects of transcriptional and translational up-regulation of dosage-sensitive Z-linked genes.
The authors used CRISPR-Cas9 technology to knock out miR-2954 in chickens, leading to early embryonic lethality in homozygous knockout males. This lethality is likely caused by the specific upregulation of dosage-sensitive Z-linked target genes. Evolutionary gene expression analyses further demonstrated that these target genes underwent both transcriptional and translational upregulation on the single Z chromosome in females. The findings suggest that evolutionary pressures following W gene loss drove the upregulation of dosage-sensitive Z-linked genes in both sexes, with miR-2954 emerging to offset the resulting excess of transcripts in males. This study provides insights into the complex interplay between gene dosage, sex chromosome evolution, and the emergence of regulatory mechanisms in birds.

[1] https://doi.org/10.1038/s41586-025-09256-9

IMPROVED DNA REPAIR IN LONG-LIVED BOWHEAD WHALE

A study on the bowhead whale, the second-largest mammal and one of the longest-lived (>200 years), shows that extreme longevity can result from exceptionally efficient and accurate DNA repair (1). Bowhead cells exhibit enhanced homologous recombination and non-homologous end joining, highly faithful double-strand break repair, and markedly reduced mutation accumulation. A key player is CIRBP, which is expressed at unusually high levels and promotes DNA-end protection and precise repair. Instead of eliminating damaged cells through apoptosis, bowheads preserve them by repairing DNA, limiting genomic instability, inflammation, and cancer risk.
This complements findings in the naked mole-rat (2; see earlier post), where evolutionary changes in cGAS boost homologous recombination and delay aging. Although the molecular solutions differ, both species converge on the same principle: improved DNA repair extends health span and delays aging. By contrast, elephants use a different strategy — multiple TP53 copies — to enhance apoptosis.
The study also addresses Peto's paradox: large, long-lived animals were expected to accumulate more mutations (since many arise during DNA replication), yet whales display lower mutation

rates, showing that exceptional genome maintenance can solve this paradox.
Overall, these convergent findings reinforce the concept that the progressive accumulation of mutations is a central driver of aging.

[1] https://www.nature.com/articles/s41586-025-09694-5
[2] https://www.ncbi.nlm.nih.gov/pubmed/41066557

A FATHER'S WORKOUT CAN BOOST HIS OFFSPRING'S ENDURANCE

Heredity and exercise. My genetics teachers used to repeat a simple idea: you can train hard to become a champion runner, but only your DNA will help your children become one — your exercise will not.
Now, a new paper challenges that classical view. A study in Cell Metabolism (1) shows that paternal endurance training in mice improves the aerobic capacity and metabolic health of their offspring — even when the offspring never exercised. Mechanistically, exercise remodels sperm microRNAs, which are delivered to the embryo and suppress NCoR1, a repressor of mitochondrial biogenesis pathways coordinated by PGC-1α. This early embryonic shift promotes enhanced mitochondrial function and oxidative muscle phenotype in the next generation. Importantly, injecting only sperm small RNAs from exercised males reproduces the effect, and restoring NCoR1 in embryos cancels it.
In short, this work provides strong experimental evidence that paternal exercise can transmit endurance advantages via sperm-borne microRNAs, illustrating a non-genetic, epigenetic pathway of intergenerational inheritance of fitness traits.

[1] https://www.sciencedirect.com/science/article/pii/S1550413125003882?via%3Dihub

ANCIENT GENOMIC PASSENGERS (LINE-1), MODERN NEURAL ARCHITECTS

For decades, most non-coding sequences — transposable elements in particular — were dismissed as "junk DNA," the inert debris of genomic evolution and largely viewed as genomic parasites. This view began to shift with the ENCODE project, which revealed that much of the non-coding genome is biochemically active and potentially regulatory. A recent study (1) builds on this perspective by showing that thousands of evolutionarily young LINE-1 copies are actively expressed in human pluripotent stem cells and early brain organoids, where they function as cis-regulatory elements and alternative promoters for nearly one hundred protein-coding and non-coding genes, including key neurodevelopmental regulators. Locus-specific CRISPR interference reveals that silencing these L1 promoters abolishes L1-driven transcripts and disrupts neural differentiation, producing smaller cerebral organoids and broad transcriptional shifts. These findings demonstrate that human-specific L1 insertions are not genomic bystanders but are contributors to early brain development — likely influencing primate and human brain evolution by transforming former "junk" into essential regulatory circuitry.

[1] https://pubmed.ncbi.nlm.nih.gov/40848716/

SKEWED X-INACTIVATION: CAUSES AND ITS IMPACT ON DISEASE

Skewed X inactivation can lead to the manifestation of X-linked disorders in heterozygous females. But what actually drives this skewing? A review in Nature Reviews Genetics (1) proposes that heterozygous variants can give cells a competitive advantage or disadvantage, that creates clonal competition between cells expressing one or the other X chromosome. The paper explores how these selective forces shape development and influence disease expression.

Reported examples
• STAG2 variants: In mouse models, STAG2-variant clones contribute normally to many tissues but are excluded from the lymphoid lineage when competing with wild-type clones. Notably, these same variants can produce full lymphocyte lineages when no wild-type competitors are present, showing that the disadvantage is relative, not intrinsic.
• HDAC8 and STAG2 in humans: Female carriers of heterozygous mutations frequently show strong skewing in blood in favor of the X chromosome with the wild-type allele, consistent with selection against clones expressing the mutant variant.
• Immunodeficiency genes (IL2RG, BTK, WAS, NEMO): These X-linked mutations impair the survival or maturation of specific immune cell types. In heterozygous females, only clones

expressing the wild-type allele can complete lymphocyte development, producing dramatic skewing driven by cell-intrinsic fitness differences.

• ABCD1 (X-linked adrenoleukodystrophy): Interestingly, in this case blood cells skew toward the mutant allele, even though the disease manifests in the brain. This shows that competition and skewing are tissue-specific, and that selection in one compartment (blood) does not predict disease risk in another (brain microglia).

Overall, the article argues that skewed X inactivation often reflects underlying competitive interactions between clones with different X-linked alleles. Rare variants, tissue-specific fitness effects, and developmental bottlenecks collectively determine which clones dominate. These processes may modulate the severity of X-linked diseases in females and shape X-linked genetic diversity in human populations.

[1] https://www.nature.com/articles/s41576-025-00840-3

CHROMOSOME POLYMORPHIC VARIANTS: NO EVIDENCE OF HARM

In the last two decades at least 38 publications have claimed that chromosome polymorphic variants (CPs) are harmful. Another series of 16 publications found no evidence of harm. A recent paper[1] has critically analysed all 54 articles.

Papers concerning all variants in both series have the same major drawback: lack of a clear definition of a variant. Anyhow all papers in the second series have suitable controls. Papers claiming harm, however, have several other drawbacks: absent or inadequate controls; classification of chromosome abnormalities as CPs, incorrect identification of CPs; absence or poor quality of chromosome images. In fact, only one of the 33 articles with controls had no apparent problems with CP identification

The only unequivocally identifiable variant in these studies is inv(9)(p12q13). Five papers in the first series claim that it is associated with a wide range of phenotypic abnormalities. Six studies in the second series show that it is not associated with adverse effect on phenotype, fertility, pregnancy loss or risk of aneuploidy. In addition, the frequency of inv(9)(p12q13), which was recorded in 26/38 papers in the first and 9/16 papers in the second series, was not different from that in the general population.

In short, critical analysis of the 54 papers has provided no evidence that the CPs are harmful.

Sequencing of pericentromeric heterochromatin is in its early stages; fully understanding its structure and function will take some time. Information from hundreds of thousands of genomes will be needed before any possible association between heterochromatin and disease can be studied.

The author concludes that while we need to keep an open mind about any new insights that may emerge, there is at present no convincing evidence to contradict the information on chromosomal polymorphic variants as published in the International System for Human Cytogenomic Nomenclature (ISCN, 2024).

[1] https://doi.org/10.1016/j.ejmg.2025.105056

SPERM MUTATIONS AND AGING

As men age, the spermatogonial stem cells (SSCs) that continuously produce sperm gradually accumulate DNA mutations. Two complementary studies by Neville et al. (1) and Seplyarskiy et al. (2) [News&Views (3)] show that some of these mutations are not merely passive products of aging but actually confer a selective growth advantage to mutant SSCs. As these mutant clones expand in the testis, they become over-represented in the sperm pool, increasing the probability that such mutations are transmitted to offspring.

Using ultra-sensitive NanoSeq sequencing of bulk sperm, Neville et al. quantify a linear accumulation of approximately 1.7 new mutations per haploid genome per year, driven by canonical age-related mutational signatures. They estimate that the fraction of sperm carrying a disease-causing mutation rises from ~2% at age 30 to ~4.5% at age 70, due to the steady growth of many small clones, rather than the dominance of a few large ones. They identify about 40 genes under positive selection in the male germline, using dN/dS metrics and targeted sequencing.

Seplyarskiy et al., analyzing ~55,000 parent–child trios with a statistical model ("Roulette"), independently detect 40 genes enriched for de novo mutations beyond what would be expected by chance. These include both gain-of-function "hotspot" mutations and loss-of-function alleles that appear repeatedly in sperm, consistent with selective clonal expansion. Their results hold in additional cohorts (>6,000 trios), suggesting

these driver mutations act broadly in the germline.
Together, the studies expand the list of driver genes beyond the classical RAS–MAPK pathway (long known from "selfish spermatogonial selection") to include genes involved in WNT, TGFβ–BMP, and epigenetic regulation. Although only 17 genes overlap between the two studies, the pathway-level concordance is strong. This age-dependent clonal selection in the male germline therefore represents an evolutionary trade-off: it increases the individual risk of transmitting pathogenic mutations, yet simultaneously contributes to the emergence of new genetic variants that enrich human genetic diversity and long-term adaptability.
A key implication is that germline selection can enrich deleterious mutations in sperm faster than natural selection can remove them from the population. This means that some genes may appear "disease-associated" in de novo mutation studies not because they cause disease, but because mutant SSCs outcompete normal ones. This insight suggests the need to annotate germline variants in public databases with information about positive selection in SSCs.

Overall, the work provides the most comprehensive picture to date of how age-related mutation and clonal selection sculpt the male germline — influencing disease risk in children and contributing to human genetic diversity.

[1] https://www.nature.com/articles/s41586-025-09448-3
[2] https://www.nature.com/articles/s41586-025-09579-7
[3] Nature Nov. 13, 2025, pag. 324

GENOTYPE–PHENOTYPE CORRELATION IN HAPLOINSUFFICIENT GENES

Large-scale genomic screenings have revealed that individuals in the general population can carry pathogenic, even "fully penetrant", Mendelian mutations without developing the expected disease (see 1). This prompted a fundamental shift in the understanding of genotype–phenotype relationships. Crucially, these observations are possible only when surveying ostensibly healthy individuals, rather than focusing exclusively on patients
Within this conceptual framework, the study by Blair and Risch (2), leveraging the scale of the UK Biobank, investigates why certain variants predicted to cause severe haploinsufficiency do not generate the anticipated clinical phenotype. By integrating population-level variant annotation with functional assays, the authors show that many alleles currently classified as loss-of-function are not truly null but instead retain residual allelic activity sufficient to buffer the organism against disease. Rather than a binary ON/OFF model, the data reveal a continuum of allelic function, where even modest residual activity can significantly mitigate pathogenicity.
Taken together, these findings highlight how incomplete penetrance may stem either from resilience within the variant itself, or from resilience provided by the broader genome. Both levels challenge classical deterministic models and emphasize how dynamic, multilayered, and context-dependent genotype–phenotype relationships truly are.

[1] https://pubmed.ncbi.nlm.nih.gov/27065010/
[2] https://www.cell.com/ajhg/abstract/S0002-9297(25)00427-6

Mir465, THE X CHROMOSOME, AND HYBRID STERILITY

Hybrid sterility is among the most striking manifestations of reproductive barriers, ultimately driving reproductive isolation and speciation. A disproportionate contribution of the X chromosome has long been recognized in this process. Mouse hybrids between subspecies of Mus musculus provide an exceptional system to dissect this phenomenon, where male infertility arises from the interaction between meiotic regulation, recombination dynamics, and X-linked incompatibilities. Jansa et al. (1) reveal that the previously identified male sterility Hstx2 locus on the X chromosome corresponds to a copy-number variable Mir465 microRNA cluster, and identify this variation as a central determinant of hybrid male sterility.
In non-hybrid strains, Mir465 copy number lies within a physiological range that preserves the transcriptional programs required for efficient meiotic double-strand break (DSB) formation, crossover repair, and proper progression through pachytene. In hybrids, however, the asymmetric Mir465 dosage inherited from the two parental subspecies, due to differences in copy number, disrupts this balance. Dosage-dependent misregulation of Mir465 targets and alters the expression of key meiotic genes, shifts the timing and efficiency of DSB repair, and ultimately reduces crossover numbers below the threshold

needed to stabilize homolog pairing. These defects are particularly severe on the X chromosome, where Mir465 resides and where meiotic regulation is already constrained by the requirement for meiotic sex chromosome inactivation (MSCI).
As a consequence, hybrid males exhibit pronounced asynapsis, activation of pachytene checkpoints, and apoptotic loss of spermatocytes, leading to reduced sperm output or complete sterility. Hybrid male infertility thus emerges not from Mir465 per se, but from divergence in Mir465 copy number and expression that destabilizes the X-linked control of meiosis.
A final point is that, in this system, speciation is driven by variation at a single, rapidly evolving locus; in this case it is a tandem-repeat locus, which has an inherent tendency to undergo duplication or deletion, making it especially prone to copy-number variation. This is remarkable, because it shows how the expansion of one genomic element can be sufficient to tip the balance toward reproductive isolation. The effect is also strongly male-biased, consistent with the heightened vulnerability of male meiosis to regulatory perturbations. Spermatogenesis involves a tightly constrained transcriptional program, extensive chromatin remodeling and the unique challenge of meiotic sex-chromosome inactivation, all of which make the male germline particularly sensitive to dosage- and timing-related disruptions.

[1] https://www.ncbi.nlm.nih.gov/pubmed/41037637

A DEEP LOOK INTO SOMATIC MOSAICISM

Somatic mosaicism is now recognized as a pervasive feature of human biology, with diverse classes of somatic mutations accumulating across tissues over time. The study by Luquette et al., in bioRxiv (1) aims to characterize somatic mosaicism in unprecedented depth and represents the first output of a dedicated consortium established for this purpose. Using single-cell PTA sequencing on lung and colon samples from a 74-year-old deceased individual, the authors obtain a high-resolution view of somatic genomic diversity in normal tissues. They showed not only extensive catalogs of point mutations but also a remarkably rich spectrum of large-scale chromosomal alterations, including full-chromosome aneuploidies, broad sub-chromosomal copy-number changes, and complex structural rearrangements that remain invisible in bulk sequencing. Loss of chromosome Y emerges as the most frequent whole-chromosome event, accompanied by occasional XYY gains arising independently in distinct developmental lineages. The study also identifies several copy-neutral loss-of-heterozygosity events, whose genomic signatures are consistent with mechanisms of somatic homologous recombination—such as mitotic recombination, gene conversion, or break-induced replication—although the authors do not discuss the mechanistic interpretation. In addition, V(D)J-mediated deletions in T-cell receptor loci (a physiological somatic recombination process that generates T-cell receptor diversity) highlight the ability of single-cell sequencing to detect programmed DNA remodeling. Together, these findings demonstrate that normal tissues harbor a far broader and structurally more complex array of chromosomal variation than previously appreciated, underscoring the power of single-cell genomics to capture the full scale and complexity of somatic genome instability.

[1] https://doi.org/10.1101/2025.10.31.685648 (bioRxiv)

DE NOVO MUTATION RATE IN ART IN MICE

Assisted reproductive technologies (ART) are widely used in human fertility treatment, yet their potential impact on genome integrity remains insufficiently understood. Using a rigorously controlled mouse model, Blanco-Berdugo et al. (1) demonstrate that a standard ART protocol induces a ~30% increase in de novo single-nucleotide mutations compared with natural conception. Although the mutational spectra and genomic distribution of variants remain broadly comparable across cohorts, the systematic elevation in mutation rate indicates that the ART environment modestly enhances mutational vulnerability during gametogenesis or very early embryogenesis. This experimental evidence, obtained in an inbred mammalian system under tightly controlled genetic and environmental conditions, highlights a biological mechanism that could be relevant for humans. Given the rapidly increasing global reliance on ART and the fundamental differences between epigenetic and mutational processes, these findings underscore the urgent need to investigate whether similar mutagenic effects occur in human embryos, particularly in the context of ovulation stimulation,

culture conditions, and fertilization techniques such as ICSI. While the authors caution that mouse results cannot be directly extrapolated to humans, their work raises an essential question for reproductive medicine: whether ART may subtly shape the human germline mutational load, with possible implications for long-term health of the offspring.

[1] https://pubmed.ncbi.nlm.nih.gov/41233158/

INVESTIGATIVE GENETIC GENEALOGY

Investigative Genetic Genealogy (IGG) has transformed the ability to identify unknown individuals, providing answers in over 1300 cases since 2018. Its value extends far beyond identifying perpetrators: IGG is equally vital for giving names back to unidentified human remains, thus restoring dignity to victims and providing closure for families.

A key conceptual difference separates IGG from traditional forensic genetics. Forensic laboratories typically use VNTR/STR panels, optimized for direct individual identification and CODIS-style database matching. IGG instead relies on dense SNP genotyping arrays, because only SNP data are compatible with genealogical databases used for long-range kinship inference.

The reason is fundamental: SNP profiles allow detection of segments of DNA identical by descent (IBD) shared between the unknown individual and genetic cousins who have voluntarily uploaded their data to platforms such as FamilyTreeDNA, GEDmatch Pro, or DNA Justice. By quantifying and mapping these IBD segments, IGG practitioners can infer degrees of relatedness and progressively restrict the search to specific families that share common ancestors with the unknown subject. Through genealogical reconstruction, integrating public records, family histories, and demographic information, these families are narrowed down to a small set of potential individuals, who are then confirmed or excluded using traditional forensic methods.

By combining long-range IBD-based kinship signals with classical genealogy, IGG reduces the need for broad investigative sweeps and offers a less invasive, yet far more powerful, approach to resolving cold cases. In doing so, it advances both justice and humanitarian identification efforts.

This is the topic of the article by D. Gurney (1).

[1] https://www.ncbi.nlm.nih.gov/pubmed/41365744

MISSING HERITABILITY

In studies based solely on affected individuals, the link between a variant and a clinical phenotype seemed straightforward and deterministic. With the advent of large-scale population sequencing, however, it has become clear that many people carry variants previously linked to severe disorders yet display no signs of disease. This shows that a mutation associated with a phenotype does not necessarily cause disease, and that penetrance must be reconsidered in the context of genome-wide variation.

The study by Wainschtein et al. (1) leverages whole-genome sequencing from 347,630 UK Biobank participants to investigate this discrepancy. By analysing over 40 million variants, the authors quantify how much heritable phenotypic variation is attributable to rare versus common variants. They find that rare variants account for roughly 20% of total heritability, with important contributions emerging not only from coding sequences but also from non-coding regions, which explain the majority of rare-variant heritability. The analysis identifies hundreds of rare-variant associations and shows that, for several traits—especially metabolic traits such as lipid levels—a significant proportion of the rare-variant contribution can already be assigned to specific loci.

Together, these results explain why some carriers of mutations historically labelled as pathogenic remain unaffected: clinical outcomes depend on the combined effect of the entire genomic background, rather than on a single mutation considered in isolation. The work provides a more nuanced framework for interpreting penetrance and variant pathogenicity in the era of population-scale genomics. In summary, the work demonstrates that the "missing" heritability is largely hiding in rare variants and can be successfully mapped using large-scale whole-genome sequencing.

[1] https://www.nature.com/articles/s41586-025-09720-6

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1st Vice President	**K. Madan**	**Treasurer**	**F. Pellestor**
2nd Vice President	**P. Heslop-Harrison**		

ECC SCIENTIFIC PROGRAMME COMMITTEE

Joris Vermeesch (Chair)
Mariano Rocchi
Damien Sanlaville
Emanuela Volpi
Orsetta Zuffardi

E.C.A. News

- The 2025 General Assembly of the E.C.A. with Board elections took 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.
- Renewal of the Board in 2025: the following members were elected or re-elected at the General Assembly: J.S. Heslop-Harrison (United Kingdom), K. Madan (the Netherlands), M.R. Pinto Leite (Portugal), C. Haferlach (Germany), J. Drabova (Czech Republic).
- Committee election at the Goldrain Board meeting: J.-M. Dupont (President), K. Madan (First Vice-President), P. Heslop-Harrison (Second Vice-President), M. Rocchi (General Secretary), F. Pellestor (Treasurer).

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 32)

  Goldrain Course in Clinical Cytogenetics
  to be held in Goldrain Castle (South Tyrol, Italy) 25-31 August 2026 (see page 33)
  (The course was fully booked for 2025, 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. GENERAL ASSEMBLY JULY 2025

Minutes of the General Assembly held on June 30, 2025 in KU Leuven, Leuven, Belgium.

Approximately 37 members of the Association were present. All active members were invited to the General Assembly and had been sent postal ballots.
The President Mariano Rocchi opened the Assembly at 18.00 and welcomed those attending. Voting was closed for the Board Elections. Minutes of the General Assembly held on 23 August 2024 in Goldrain, Italy and published in Newsletter 55, January 2025, were approved.

Reports of the Committee

The General Secretary gave an overview of the status of the membership. The Association has 1380 members as of May 2025, among them 324 active members from 53 countries. We had 10 new members in 2024, and 49 between January to May 2025.
On behalf of the Treasurer, the General Secretary presented main points of the financial status of the Association. As it was a year without a conference, expenses were limited. Total income was approximately €7600 and expenses, largely for the Nîmes and Goldrain courses including fellowships, were €12,000. The Association has a current balance of €118,000. Considering the last conferences this result was regarded as satisfactory. The accounts were approved by vote of the membership.

15th European Cytogenomics Conference, Leuven

A number of adjustments were made to avoid a deficit from the conference: a university venue instead of a conference centre, 3 instead of 4 days and organizing Workshops before the Opening Ceremony. Hands-on workshops, organized for the first time by Bionano, UCSC, Illumina and Nanopore, were well attended (c. 77 people) and well-received by the membership.
Overall, there were 315 participants and five fellowships and five poster prizes were awarded. The number of trade exhibitors/sponsors was 11. All were thanked. The local Organizer, Joris Veersmeesch, was thanked in particular for his contribution to organization of the 15th ECC in Leuven.

Cytogenetic courses

The European Advanced Postgraduate Course in Classical and Molecular Cytogenetics and the Goldrain Course in Clinical Cytogenetics had been successful. The Goldrain course was at maximum capacity with 42 students. The Nîmes course had 25 students both in 2024 and 2025 .

Board elections

The following Board Members had been proposed for re-election: Pat Heslop-Harrison (GB), Kamlesh Madan (NL) and Rosario Pinto Leite (PT). Two new Board Members, Claudia Haferlach from Germany and Jana Drabova from The Czech Republic , were proposed for election.
61 votes were received: 58 'yes', 1 invalid, 1 blank and 1 'no'. So, the candidates were duly elected.
The President invited suggestions from the Membership for the location of the 2027 16th European Cytogenomics Conference.
There was a discussion about the involvement of early-career scientists in the organization of the Congress and management of the Association.
There being no further business, the President closed the General Assembly at 18.30.

Minutes of the E.C.A. Board meeting held in Leuven, July 1st 2025

A meeting of the E.C.A. Board of Directors was held in Leuven on Tuesday I July 2025

Following members were present :
Mariano Rocchi (President), Jean-Michel Dupont (General Secretary), Kamlesh Madan (1st vice President), Pat Heslop Harrison (2nd vice President), Konstantin Miller, Joan Blanco Rodriguez, Rosario Pinto Leite, Elisabeth Syk Lundberg, Ana Lindstrand, Jose Garcia Sagredo, Roberta Vanni, Franck Pellestor.

Apologies were received from:
Meral Yirmibes, Claudia Haferlach and Jana Drabova
The President opened the meeting at 12:30.
The General Secretary congratulated the elected and re-elected members.
The following three topics were discussed:

Meeting with Dekon

The members of the E.C.A. committee reported on the outcome of the meeting with DEKON, held to discuss details and procedures of the conference organization.

In accordance with best practice for governance of not-for-profit associations working with suppliers, alternative options of working with another company or a society with experience in conference organization and membership were considered. The Board decided to continue working with Dekon on the current shared-risk basis.

Committee election

The term of office of the President, Mariano Rocchi, expires at the end of September; he cannot be re-elected according to the statutes of the Association. Furthermore, the Treasurer, Thierry Lavabre-Bertrand did not stand for re-election, so a new Treasurer is needed.

Various possible candidates were discussed for both positions. It was decided to hold a dedicated board meeting during the Goldrain Course, where all members can be present, either on site, those teaching in the course, or online. The meeting is scheduled for August 27, 2025, from 18:00 to 19:00 CET.

Venue of the 16th European Cytogenomics Conference, 2027

Several spontaneous applications have been received for hosting the next E.C.A. conference

Geneva, Switzerland

Stockholm, Sweden

Brno, The Czech Republic

Poland had also expressed an interest

All have been asked to provide us with a more detailed proposal with the location, available rooms and exhibition area and preliminary prices so that we can make a decision together with the help of DEKON.

The decision should be reached by the end of this year.

No other topics being discussed, the President closed the meeting at 13:45.

Minutes of the E.C.A. Board meeting held on 27th August 2025 in the Goldrain Castle, Italy.

The following members were present:

In person: Mariano Rocchi (President), Jean-Michel Dupont (General Secretary), Kamlesh Madan (First Vice-President), Konstantin Miller

Online via Zoom: Pat Heslop-Harrison (Second Vice-President), José M. Garcia-Sagredo, Roberta Vanni, Elisabeth Syk-Lundberg, Anna Lindstrand, Claudia Haferlach, Franck Pellestor, Jana Drabova

Apologies were received from Joan Blanco Rodriguez and Rosário Pinto Leite.

The President, Mariano Rocchi, opened the meeting at 18:10 and welcomed those attending.

1. Minutes

The Minutes of the Board meeting held Tuesday 1st July 2025 in Leuven were approved and will be published in the next Newsletter.

2. Committee and Board elections

The Committee positions have to be renewed every 3 years. There were two open positions: The President, as the current president has completed two consecutive terms in office and the Treasurer, as the current treasurer did not stand for re-election to the board. After discussion among the board members, the Board elected the Officers as follows:

President: Jean-Michel Dupont

First vice President: Kamlesh Madan

Second vice President: Pat Heslop Harrison

General Secretary: Mariano Rocchi

Treasurer: Franck Pellestor

Those elected and re-elected accepted the positions and were thanked.

Meral Yirmibes has resigned from the Board. It was agreed that the vacancy will be filled at the next Annual General Meeting.

The new officeholders took their new positions.

3. Nomination of new the chair for Scientific Program Committee and coordinators of the Permanent Working Groups (PWGs) on Neo¬plasia and on Animal, Plant and Comparative Cytogenetics.

The former President Mariano Rocchi acknowledged the outstanding contribution of Joris Vermeesch to the work of the Scientific Program Committee and nominated him as chair of the new Scientific Program Committee, with authority to appoint new members.

Board members were asked to think of possible candidates for the coordinator of the PWG on Neoplasia and to share the information with Roberta Vanni. Alla Krasikova, an active member of the association, was confirmed as co-chair of the PWG on Animal, Plant and Comparative Cytogenetics.

4. Report on 15th European Cytogenomics Conference held in Leuven

The New President presented the first result and final balance of the Leuven Conference. The Conference was successful with respect to attendance, excellent talks, and net¬working. So, ECA is delivering a valuable benefit to members and the wider community of cytogeneticists. The number of attendees and sponsors was similar to the previous conference in Montpellier.

Sessions were well attended, particularly the Keynote opening and closing lectures, which were highly successful. The pre-conference Workshops, which were attended by 20% of the participants, were also appreciated

The final survey organized by Dekon showed that participants were very satisfied with the scientific content and quality of the conference, but there is room for improvement in aspects of organization and catering.

The final balance of the conference is positive. Thus, the choice of a university and the revised conference set up in three instead of four days (plus workshops and working groups) had a positive effect. In general terms, and to be considered by the Scientific Committee, a similar structure will most likely be adopted for 2027.

5. Preparation of the 16th European Cytogenomics Conference, 2027

In Leuven, 4 proposals were received: Geneva, Stockholm, Brno and Wroclaw.

The President will send the information on the venue in Leuven (number of rooms, size of exhibition hall etc.) by the beginning of September, so that the board can receive preliminary proposals from each potential venue by the end of September. These can be discussed further with Dekon. The final objective is to decide the venue for 2027 by the end of this year. Venues may also be considered for 2029.

Next Board meeting will be organized in Nîmes during the next course, European Diploma in Classical and Molecular Cytogenetics, in March 2026.

No other subject being put forward, the President closed the session at 19:00

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.

19th Goldrain Course in Clinical Cytogenetics

August 25 – 31, 2026
(arrival Aug. 24, departure Sept. 1)

This course continues the legacy of Albert Schinzel, who founded it in 2007 and passed away on 12 September 2025.

DIRECTORS

M. Rocchi (Bari, Italy), **J.-M. Dupont** (Paris, France);

PROGRAMME COMMITTEE

M.Rocchi, J-M. Dupont, K. Miller, K. Madan, A. Baumer, E. Klopocki,

FACULTY

D. Bartholdi (Berne, Switzerland), A. Baumer (Zurich, Switzerland), G. van Buggenhout (Leuven, Belgium), J.M. Dupont (Paris, France), E. Errichiello (Pavia, Italy), E. Klopocki (Würzburg, Germany), T. Krones (Zurich, Switzerland), K. Madan (Leiden, The Netherlands), K. Miller (Hannover, Germany), R. Pfundt (Nijmegen, The Netherlands), M. Rocchi (Bari, Italy), J. Wisser (Zurich, Switzerland), O. Zuffardi (Pavia, Italy)

LOCATION

Goldrain Castle, Goldrain, South Tyrol, Italy

COURSE DESCRIPTION

The course is focused on phenotypic findings, mechanisms of origin and transmission, correlations of clinical patterns with chromosomal imbalance and modern ways of diagnosis of the latter. Special attention is paid to an understanding how deletions and/or duplications of chromosomal segments cause developmental defects. The course also addresses the optimal application of the diagnostic possibilities, both pre- and postnatally and including molecular cytogenetic methods for a precise determination of segmental aneuploidy.

TOPICS

Dysmorphic findings in chromosome aberrations: formation and interpretation – The adult and elderly patient with a chromosome aberration – Follow-up studies in patients with chromosome aberrations – Clinical findings associated with chromosome aberrations – Microdeletion syndromes: clinical pictures – prenatal cytogenetic diagnosis – Mosaics and chimeras – imprinting and uniparental disomy - Epidemiology of chromosome aberrations – Chromosome aberrations in spontaneous abortions and stillborns – Harmless chromosome aberrations – Risk assessment in structural chromosome aberrations Extra small supernumerary chromosomes – Genomic variation: a continuum from SNPs to chromosome aneuploidy – Pre-implantation cytogenetic diagnosis – Ultrasound findings indicative of chromosome aberrations – Ethical issues in the context of cytogenetic diagnosis – Non-invasive prenatal cytogenetic diagnosis. ISCN - Practical exercises in cytogenetic nomenclature – Accreditation of cytogenetic laboratories - Accreditation of cytogenetic laboratories – Optimal use of available techniques in clinical cytogenetics – NGS – SNP arrays and Array-CGH: principles, technical aspects; evaluation of the results – MLPA - QF-PCR - FISH techniques and their interpretation – Optical genome mapping – Introduction and practical exercises with database for phenotypical and variant interpretation - Students presentation of cases with difficult-to-interpret chromosome aberrations. Introduction to modern genetic editing techniques. - Practical exercises will be offered with the ISCN system for chromosome aberrations and with cytogenetic, genomic, and phenotypical databases.

Students will have the opportunity to present their own observations and cytogenetic findings which are difficult to interpret, and to perform a test at the end of the course.

The are **40** available places, assigned on **first come** - **first served** basis. In 2025 all slots were filled by mid-April.

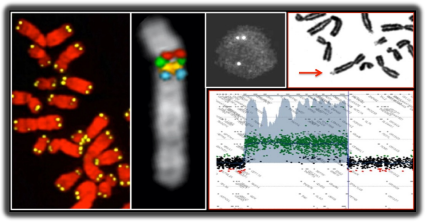
This was the last course that Albert attended in person

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

Contacts:
mariano.rocchi@uniba.it
jean-michel.dupont@aphp.fr

Full scholarships will be available.
Application deadline: **March 31, 2026**

SCHLOSS GOLDRAIN
Bildung und Kultur · Formazione e Cultura



Fees: ***€1.700*** *– single room*
€1.450 *– double room*
The fee includes tuition, course material, free access to internet, accommodation for 8 nights, all meals, coffee breaks and a ½ day excursion. Travel is not included.