MALE INFERTILITY

After decades of deadlock during which deletions of the long arm of the Y chromosome dominated the field, in just a few years exome sequencing and now trio-based Whole Exome Sequencing (WES) has provided a new picture of the genetics underlying the impairment of sperm production. Although WES already identified a number of male infertility-associated gene variants with autosomal recessive or X-linked inheritance, the etiology in approximately 40% of affected individuals remained unknown. "A de novo paradigm for male infertility[1]", Nat Comms, signed by Joris Veltman and over 40 co-authors, demonstrates how the search for rare de novo variant in trio-based exome sequencing data in a cohort of 185 infertile males detected and validated 192 rare mutations (MAF <0.1%), which altered 145 proteins. The *de novo* point mutations affected several genes, all autosomal except one on the X chromosome, none of which were already known to be involved in human male infertility with autosomal dominant inheritance. The variants were of the loss-of-function or missense type in genes intolerant to loss-of-function or missense variants, respectively. The situation, therefore, parallels what has been amply demonstrated in other conditions, such as neurodevelopmental disorders. Furthermore, in rare cases, the de novo mutation, of paternal origin, was associated with a variant inherited from the mother.
An analysis through the STRING database[2] suggested that the proteins affected by the de novo pathogenic variants share common biological functions with a possible link to mRNA splicing.

1- Oud MS, ..., Veltman JA: A de novo paradigm for male infertility. Nature Communications 13 *in press* (2022)
https://www.nature.com/articles/s41467-021-27132-8#auth-R__M_-Smits

2- https://string-db.org