THE COMPLEXITY OF IDENTIFICATION OF PATHOGENIC VARIANTS

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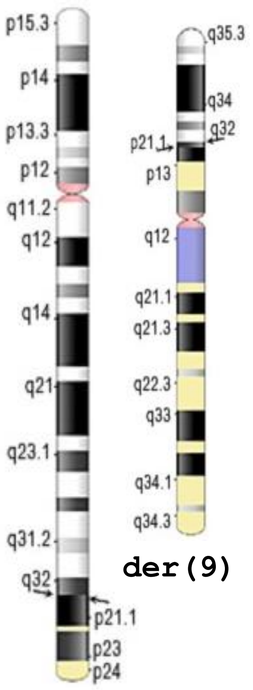
• Introduction •

Natural occurring genomic variant, from single nucleotide to balanced, unbalanced and complex rearrangements, spanning large chromosomal regions, has been reported to cause human pathologies. As such, we present cases with neurodevelopmental disorder, infertility, and recurrent miscarriage, which reflect the complexity of the identification of pathogenic variants, considering the variation spectrum, the underlying pathogenic mechanisms, and the heterogeneous clinical presentations.

• 46,XY,t(5;9)(q32;p21.1)mat •

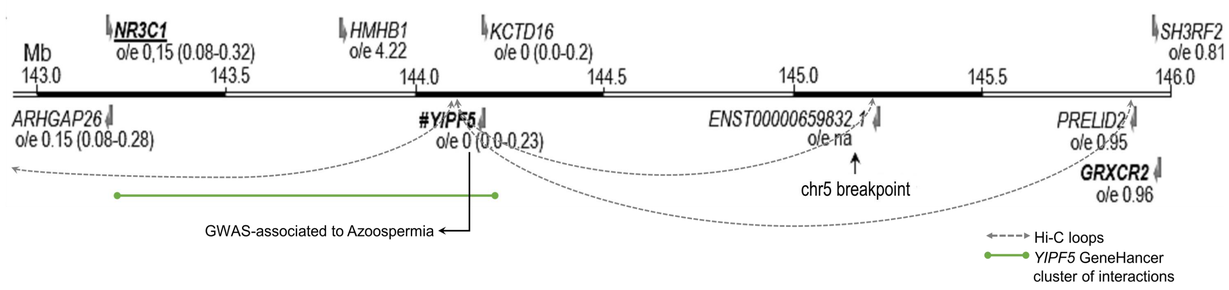


A maternal translocation was studied in a proband with **oligoasthenozoospermia.**

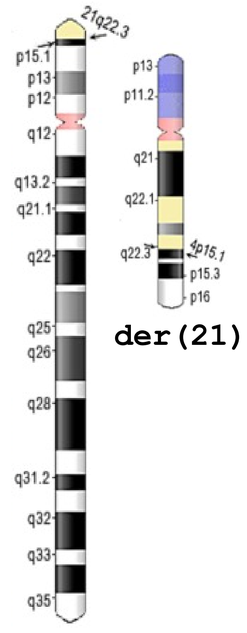
Only an hypothetical lncRNA, ENST00000659832.1 is disrupted in chromosome 5.

The ***YIPF5*** located upstream of the chromosome 5 breakpoint was indicated as **candidate gene for position effect** [1], due to:

- GWAS association to azoospermia;
- Drosophila knockdown of this gene reveals its important role in male fertility;
- High expression in testis, according to GTEx;
- Breakpoint-disrupted Hi-C loops involving the GeneHancer cluster of interaction of the gene, potentially mediating the position effect.



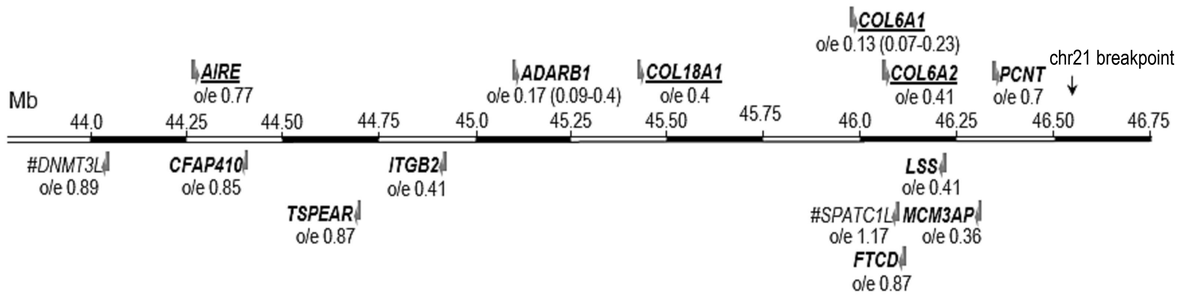
• 46,XY,t(4;21)(p15.1;q22)•



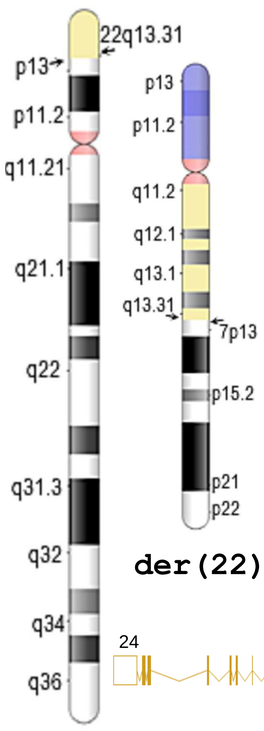
A translocation was identified in a proband with **oligozoospermia.**
Neither of the breakpoints disrupt protein coding or non-coding RNA genes.

Chromosome 21 breakpoint region gene ***SPATC1L*** was pointed as **position effect candidate gene** [1], due to:

- Gene function in maintenance of sperm head-tail junction integrity;
- High expression in testis, according to GTEx;
- Association to subfertility in Spatc1 haploinsufficient mice;
- GWAS data and disruption of the GeneHancer cis-acting regulatory interactions cluster by the breakpoint.



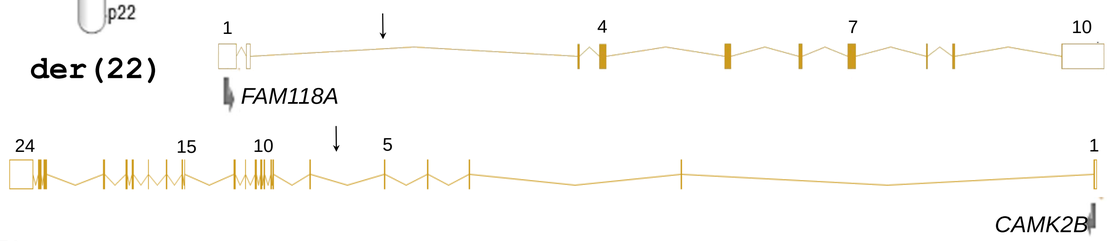
• 46,XY,t(7;22)(p13;q13.31)dn •



A *denovo* translocation was identified in a proband with **intellectual disability (ID)** and **recurrent miscarriage.**

The **7p13 breakpoint disrupts the *CAMK2B* in IVS5.** The 22q13.31 breakpoint disrupts the *FAM118A* in IVS2.

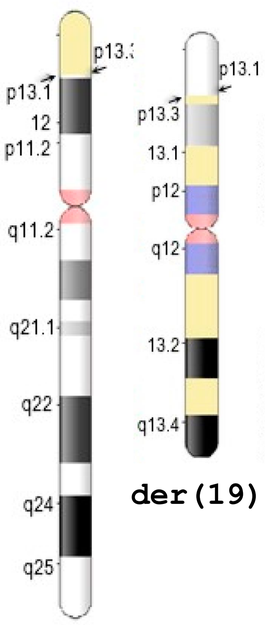
CAMK2B has been reported to lead to AD mental retardation, mainly characterized by ID, language impairment, and behavioral anomalies, **explaining the ID phenotype of the proband.**

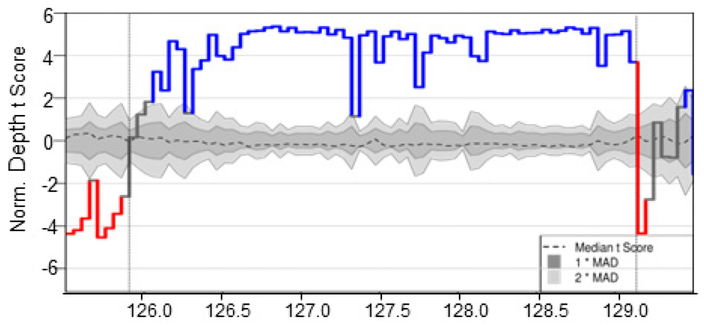


Based on previous studies, chromosome 22 translocation carriers show a high risk of unbalanced spermatozoa and spontaneous abortion.

Therefore the translocation involving chromosome 22 is a plausible explanation for recurrent miscarriage reported in this family [1].

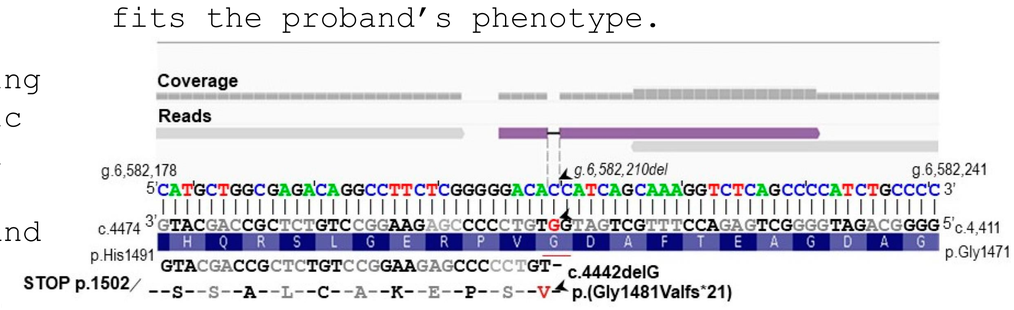
• 46,XX,t(17;19)(p13.1;p13.3)mat•





A familial translocation disrupting ***GSG1L2***, a 3.2 Mb chromosome 2 duplication encompassing the phenotype-associated ***PROC*** and ***HS6ST1*** genes, and a novel frameshift variant within exon 30 of ***CHD4*** have been identified in the proband. ***CHD4*** is associated to the neurodevelopmental phenotype, **Sifrim-Hitz-Weiss syndrome**, which fits the proband's phenotype.

Considering pathogenic potential of each variant and the proband's phenotype, we **classified the *CHD4* mutation as disease-causing[2].**



• Conclusion •

These cases highlight intricacy of pathogenic mechanisms leading to human disorders, the necessity for identification and evaluation of the "full" spectrum of genomic and genetic variants, of comparative reverse phenotyping, including patients with pathogenic variants affecting the same genes. Finally, highlight the need of introducing a more precise genomic medicine in clinical practice.

• Methods •

Genomic sequencing (GS) was applied. Variants were identified from GS data mapped against reference human genome and confirmed through Sanger sequencing. Results were interpreted using SVInterpreter, Exomiser, genotype-phenotype correlation and convergent genomic data.

• References •

[1] David *et al.*, Gene (2023)
[2] Da Silva *et al.*, Biomedicines (2023)

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