In the present case, the use of array-CGH and karyotype analysis provided a better understanding of the chromosome imbalance, therefore stressing that in many circumstances it is very important to rely on them as complementary techniques.

Genotype-phenotype correlations are crucial for genetic counselling and the orientation of medical decisions.

P54 – AUTOSOMAL DOMINANT INTELLECTUAL DISABILITY 43 – NOT ALWAYS *DE NOVO*.

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Introduction: Moderate to severe intellectual disability (previously known as mental retardation) with autosomal dominant inheritance (MRD) is very often caused by de novo variants. Pathogenic variants in MRD disorders with complete penetrance are frequently presumed to be de novo in the absence of segregation studies. In those instances, a theoretical recurrence risk estimated at 1% or lower is given to healthy parents.

MRD43 (# 616977) is an intellectual disability syndrome with neurological manifestations associated with loss-of- function *HIVEP2* heterozygous variants.

Clinical case: A 33-mo boy referred to Genetics for moderate developmental delay, hypotonia, wide-based gait, dysmorphic features, strabismus, and hypermetropia. He was the only child to healthy non-consanguineous parents with unremarkable family history. Array-CGH and general biochemistry were inconclusive. Brain MRI showed mild encephalic white matter reduction and corpus callosum hypoplasia. WES-based NGS panel with 1502 developmental delay/ID genes disclosed a previously described heterozygous nonsense pathogenic *HIVEP2* variant [c.2827C>T p.(Arg943*)], establishing an MRD43 diagnosis. Segregation studies showed the variant was present in the mother with somatic mosaicism in 15% of peripheral blood cells. After genetic counselling with a maximum recurrence risk of 50%, the couple opted for PGD and preliminary haplotype studies are ongoing.

Discussion: To our knowledge, this description of an inherited *HIVEP2* pathogenic variant is unique in the literature. The maternal mosaicism was well tolerated despite considerable expression in the blood sample and, likely, in the gonadal tissue. This clinical case highlights that a previously reported pathogenic variant in an MDR gene can in fact be inherited, dramatically increasing the recurrence risk and significantly impacting parents' reproductive options. Parental testing should be mandatory for pathogenic variants in this context, especially when parents consider further family planning.

P55 – PRENATAL DIAGNOSIS OF CONGENITAL HEART DISEASE IN A FETUS WITH A 8p23.1 INTERSTITIAL DELETION

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Introduction: Congenital heart disease (CHD) is the most common form of birth defects. The incidence of CHD is about 0.8% to 1% in live-born, full-term births, and it is ten times higher in preterm infants (8.3%). The atrioventricular septum defect (AVDS) is the most common CHD detectable in utero. AVSD is known to occur in either a nonsyndromic (isolated) form or, more commonly, as part of a malformation syndrome.

Methodology: A 30-year-old woman at 12 weeks of gestation was referred for prenatal diagnosis due to fetal AVSD.

Chromosomal microarray analysis (CMA) was carried out after a normal molecular rapid aneuploidy test result.

Results: CMA identified, in a male fetus, a 3.11 Mb interstitial deletion at 8p23.1 - arr[GRCh37] 8p23.1(8824857_11935465)x1.

This region encompasses 17 OMIM genes including *GATA4*. This protein is thought to regulate genes involved in embryogenesis and in myocardial differentiation and function.

Parental testing was requested and CMA was performed revealing that the deletion is *de novo*.

Discussion: Deletions and mutations of the *GATA4* gene are associated with cardiac septal defects.

This deletion has a pathogenic clinical significance.

The AVSD found in the fetus can be explained by the observed genomic change.

Interstitial deletions of 8p23.1 are associated with a variable spectrum of anomalies that include congenital heart malformations. The prevalence is unknown but 8p23.1 deletions are rare. Most 8p deletions occurs *de novo*.

The accuracy of cardiac defects in obstetric ultrasound and the identification of the genetic cause provide more knowledge for the genetic counseling. The parents opted to terminate the pregnancy.

P56 – THE GENETIC ANALYSIS OF PORTUGUESE PATIENTS WITH CEREBELLAR ATAXIA, NEUROPATHY, VESTIBULAR AREFLEXIA SYNDROME (CANVAS): A FREQUENT AND GENETICALLY COMPLEX CLINICAL ENTITY

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