Genome sequencing identifies a homozygous inversion disrupting QDPR gene as a cause for dihydropteridine reductase deficiency

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Background: Disturbances in tetrahydrobiopterin (BH₄) synthesis or regeneration cause errors in phenylalanine (Phe) metabolism and neurotransmitter synthesis, leading to hyperphenylalaninaemia (HPA) [1]. BH₄ supply in the organism is regenerated by dihydropteridine reductase (DHPR), encoded by the quinoid dihydropteridine reductase (QDPR) gene [2]. Biallelic pathogenic variants in QDPR lead to BH₄-deficient HPA, accompanied with a severe biogenic amines deficiency (OMIM #261630).

Methods: The proband presented muscular rigidity, lack of eye contact, and other neurological symptoms. At 6m of age DHPR deficiency was diagnosed. Initially QDPR sequencing, exome sequencing (ES) and QDPR mRNA PCR was carried out. Trio genome sequencing (GS) was finally performed to investigate for a homozygous rearrangement disrupting the QDPR gene.

Results: GS identified a possible breakpoint at Chr4(GRCh38):g.17505522 locating to intron 2 of QDPR. The other breakpoint was located to Chr4(GRCh38):g.8398067, intron 8 of ACOX3 gene. A 9 Mb inversion in 4p was suspected. Post hoc analysis with structural variant (SV) callers detected the variant as homozygous in the proband and heterozygous in both parents. PCR and Sanger sequencing using specific primers was used to validate the inversion; (Figure 1). No pathogenic variants were found by QDPR sequencing and ES, neither by karyotyping (Figure 2) nor cDNA PCR.

Discussion: This case illustrates the advantages of GS and importance of SVs in genes where SVs have not been previously implicated as a disease mechanism [3]. Balanced SVs remain difficult to detect using common molecular DNA variant detection assays. GS has facilitated detection of some disease-causing inversions. To our knowledge, this is the first report on a large pure (not complex) disease-causing homozygous inversion detected by GS.

References: