

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.

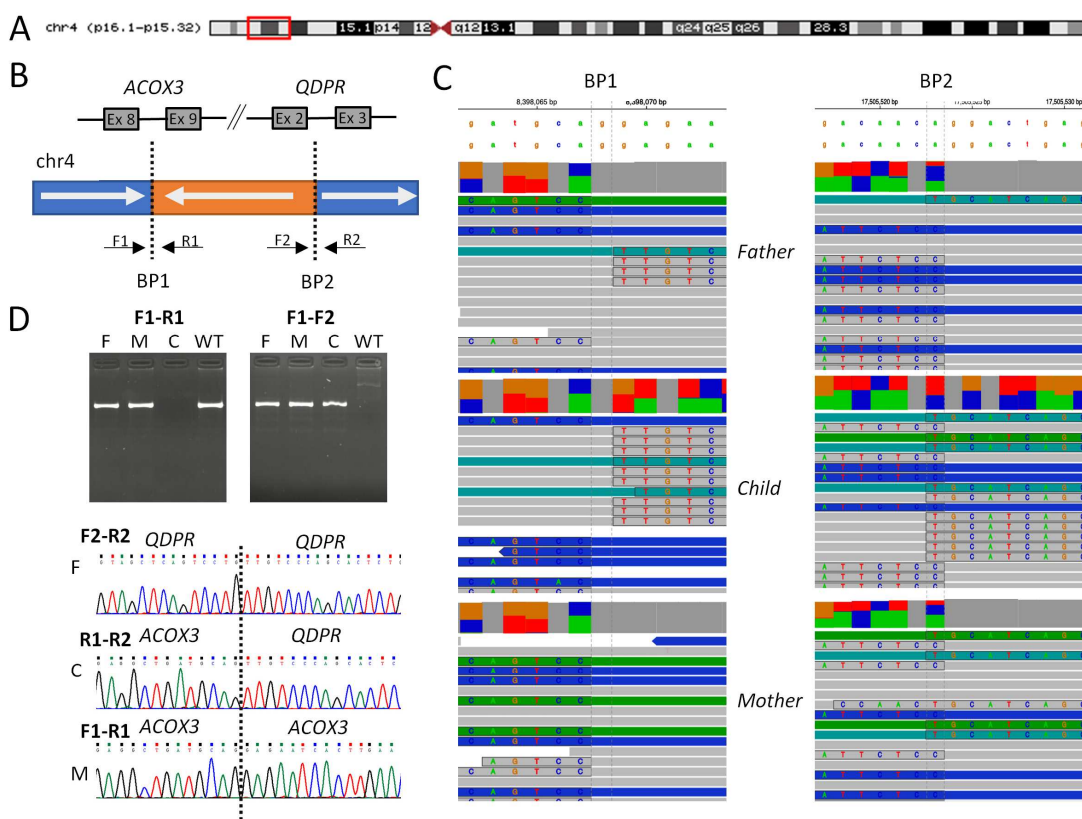


Figure 1. A. Chromosome 4 ideogram. The described 9-Mb inversion is marked by the red box. B. Scheme of the inversion in the context of *ACOX3* and *QDPR* genes. F1, R1, F2, R2 schematically represent the PCR primer design relative to the reference (WT) genome. C. The aligned sequencing reads around detected breakpoints BP1 and BP2 visualized using The Integrative Genomics Viewer (IGV). Soft-clipped nucleotides are highlighted and nucleotides shown. D. Validation studies confirming the variant by PCR using primers F1-R1 and F1-F2. C – child, M – mother, F – Father, WT – wild-type control.

Figure 2. Karyotype analysis from peripheral blood lymphocytes of the parents of the DHPR proband with 9 Mb inversion does not reveal observable pattern abnormality



References:

- [1] Opladen et al., 2012. *J Inherit Metab Dis*, 35(6), 963-973.
- [2] Blau, 2016. *Hum Mutat*, 37(6), 508-515.
- [3] Collins et al., 2017. *Genome Biol*, 18(1), 36.