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Reclassification of a homozygous variant in the *SPR* gene that is implicated in dopa-responsive dystonia due to sepiapterin reductase deficiency

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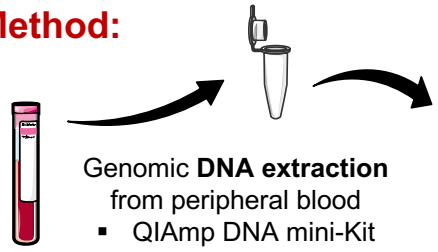
Background and objectives

The proband is a nine-year-old boy, born to consanguineous parents of Palestine origin. He showed developmental and gross motor delay. He gained head control at 9 months, started sitting at 2 years and walking at 3 years. On examination, he had hypotonia, ataxia and periventricular leukomalacia.

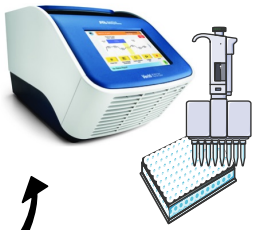
Whole-exome sequencing (WES) of the proband and parents was performed to identify possible genetic variation(s) that may contribute to the proband's clinical presentation.

Method:



Genomic **DNA extraction** from peripheral blood
- QIAmp DNA mini-Kit (Qiagen, Germany)

Mechanical fragmentation
- LE220-plus Focused-ultrasonicator (Covaris, USA)



Library preparation and target enrichment
- TruSeq DNA Exome (Illumina, USA)

Quality control
- Agilent 4200 TapeStation (AgilentTechnologies, USA)
- Qubit 4.0 Fluorometer (Invitrogen, USA)

Sequencing with paired-end reads (2x150bp)
- NovaSeq 6000 platform (Illumina, USA)

Bioinformatics Analysis
- In-house developed pipelines
- Illumina DRAGEN Bio-IT platform
- VarSeq 2.2.4 software, different databases and in silico algorithms

Results:

1. WES analysis of the proband revealed a novel homozygous variant of unknown significance (VUS) in the *SPR* gene, encoding sepiapterin reductase enzyme.

Disease	Gene/Transcript	Variant
Dystonia, dopa-responsive, due to sepiapterin reductase deficiency (OMIM# 612716)	*SPR* (NM_003124.5)	c.560A>G (p.Glu187Gly)

2. Bioinformatic prediction tools (SIFT / PolyPhen-2 / MutationTaster / PDBePISA) indicated that this variant may have a damaging effect on protein function.
3. Cerebrospinal fluid (CSF) evaluation:

Neurotransmitter metabolites in CSF*	Patient result (nmol/L)	Reference range (nmol/L)
5-Hydroxyindoleacetic Acid	7 Low	66-338
Homovanillic Acid	93 Low	218-852
3-O-methyldopa	6	<100

*Electrochemical detection (ECD) coupled with high-performance liquid chromatography (HPLC)

Conclusion:

Biallelic pathogenic variants in the *SPR* gene cause dopa-responsive dystonia due to sepiapterin reductase deficiency (OMIM# 612716).

The variant detected in this study has not been reported in individuals with SPR-related disorders and not identified in large population databases.

Although computational predictions indicated that this change could be damaging, the predictions are not emphatic enough to prove a role in disease. CSF from the patient was biochemically evaluated for SPR deficiency and findings confirmed the diagnosis.

This study may enable reclassification of a *SPR* variant, c.560A>G (p.Glu187Gly), from VUS to likely pathogenic.