Genomic Sequencing Return of Results

Prepared by **Dr. Smith**

30 June 2025

Patient's name: Peter Jones

Patient's age and sex: 2-year-old boy

Authorizing Clinician: Dr. Smith

Principal reason for testing:

- CT or MRI: brainstem atrophy or hypoplasia

Other key findings:

- Microcephaly
- Nystagmus

Consanguinity of parents (relatedness) is 1st cousins

Ethnicity: (unspecified)

Diagnosis # 1

Cerebellar ataxia, impaired intellectual development, dysequilibrium syndrome, VLDLR-related

Mode of inheritance: Autosomal recessive

Gene symbol (HGNC): *VLDLR*

Gene name: Very low density lipoprotein receptor

Relevant variant:

Biallelic in proband, shared with both parents

Chromosomal position: chr9:2643480

Sequence: NM_003383.3:c.1249_1255delTACAAGT;

Effect: frameshift

Pertinent positive findings of the patient for this diagnosis:

- Microcephaly (onset at ~1 month old)
- Nystagmus (onset by ~1 month old)
- Hyperreflexia (onset by ~6 months old)
- VLDLR gene variants (biallelic) (present)
- CT or MRI: brainstem atrophy or hypoplasia (present)

Pertinent negative findings of the patient for this diagnosis:

- (none entered)

Prognosis for Cerebellar ataxia, impaired intellectual development, dysequilibrium syndrome, VLDLR-related

Signs and Symptoms	At what age do people with this disease have these findings?

	Birth	1 month	3 months	6 months	1 year	3 years	6 years	10 years	15 years	25 years	40 years	60 years	80 years
Ataxia	Few	Few	Some	Some	Most	Most	Most	Most	Most	Most	Most	Most	Most
Intellectual / cognitive disability (dementia, speech delay included)	NA	Few	Few	Some	Most	Most	Most	Most	Most	Most	Most	Most	Most
Motor developmental delay	NA	Few	Few	Some	Some	Most	Most	Most	Most	Most	Most	Most	Most
Gait disturbance	NA	NA	NA	NA	Some	Most	Most	Most	Most	Most	Most	Most	Most
Tremors of limbs, trunk or head	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Eye movement deficit (strabismus included)	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Hypotonia	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Nystagmus	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Hyperreflexia	Few	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Foot exam: pes planus	Few	Few	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Seizure movements	Few	Few	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Cataracts	Few	Few	Few	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some
Dysarthria or abnormal sound character	NA	NA	Few	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some
Microcephaly	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few
Stature short	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few
Findings detected by laboratory tests													
VLDLR gene variants (biallelic)	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most
CT or MRI: cerebellar atrophy or hypoplasia	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most
CT or MRI: pontine atrophy or hypoplasia	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
CT or MRI: brainstem atrophy or hypoplasia	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
CT or MRI: lissencephaly	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
KEY	None or NA			Few is ≤ 30%			Some is > 30%				Most is > 85%		

Links for the disease

- GeneReviews: VLDLR-Associated Cerebellar Hypoplasia
- Orphanet entry 1766
- OMIM entry 224050

Incidental ("secondary") findings

(No incidental ("secondary") genes called)

SimulConsult Analysis and Quality Parameters

Quality metrics for annotated variant table

Read 47 rows with 47 variant locations from file TinyTrio.tsv
Number of genomes analyzed: 3: Peter (male), Mama, Papa
RsID listed for 74% of variants
Proband monoallelic variants 87%
Proband variants overlapping with mother 64%
Proband variants overlapping with father 79%
De novo proband variants = 3 of 37 with severity score >1

Frequent de novo variants removed = 2 of 37 with severity score >1
Loss of heterozygosity variants = 0 of 37 with severity score >1

General settings for processing

Frequency too common to consider: cutoff threshold: 0.1
Frequency too common for incidental ("secondary") disease: cutoff threshold: 0.01
Frequency too common for monoallelic: cutoff threshold to reduce variant severity by one: 0.01
Frequencies: maximum of frequency columns 1 and 2
Quality of call: cutoff threshold: 10.0
Depth of read: cutoff threshold: 4
De novo variants: add 1 to Variant Severity if fewer than: 20
De novo variants: subtract 1 from Variant Severity if more than: 100
De novo variants: subtract 2 from Variant Severity if more than: 1000
Pathogenicity model: Loss of function

Conservation Scores

Conservation scores used: Gerp, PhyloP
Gerp threshold above which add 1 to variant severity: 0.0
PhyloP threshold above which add 1 to variant severity: 0.5

Functional Scores

Functional scores used: PolyPhen, Mutation Taster, Sift
PolyPhen threshold above which add 1 to variant severity: 0.5
Sift threshold below which add 1 to variant severity: 0.05

Severity Score Calculations

Severity scores for gene variants are calculated beginning with the type or effect of variant (e.g. synonymous, missense, frameshift) and then modifying the initial score based on several measures, including:
- Functional scores
- Conservation scores
- Frequencies, as provided by the lab
- Pathogenicity scores, as provided by the lab

Note: Determination of significance of primary, secondary and any incidental ("secondary") findings and their selection for reporting were done by clinicians, using all the above, external resources and the SimulConsult® Genome-Phenome Analyzer as inputs.

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