Zellweger spectrum disorder: The case of a missing *PEX1* allele in a fetus with multiple congenital anomalies

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Introduction

PEX1 and *PEX6* encode ATPases that are essential for peroxisome biogenesis, maintenance, and prevention of peroxisome degradation. Biallelic variants in either gene are associated with the peroxisome biogenesis disorder known as Zellweger spectrum disorder (ZSD). This is an autosomal recessive disorder with a broad phenotypic spectrum where severity is inversely correlated with residual protein function[1].

Prenatal Case Presentation

Trio genome analysis was performed on a fetal sample from a patient enrolled in the Prenatal Genetic Diagnosis by Genomic Sequencing (PrenatalSEQ) multicenter study due to ultrasound findings that included cerebral ventriculomegaly, unilateral left clubbed foot, and a cardiac ventral septal defect.

Analysis of filtered sequence variants identified:

- a maternally-inherited pathogenic nonsense variant in *PEX1* [c.2614C>T; p.(Arg872Ter)] (see Figure 1).
- a paternally-inherited pathogenic frameshift variant in *PEX6* [c.1314_1321del; p.(Glu439fs)] (data not shown).

Digenic inheritance has not been reported for ZSD, and the fetal phenotype was non-specific, so this result was non-diagnostic.

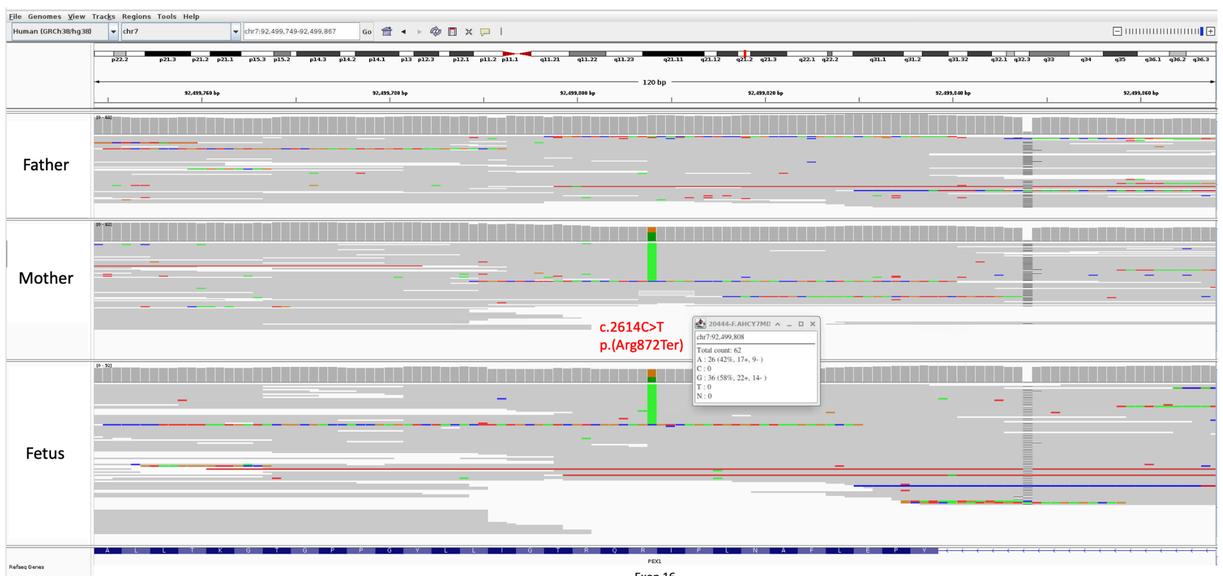

Figure 1: IGV[2] displaying aligned sequence reads for the trio at *PEX1* exon 16

Postnatal Case Presentation

Postnatally the baby had:

- severe hypotonia, respiratory distress, and dysmorphic features.
- state newborn screening that reported an elevated C26:0 ratio of 1.11 µM (cut off <0.15 µM).
- diagnostic biochemical testing that confirmed a diagnosis of a peroxisomal biogenesis disorder.

Subsequent manual review of the trio genome sequence read alignments revealed a paternally-inherited 740 bp *PEX1* deletion variant (c.2719-251_2783+425del) that removes exon 17 of 24 (see Figure 2). These compound heterozygous *PEX1* variants were clinically confirmed by Sanger sequencing and reported by UNC McLendon Molecular Genetics laboratory as consistent with a diagnosis of ZSD.

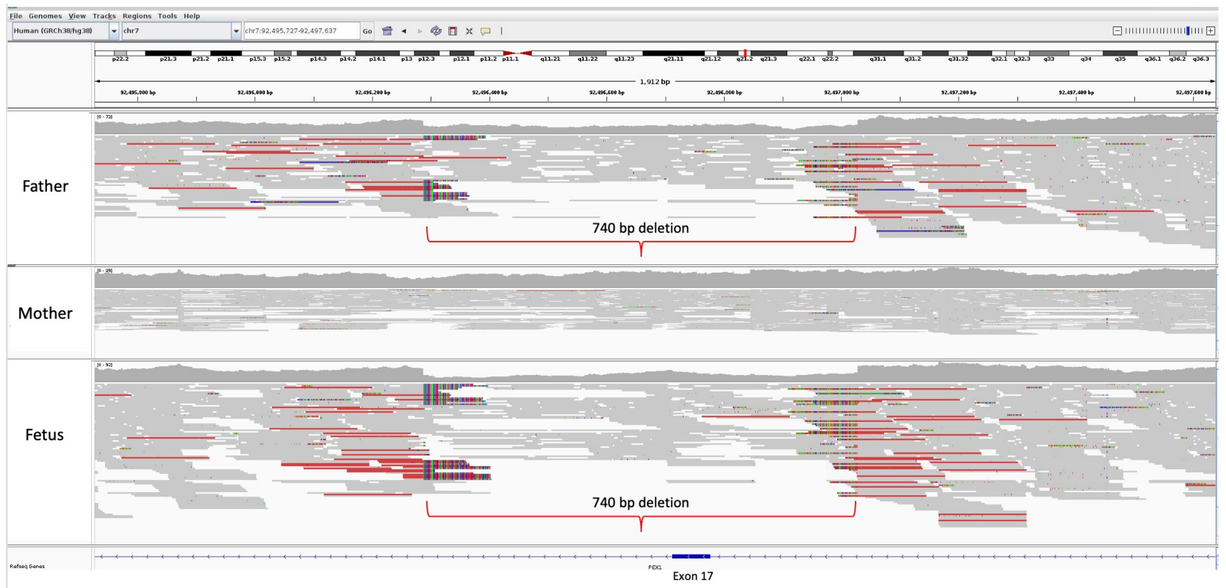

Figure 2: IGV[2] displaying aligned sequence reads for the trio over *PEX1* exon 17

UNC Clinical Reporting

Pathogenic *PEX1* c.2614C>T [p.Arg872Ter] variant:

- nonsense variant in exon of 16 of 24: expected to cause nonsense mediated decay and loss of function.
- rare: allele frequency of 0.0012% in gnomAD[3].
- pathogenic reports by multiple laboratories in ClinVar[4].
- reported as homozygous or compound heterozygous in several unrelated individuals with ZSD[5-8].

Pathogenic *PEX1* c.2719-251_2783+425del variant:

- 740 bp deletion that removes exon 17 of 24: expected to cause frameshift, nonsense mediated decay and loss of function.
- assumed rare: not reported in gnomAD[3], ClinVar[4] or the literature (however, not all single-exon deletions are detected by all genetic tests or genomic methodologies).

Concurrent Commercial Testing

Concurrently, a peripheral blood sample sent to a commercial lab for clinical sequence analysis and deletion/duplication testing of an 18-gene ZSD panel, that included *PEX1* and *PEX6,* failed to identify the 740 bp *PEX1* deletion. The clinical report concluded carrier status for both *PEX1* and *PEX6*.

Communication with the lab resulted in an update to their bioinformatic pipeline such that the 740 bp *PEX1* deletion would be identified on subsequent samples, providing reassurance to the parents that clinical prenatal testing by that lab would identify both *PEX1* variants in future pregnancies .

Conclusions

This case highlights the benefits of research studies to inform and improve clinical care and clinical genetic testing. It also serves as a caution that single-exon deletions are not detected by all genetic tests or genomic methodologies and, as exemplified in this case, may account for some of the missing diagnostic yield from clinical genetic testing.

The nucleotide and protein numbering for the human *PEX1* gene are NM_000466.3 and NP_000457.1. The genomic coordinates for the reported variants in the GRCh38 reference genome are NC_000007.14:g.92499808G>A and NC_000007.14:g.92496288_92497028del. The nucleotide and protein numbering for the human *PEX6* gene are NM_000287.4 and NP_000278.3. The genomic coordinate for the reported variant in the GRCh38 reference genome is NC_000006.12:g.42969720_42969727del.

References

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