Diagnostic Utility of Genome and Transcriptome Sequencing in Identifying *PIGL* Variants Associated with Atypical CHIME Syndrome

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Background

- CHIME syndrome is a rare autosomal recessive disorder of glycosylphosphatidylinositol (GPI) anchor biosynthesis caused by **biallelic pathogenic variants in the *PIGL* gene**.
- Classic features include colobomas, congenital heart defects, ichthyosiform dermatosis, intellectual disability, and ear anomalies.
- Additional features that are frequently reported include larger size at birth, renal/genitourinary anomalies, craniofacial dysmorphisms, short fingers, and elevated alkaline phosphatase levels.
- Recent reports have described individuals with atypical presentations lacking some of the classic phenotypic features[1,2], suggesting broader clinical heterogeneity.

Case Presentation

- 4-year-old male enrolled in the Undiagnosed Diseases Network (UDN)
- Key features: developmental delay, large for gestational age, facial dysmorphisms
- Genitourinary anomalies: hydronephrosis, renal cyst, ureteropelvic junction obstruction
- Additional findings: dry skin, no overt colobomas, cardiac status unavailable
- Prior genetic testing (2021–2022) was non-diagnostic: chromosomal microarray, autism/intellectual disability gene panel, trio-based exome sequencing

Methods

- Trio-based genome sequencing
- Structural variant analysis
- Transcriptome sequencing

Results

- Compound heterozygous *PIGL* variants were identified through genome sequencing.
- Maternal allele: recurrent/founder missense variant c.500T>C (p.Leu167Pro).
- Paternal allele: novel ~7.33 kb exon 2 deletion missed by exome-based CNV callers.
- Transcriptome sequencing demonstrated loss of exon 2, with partial nonsense mediated decay suggested by reduced transcript expression (~30% reduction) and biased allele expression at c.500 (12T:2C), confirming a deleterious functional impact.

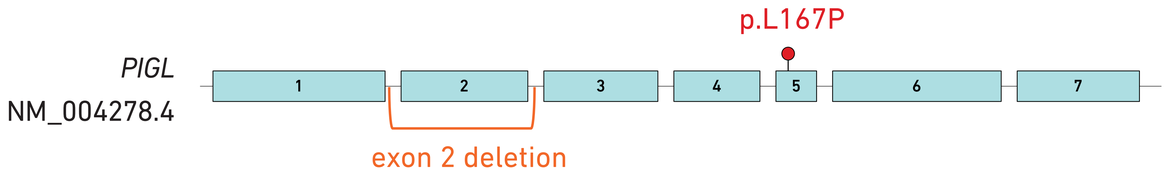

Figure 1: *PIGL* gene structure and the variants identified in the patient.

Gene	P Value	Z score	L2fc	Fold Change
PIGL	0.001625	-2.97	-0.49	0.71

Table 1: Reduced *PIGL* gene expression calculated by DROP Outrider.[3]

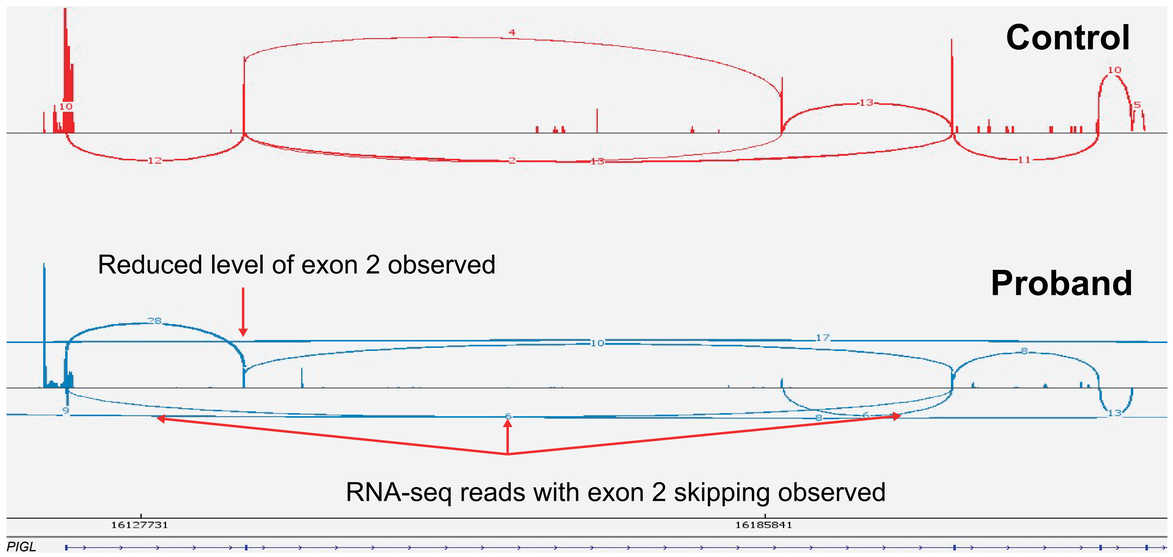

Figure 2: RNA sequencing of fibroblast-derived RNA demonstrated skipping of *PIGL* exon 2.

Why This Matters:

Genome sequencing enables exon-level copy number variant (CNV) detection beyond exome limits; transcriptomics provides functional validation.

Discussion

- CHIME syndrome exhibits **broader phenotypic variability** than traditionally appreciated.
- Individuals harboring the recurrent *PIGL* c.500T>C variant or other heterozygous pathogenic variant who **do not exhibit a classic CHIME** phenotype may warrant targeted evaluation for **exon-level deletions** with **further phenotype correlation**.
- Integrated genome and transcriptome sequencing is particularly valuable for genes with **mixed variant architectures**.
- Reanalysis of previously non-diagnostic cases may yield diagnoses when founder alleles mask a second undetected variant.

Conclusions

- Integrated genome and transcriptome sequencing enabled a definitive diagnosis in an individual with previously non-diagnostic testing.
- This case highlights the value of comprehensive molecular approaches for atypical or incomplete presentations in rare genetic disorders.

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References:

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2. Rolland M *et al.*, Child with a mild CHIME syndrome phenotype and carrying a novel p.(Asp52Asn) *PIGL* pathogenic variant in association with the previously reported p.(Leu167Pro) variant: A case report. Pediatr Dermatol. 2022. PMID: 35258128.
3. Yepez et al., Clinical implementation of RNA sequencing for Mendelian disease diagnostics. Genome Med. 2022. PMID: 35379322

Acknowledgments:

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