RNAseq Provides Evidence of Pathogenicity for a Familial *CHD3* Variant in a Patient with Macrocephaly and Global Developmental Delay

Sydney A. Lau, MS, CGC[1], Tinsley Douglas, MSc, MS, CGC[2], Sarah Dugan, MD[2], Robert Rigobello, MS, CGC[1], Lisa Salz, MS, CGC[1], Leah Campbell, MS, CGC[1], Eileen Barr, MS, CGC[1], Jason Chibuk, MS, CGC[1], Alexandra E. Isaacs, MS, CGC[1], Mei Ling Chong, PhD[1,3], Xiaonan Zhao, PhD, FACMG[1,3], Hongzheng Dai, PhD, FACMG[1,3], Christine Eng, MD[1,3]

1. Baylor Genetics, Houston, TX, USA
2. Department of Medical Genetics and Genomics, Providence Medical Group, Spokane, WA, USA
3. Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

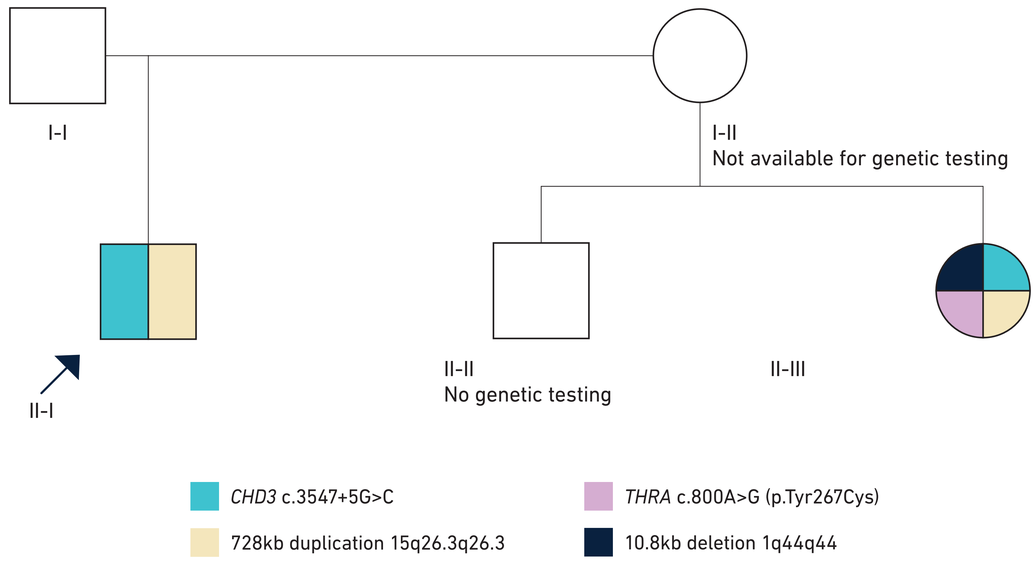
GEN194

Background

- RNA sequencing (RNAseq) can provide crucial functional data for accurate interpretation of diagnostic genome sequencing (GS) results.
- Here, we describe a patient with macrocephaly and global developmental delay (DD) who was found to carry a familial intronic variant in the *CHD3* gene, originally classified as a variant of uncertain significance (VUS).
- Pathogenic variants in *CHD3* are associated with Snijders Blok-Campeau syndrome (SNIBCPS), an autosomal dominant neurodevelopmental disorder characterized by global DD, intellectual disability (ID), hypotonia, delayed speech acquisition, and dysmorphic features.[1]
- Clinically validated RNAseq on this VUS upgraded its classification to likely pathogenic (LP). This provided impactful diagnostic information for the patient and family.

Patient History

- 5-year-old male with macrocephaly, global DD, language impairment, cognitive impairment, attention deficit hyperactivity disorder, and speech delay.
- Prenatal care was limited with possible *in utero* exposure to substances.
- Family history was significant for the mother having ID and a maternal half-brother with history of DD, now resolved, sensory processing disorder, and 99th percentile for height.
- The patient also has a maternal half-sister with hearing loss, global DD, language impairment, pulmonic stenosis, and obesity. She had several rounds of genetic testing, described below.
- **Given the similarities in the proband and sister's phenotypes, a shared condition was suspected.**



Proband GS Results

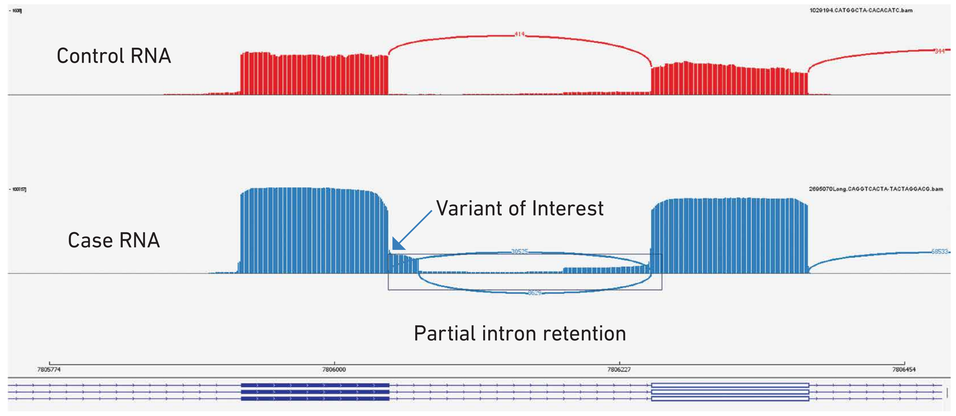
DISEASE	INHERITANCE PATTERN	GENE/ VARIANT	VARIANT TYPE	GENOTYPE	INHERITED FROM	VARIANT CLASSIFICATION
Snijders Blok-Campeau Syndrome	Autosomal Dominant	CHD3: c.3547+5G>C	Sequence Variant	Heterozygous	Unknown	Variant Of Uncertain Significance

The 15q26.3q26.3 duplication was observed in the proband's sample, but the 1q44q44 deletion and *THRA* variant were absent.

RNAseq Results

Reflex RNAseq was performed on this variant as it was predicted to impact splicing via SpliceAI (DG: 0.94; DL: 0.33).* A retained in-frame intron was identified, adding 8 amino acids that may disrupt a critical region of the protein by altering the conformation of the helicase C terminal domain. Deleterious missense variants in this domain have been reported in patients with SNIBCPS.[2,3,4]

*Donor loss (DL) represents the predicted decrease in 5′ splice site recognition probability caused by a variant, indicating potential disruption of a canonical donor site. Conversely, donor gain (DG) reflects the predicted increase in donor site probability, suggesting creation of a cryptic splice site.



Sashimi plot of *CHD3* c.3547+5G>C shows partial intron retention compared to the control RNA.

This additional functional evidence allowed the variant to be reclassified as LP.

DISEASE	INHERITANCE PATTERN	GENE/ VARIANT	VARIANT TYPE	GENOTYPE	INHERITED FROM	VARIANT CLASSIFICATION
Snijders Blok-Campeau Syndrome	Autosomal Dominant	CHD3: c.3547+5G>C	Sequence Variant	Heterozygous	Unknown	Likely Pathogenic

The 15q26.3 duplication was not considered diagnostic for either sibling despite partial overlap with a known 15q overgrowth syndrome. The 1q44q44 deletion is still being considered as part of the proband's maternal half-sister's phenotype.

Conclusions

- **Reclassification of the *CHD3* variant by RNAseq provided a genetic diagnosis for the patient and his family. The patient's phenotype is consistent with features associated with SNIBCPS.**
- **Reclassification of the variant to LP further supported the diagnosis for this patient, allowing the patient to continue receiving support services.**
- **Data from this reclassification allowed the laboratory that performed the sister's testing to reclassify this variant as LP, confirming the genetics team's suspicion that the patient and sister have the same diagnosis. The siblings have overlapping but different features of SNIBCPS, demonstrating intrafamilial variability of the condition.**
- **The half-brother was not tested, but he did not appear to have SNIBCPS after review of his history which provided reassurance to his adoptive family.**
- **This case highlights how comprehensive genomic assessment paired with RNAseq can make definitive diagnoses across multiple family members.**

Presented at the National Society of Genetic Counselors (NSGC) Annual Conference, Nov 6-10, 2025, Seattle, WA.

References:

1. Tie, X. *et al.* PMID: 39542866
2. Snijders Blok, L. *et al.* PMID: 30397230.
3. Gao, Y *et al.* PMID: 39050258.
4. van der Spek, J *et al.* PMID: 35346573.