A 10-Year-Old Male with Four Genetic Diagnoses and a Complex Multisystem Presentation

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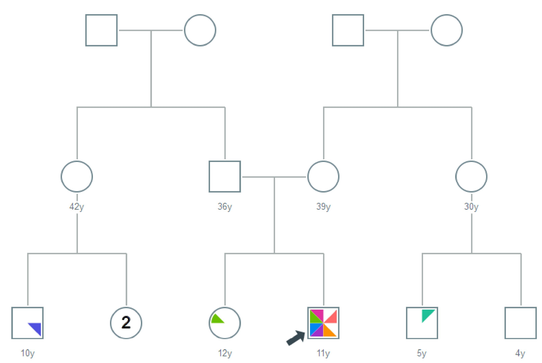
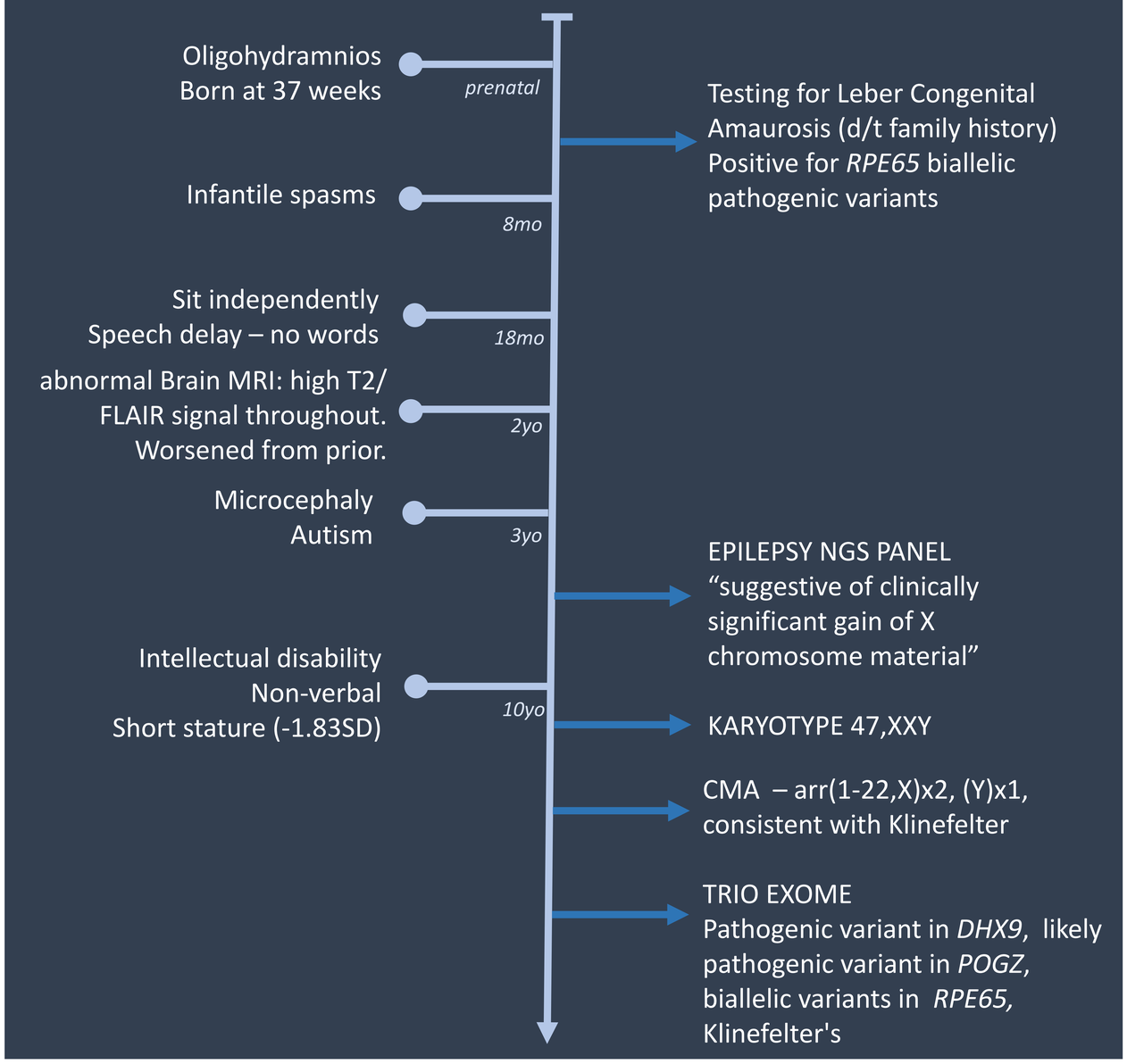
INTRODUCTION

- Recently, comprehensive exome / genome sequencing has been recommended as the first line genetic test for NDDs
- Even in well selected cohorts, genetic etiologies are only identified in up to ~50% of cases
- With comprehensive approaches to testing increasing in feasibility, cases with multiple diagnoses are being increasingly reported.
- Among 18,766 patients tested at a diagnostic laboratory, only nine cases (~0.05%) were found to have four concurrent genetic diagnoses (internal Ambry Genetics data).
- Here, we report a 10-year-old male with complex NDD features found to have four distinct genetic conditions. This case underscores the blended phenotype and the clinical management challenges that can arise when multiple genetic disorders co-occur.

Family History



Clinical Features



GENETIC TESTING RESULTS

	RPE65	Klinefelter's	*DHX9*	*POGZ*
Variant (s)	c.11+5G>A p.? and c.1249G>C p.E417Q	47,XXY	c.1704C>A p.Tyr568*	c.3540_3543del p.M1180Ifs*12
Inheritance	Recessive	*De novo*	*De novo,* dominant	*De novo, dominant*
Classification	Pathogenic	Pathogenic	Pathogenic	Likely pathogenic
Diagnosis	Leber Congenital Amaurosis	Klinefelter's	*DHX9* - related NDD	White - Sutton Syndrome
Condition Features	• LCA • EOSRD • Juvenile RP	• Mild delays and some learning differences • Tall Stature • Gynecomastia • Infertility	• GDD • Mild – severe ID • seizures • Poor speech • Brain abnormalities • Autism	• Microcephaly • GDD • Mild ID • Seizures • Visual anomalies • GI concerns • Autistic features

DISCUSSION

- Multilocus genetic variation produced a blended phenotype and increased clinical complexity.
- Overlapping features associated with the four diagnoses may synergistically influence phenotype.
- Klinefelter syndrome typically causes tall stature, this patient's short stature is better explained by coexisting conditions.
- *DHX9* and *POGZ* mutations in isolation are typically associated with milder phenotypes
- The combined effect of variants across multiple genes may account for this patient's more severe phenotype.
- No datasets in the literature show a strong correlation of mRNA or protein expression between DHX9 and POGZ across tissues or conditions. There may be an indirect functional overlap between these genes, as both are involved in transcriptional regulation, RNA-DNA processing, and chromatin organization. This remains speculative.
- Genetic counseling and clinical management included addressing each symptom individually and conveying uncertainty about projected phenotypic outcome

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