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

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Introduction

Cases of multiple genetic diagnoses in one individual have become more common in recent years as broader testing technologies have been introduced to clinical care. We report a 10-year-old patient with complex neurodevelopmental symptoms found to have four distinct genetic conditions. In 18,766 patients tested at a large diagnostic laboratory, 4 concurrent genetic diagnoses have been identified in only 9 cases (~0.05%). This case provides an opportunity to examine the blended phenotype and management challenges resulting from multiple co-occuring genetic conditions

Case Presentation

The patient presented to Emory Genetics at 10 years old due to Klinefelter Syndrome (47,XXY). At that time, clinicians noted clinical features beyond what could be explained by this diagnosis. The patient was non-verbal with intractable seizures (Lennox-Gastaut syndrome), motor delay, intellectual disability (ID), and autism; microcephaly and abnormal brain MRI demonstrating non-progressive white matter lesions; short stature (2nd percentile) and poor growth requiring G-Tube feeds from 6-8 years old; Leber Congenital Amaurosis (LCA), nystagmus and myopia; hypotonia; GI concerns including GERD, constipation and eosinophilic esophagitis; and sleep apnea requiring tonsillectomy and adenoidectomy, recurrent acute otitis media.

Diagnostic Workup

- *RPE65* targeted testing (2014): familial variants detected in proband and sister
- Epilepsy Panel (302 genes, 2023): Negative with the comment "suggestive of clinically significant gain of the X Chromosome material"
- Karyotype Chromosome Analysis (2023): 47,XXY
- SNP Array (2024): full X chromosome duplication consistent with Klinefelter syndrome (47,XXY)
- Trio Exome Sequencing (2024):
    - Pathogenic *de novo* heterozygous *DHX9* NM_001357.5: c.1704C>A p.Tyr568*, associated with *DHX9*-related Neurodevelopmental Disorder (NDD)
    - Likely pathogenic *de novo* heterozygous *POGZ* NM_015100.4 c.3540_3543del p.M1180Ifs*12, associated with White-Sutton Syndrome
    - Compound heterozygous Pathogenic variants in *RPE65* NM_000329.3 c.11+5G>A and c.1249G>C p.E417Q, associated with *RPE65*-related retinopathy

Treatment and management

Clinical management is complicated by multiple diagnoses. Reviewing each condition individually helped guide treatment decisions but required accommodation for the unique phenotype resulting from multilocus genetic contributions.

RPE65-related LCA and Klinefelter Syndrome have established clinical guidelines; the patient had prior gene therapy for LCA and follows with ophthalmology and the Emory eXtraordinarY clinic. White Sutton Syndrome *(POGZ)* and *DHX9*-related NDD are more recently described and have significant clinical overlap and variable expressivity. The patient had seen relevant specialists in neurology, ophthalmology, developmental pediatrics, GI, and ENT. Based on several reported cases with cardiac concerns in individuals with *DHX9* variants, he was referred for an echocardiogram.

Outcome and Follow-up

Four individual genetic diagnoses were identified in one patient, resulting in a complex, syndromic phenotype. Together, these explain all observed symptoms. Follow-up with relevant specialists, as needed, was recommended.

Discussion

This case demonstrates how pathogenic variation at multiple loci can produce a blended phenotype and increased clinical complexity. Overlapping features associated with *POGZ, DHX9, RPE65,* and Klinefelter may synergistically influence phenotypic expression. Although Klinefelter syndrome typically causes tall stature, this patient's short stature and broader phenotype are better explained by coexisting monogenic conditions.

DHX9 and *POGZ* mutations in isolation are typically associated with milder phenotypes, though severe presentations with absent speech and profound NDD have been reported. The combined effect of variants across multiple genes may account for this patient's more severe phenotype.

Conclusion

The diagnostic odyssey for this patient included five different genetic testing methods, but detection of all genetic findings can now be accomplished with exome and microarray alone. This case supports the 2025 American Academy of Pediatrics genetic testing guidelines, which recommend concurrent microarray and exome sequencing as first-line tests for children with NDD or ID.