Resolving the diagnostic odyssey in a patient with MNGIE and ring chromosome 22

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BACKGROUND

Comprehensive genomic technologies such as genome sequencing have **enabled timely diagnoses and improved patient outcomes**.

- However, diagnosis for rare diseases relies heavily on phenotypic assessment, specific clinical guidelines for genetic testing, and overall access to care
- Multiple molecular diagnoses are made in over 7% of patients having WGS[1]

We present a patient case report that highlights the complexities and implications of the evolving genomic medicine landscape.

CASE REPORT

Year:

2015

An adolescent female with global developmental delay and intellectual disability presents to clinic

- Diagnosis of Phelan-McDermid syndrome was made:
- Microarray – 22q13.3 terminal deletion
- Karyotype – Ring chromosome 22

- Atypical for PMS, the patient was also malnourished
- Child Protective Services became involved due to this concern

2020

- Brain MRI performed due to worsening symptoms
- MRI identified progressive white matter disease, also atypical for PMS

Differential diagnoses included metabolic, mitochondrial, and neurodegenerative disorders, as well as autoimmune encephalopathy

2022

Metabolomic profiling performed, which detected elevated thymidine

- Genome sequencing performed, identifying a pathogenic variant in TYMP on chr 22
- Due to the chr 22 deletion, she was hemizygous for this variant

AR mitochondrial neurogastrointestinal encephalopathy (MNGIE) diagnosis was made, consistent with her complex phenotype

DISCUSSION

A complete diagnosis took **over 7 years and several rounds of testing** to make for this patient. **Genomic sequencing as a first-tier test could have shortened the diagnostic odyssey** by simultaneously identifying both findings. This approach also could have potentially prevented CPS involvement.

This report also illustrates the pivotal role of **post-test genetic counseling and risk assessment** for patients with rare diseases diagnosed prior to the adoption of genomic sequencing as a first-tier diagnostic tool. **Updated, comprehensive genetic evaluations** are clinically important, especially when the phenotype deviates or is more complex than the original diagnosis.

Conclusions: First-tier genomic testing can establish a complete diagnosis for patients, including those with complex phenotypes that traditional targeted approaches could miss. Comprehensive genetic counseling prevents gaps in care due to updates in available testing and recommendations.

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References: (1) Chau, M, et al. (2023, November 1-5). Not just one: the utility of whole genome sequencing for making a dual molecular diagnosis. American Society of Human Genetics, Washington, DC.