Taking off traditional counselling Redefined approach

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Introduction

VUS are genetic variants whose association with disease risk is not clearly established, making it difficult to determine their clinical significance. The presence of VUS can lead to uncertainty for patients and healthcare providers, complicating decision-making processes regarding disease risk assessment, surveillance, and treatment strategies.

Ongoing research and advancements in genetic databases are essential to reclassify VUS, thereby improving the accuracy and utility of genetic testing in personalized medicine.

82% A survey of genetic counselors found that 82% reported encountering patients with VUS, highlighting the need for improved interpretation tools and guidelines

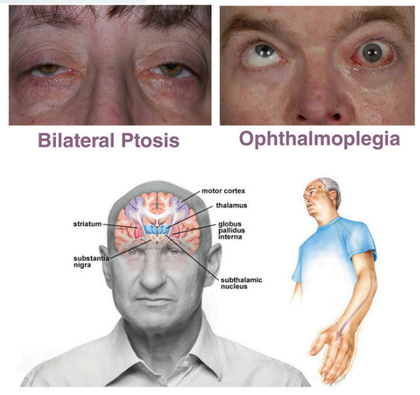
- Research indicates that around 10% of VUS are reclassified within a five-year period, with the majority being downgraded to benign.
- Studies suggest that up to 20-30% of genetic test results may include at least one VUS.
- VUS varies among different populations

Oculopharyngodistal myopathy-4

Oculopharyngodistal myopathy-4 is an autosomal dominant neuromuscular disorder characterized by progressive ptosis, ophthalmoparesis facial and masseter weakness, and muscle weakness in the distal limbs. Initial symptoms typically appear in the second or third decades of life

Incomplete penetrance

In one generation, individuals might possess a specific variant of a gene linked to a hereditary condition but remain symptom-free. However, in subsequent generations, the same gene variant can manifest as a distinct phenotype, indicating the condition. This variability can be influenced by factors such as environmental conditions, genetic background, and epigenetic modifications.



Investigations

Whole Exome Sequencing (WES) revealed a Variant of Uncertain Significance (VUS) in the RILPL1 gene (NM_178314.5), specifically the Pro266Thr (c.796C>A) mutation. Given the gene's association with neuromuscular and neurodegenerative conditions, further investigation was warranted.

Results & Reclassification

Segregation analysis revealed that the patient's father, though asymptomatic, carried the same Pro266Thr variant, indicating incomplete penetrance. The patient's symptomatic siblings also carried the variant. Both of the patient's children were found to carry the variant, raising concerns for their future health. Pedigree analysis showed that a daughter from the patient's father's first marriage exhibited similar symptoms and carried the same variant. These findings provided compelling evidence for the variant's pathogenicity, leading to its reclassification from a VUS to Pathogenic.

Background

Pre-test Counselling → **Post-test Counselling** → **Reclassification**

A male patient from a non-consanguineous marriage presented with bilateral ptosis, ophthalmoplegia, parkinsonism, generalized muscle fatiguability, seizures, hallucinations, and myoclonic jerks. Despite severe symptoms, his MRI brain scans were normal. The patient's mother had passed away, but similar symptoms in his siblings suggested a hereditary condition.

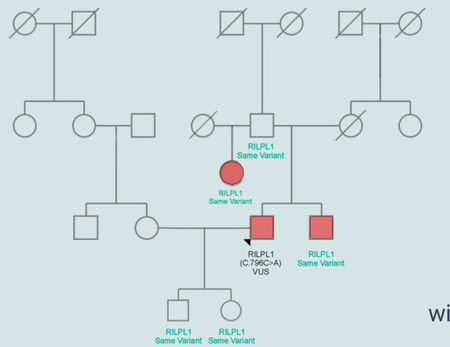
Clinical details

The patient exhibited significant neuromuscular and neurodegenerative symptoms, yet brain MRI scans showed no abnormalities, suggesting a genetic basis for the disease.

Family history

The patient's siblings exhibited similar symptoms, indicating a hereditary pattern. The patient's 72-year-old father was asymptomatic, highlighting incomplete penetrance.

Pedigree



RILPL1
(C.796C>A) VUS

The same Pro266Thr variant within the generations.

Genetic counselling

With the reclassification of this variant from a VUS to Pathogenic, there is a significant increase in the family's anxiety and concern, especially as the proband's children also carry the variant. Genetic counselling focused on providing essential psychological support, helping the family understand the implications of the variant Furthermore, it facilitated a crucial connection between the family and neurologists, ensuring a coordinated approach to ongoing management and care.

Conclusion

This case underscores the critical role of **Genomic variants in personalized healthcare.** Comprehensive genetic analysis and family studies led to the reclassification of a VUS to pathogenic, significantly influencing clinical management. Genetic counselling facilitated precision diagnosis and personalized healthcare, demonstrating its vital role in improving patient outcomes.