

A Novel GNAL Mutation Identified by Whole Exome Sequencing is Associated with Familial Generalized Chorea

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Objective

To report a unique case of familial generalized chorea and a likely genetic etiology identified using whole exome sequencing.

Background

- Chorea is a continuous, irregular, involuntary abnormal movement that flows randomly from one body part to another.
- It can be seen in primary inherited neurologic disorders, as well as in autoimmune, metabolic, and other conditions and can lead to significant functional impairment.
- Although there are numerous causes of hereditary chorea, in the absence of clues to a specific diagnosis on history, examination, or neuroimaging, the etiology may prove elusive without sophisticated genetic testing.
- To an increasing extent, whole exome sequencing is being employed to this end.

Methods

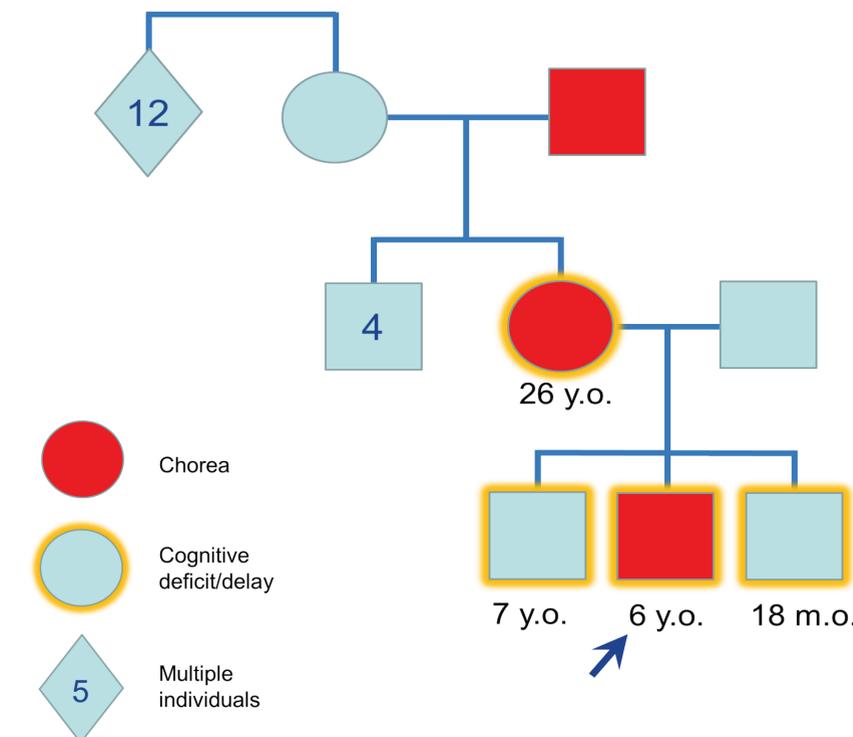
- We describe a 6 year-old boy with global developmental delay.
- At 24 months of age, he developed persistent, continuous, random-appearing generalized involuntary movements that interfered with walking and manual tasks.
- His mother also has cognitive deficits, and had onset of similar-appearing generalized chorea at age 7.
- His two siblings also have developmental delay.
- The estranged maternal grandfather also was reported to have similar movements.
- Extensive workup was unrevealing, including:
 - Brain MRI and chromosomal microarray
 - Serum copper and ceruloplasmin
 - Huntington disease (HTT) gene sequencing
 - Benign hereditary chorea (NKX2-1) gene sequencing
 - Huntington disease-like 2 (HDL2) gene sequencing
- Whole exome sequencing was performed.

Results

- Whole exome sequencing revealed a heterozygous c.334C>A (p.Q112K) novel variant of unknown clinical significance (VUS) in the GNAL gene.
- FISH analysis confirmed the same mutation in his mother.
- Deleterious mutations in GNAL are known to be the cause of dystonia 25 (DYT25), an autosomal dominant focal dystonia that typically involves the neck and face, but have not previously been described in association with chorea.

Conclusions

- Whole exome sequencing has quickly become a powerful tool in determining specific gene defects related to heritable disorders.
- The use of this and emerging technologies like whole genome sequencing can be vital to the identification and, optimistically, the eventual molecular treatment of disorders such as this.



References

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