Novel PLP1 gene mutation discovered by whole genome sequencing in brothers with infantile onset dopa-responsive dystonia and delayed central nervous system demyelination

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Neuropathological mutations in PLP1 are rare but have been noted to cause both dystonia and an leukodystrophy. We report the clinical features and identification of a novel PLP1 gene mutation (c.617T>A, p.M206K) in two affected male siblings.

Methods

We performed whole genome sequencing including both affected siblings and their unaffected sister. Candidate gene variant discovery analysis involved heuristic filtering and probabilistic approaches facilitated by Golden Helix and VAAST software analyses, respectively, revealing an X-linked mutation in the PLP1 gene (proteolipid protein 1 gene, c.617T>A, p.M206K) in the two affected male siblings and the mutation was heterozygous in their carrier mother, who was a carrier. This mutation was not found in the NCBI dbSNP135, 1000 Genomes, or HMDP databases and appears novel. The PLP1 protein is the predominant myelin protein present in the CNS, playing a role in the stabilization and maintenance of myelin sheaths and myelin in PLP1 have been reported to cause both dystonia and leukodystrophy. The lack of early CNS dysmyelinating/demyelinating features and CSF studies indicating a possible diagnosis of dopa-responsive dystonia contributed to a substantial delay in diagnosis. This report emphasizes the value of whole genome sequencing for causal variant discovery in children with undiagnosed neurologic disorders.

Results

Figure 1: Family Pedigree

Figure 2: Flowchart of Variant Filtering and Causal Variant Discovery Methods

Figure 3: Sanger Sequencing of PLP1 variant

Figure 4: Multiple protein sequence alignment PLP1

Figure 5: Protein position of p.M206K compared to known PLP1 mutations causing PMD

PLP1 (proteolipid protein 1):
- Major myelin protein in CNS
- Found on the surface of oligodendrocytes
- PLP1 mutations cause Pelizaeus-Merzbacher Disorder (PMD) - an X-linked dysmyelination disorder

PLP1 gene

HMG variants

Neuron

Oligodendrocytes

Development and matured

Amnion, Axon Scaffolding

Myelin

Normal, Efficient Neuron Signaling

Dysfunctional PLP1

Abnormal, Inefficient Neuron Signaling

Pelizaeus-Merzbacher Disorder (PMD)

Figure 4: Several species sequences for a section of the PLP1 protein are shown, with the species name on the right of the sequence. Amino acid changes from the Human sequence are in bold blue text. Amino acid 206 where the family mutation (p.M206K) is located is boxed in red, as well as the K in the first row above the multiple sequence alignment which is the family mutation. The other positions with amino acid changes in red at the top of the figure are nearly variants that are listed in HMDP as causative of Pelizaeus-Merzbacher disease (PMD). PLP1 is a member of the larger PLP/DM family, and for some earlier sequences the amino acid at this position is Glutamine (Q) in shark and fish, e.g. astaeryl PLP1. Even as the novel lysine (K) was not seen in these multiple sequence alignments at amino acid residue 206.

Conclusions:
- The PLP1 missense variant (c.617T>A, p.M206K) was found by both Vaast and Golden Helix variant discovery methods.
- The presence and the segregation of this variant with disease was confirmed by Sanger sequencing.
- This variant was not found in dbSNP135, 1000 Genomes, or HMDP, so it appears to be a novel variant.
- The novel PLP1 mutation (c.617T>A, p.M206K) to lysine was not seen in other species in the MSA.
- Several variants of known pathogenicity for Pelizaeus-Merzbacher disease have been reported near the p.M206K variant.

The PLP1 mutation (c.617T>A, p.M206K) segregated with disease in the family with an X-linked inheritance pattern.

Symptoms correlate with Pelizaeus-Merzbacher disease: Leukodystrophy, dystonia, seizures, progressive spasticity.

Delayed onset of CNS demyelination made clinical diagnosis difficult, while genome NGS discovered the disease gene.

A neurological disorder of unknown genetic etiology was elucidated by genome NGS to be an atypical case of PMD.