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Researchers identify mitochondrial mutation linked to congenital myasthenic syndrome

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Although significant progress has been made over the last 25 years to identify genetic abnormalities associated with congenital myasthenic syndromes (CMS), many patients remain genetically undiagnosed. A report in the inaugural issue of the *Journal of Neuromuscular Diseases* identifies a gene defect in mitochondria, specifically the citrate carrier SLC25A1, that may underlie deficits in neuromuscular transmission seen in two siblings.

"While mitochondrial gene defects can cause a myriad of neurological disorders including myopathies and neuropathies, these have not been specifically implicated in defects of the neuromuscular junction," says Hanns Lochmüller, MD, Professor of Experimental Myology, Institute of Genetic Medicine, MRC Centre for Neuromuscular Diseases, Newcastle University, Newcastle upon Tyne, UK.

Of the 19 genes that have been implicated in CMS, most express proteins involved in neuromuscular synapse development and function. These mutations usually involve post-synaptic proteins. The current study shifts the area of impairment to the presynaptic region.

Investigators conducted genomic analyses of two patients who are brother and sister. The pair was born to healthy parents who were first cousins. "The family history was highly suggestive of autosomal recessive inheritance," notes Dr. Lochmüller. Since childhood, the 33-year-old brother had displayed some speech and motor problems that worsened with exercise and improved with rest. He had mild bilateral

ptosis (drooping of the eyelid), speech difficulties, and mild learning disabilities. His 19-year-old sister showed delayed development including recurrent falls, fatigable limb weakness, intermittent double vision, and some drooping of facial muscles.

The investigators performed homozygosity mapping and whole exome sequencing to determine the underlying genetic cause of the siblings' condition and successfully identified a homozygous mutation in the SLC25A1 gene. SLC25A1 is a mitochondrial citrate carrier believed to be a key component in many important biological processes, such as fatty acid and sterol biosynthesis, gluconeogenesis, glycolysis, maintenance of chromosome integrity, and regulation of autophagy.

Using electrophysiologic techniques, researchers were able to show clear abnormalities in the neuromuscular junctions of the patients, as evidenced by increased jitter or jitter with blocking of muscle fibers.

Researchers also found evidence that SLC25A1 may be required for normal neuromuscular junction formation by looking at the effects of reduced expression of SLC25A1 in zebrafish embryos. Anatomically, while the muscle fibers appeared normal, presynaptic motor axon terminals were shortened and grew erratically, with no evidence of complete synapse formation. They also saw structural changes in the brain and heart, which mirrored abnormalities seen in humans.

"It is still not clear how deficits in a mitochondrial citrate carrier result in neuromuscular junction defect," comments Dr. Lochmüller. However, while mutations in SLC25A1 may prove to only be a rare cause of CMS, he and his co-investigators advise clinicians that should a patient show fatigable weakness, it may be appropriate to test for SLC25A1 mutations and consider screening for cardiac and metabolic defects should these mutations be found.

"We aimed to identify the underlying molecular defect in this family ever since we met them first in clinic more than 20 years ago," adds co-investigator Kate Bushby, MD, Professor of Neuromuscular Genetics, Institute of Genetic Medicine, MRC Centre for Neuromuscular Diseases, Newcastle University. "We are pleased that latest sequencing technology has resolved this long-standing diagnostic puzzle, which helps us in counseling and treating them more effectively".

Congenital myasthenic syndromes (CMS) are a group of inherited neuromuscular disorders characterized by muscle weakness (myasthenia). Typical symptoms include weakness of muscles controlling limbs, as well those involved with control of the eyes, respiration, and movements of the face, head, and neck (due to involvement of the corticobulbar tract). The symptoms are fatigable, meaning that they worsen with repetition, and severity of the deficits can range from mild to severe.

More information: "Mutations in the Mitochondrial Citrate Carrier SLC25A1 Are Associated with Impaired Neuromuscular Transmission," by Amina Chaouch et al.
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