Abstracts

Articles appearing in the April 2018 issue

Truncating *SLC5A7* mutations underlie a spectrum of dominant hereditary motor neuropathies

Objective To identify the genetic cause of disease in 2 previously unreported families with forms of distal hereditary motor neuropathies (dHMNs).

Methods The first family comprises individuals with dHMN type V, which lacks the cardinal clinical feature of vocal cord paralysis characteristic of dHMN-VII observed in the second family. Next-generation sequencing was performed on the proband of each family. Variants were annotated and filtered, initially focusing on genes associated with neuropathy. Candidate variants were further investigated and confirmed by dideoxy sequence analysis and cosegregation studies. Thorough patient phenotyping was completed, comprising clinical history, examination, and neurologic investigation.

Results dHMNs are a heterogeneous group of peripheral motor neuron disorders characterized by length-dependent neuropathy and progressive distal limb muscle weakness and wasting. We previously reported a dominant-negative frameshift mutation located in the concluding exon of the *SLC5A7* gene encoding the choline transporter (CHT), leading to protein truncation, as the likely cause of dominantly inherited dHMN-VII in an extended UK family. In this study, our genetic studies identified distinct heterozygous frameshift mutations located in the last coding exon of *SLC5A7*, predicted to result in the truncation of the CHT C-terminus, as the likely cause of the condition in each family.

Conclusions This study corroborates C-terminal CHT truncation as a cause of autosomal dominant dHMN, confirming upper limb predominating over lower limb involvement, and broadening the clinical spectrum arising from CHT malfunction.

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Diagnostic odyssey of patients with mitochondrial disease: Results of a survey

Objective To document the complex “diagnostic odyssey” of patients with mitochondrial disease.

Methods We analyzed data from 210 Rare Diseases Clinical Research Network Contact Registry participants who were patients with a biochemical deficiency or self-reported diagnosis of mitochondrial disease, or their caregivers.

Results Participants saw an average of 8.19 clinicians (SD 8.0, median 5). The first clinician consulted about symptoms was typically a primary care physician (56.7%), although 35.2% of participants initially sought a specialist. Of note, 55.2% of participants received their diagnosis from a neurologist, 18.2% from a clinical geneticist, and 11.8% from a metabolic disease specialist. A majority of the participants (54.6%) received 1 or more nonmitochondrial diagnoses before their final mitochondrial diagnosis. In their pursuit of a diagnosis, 84.8% of participants received blood tests, 71% a muscle biopsy, 60.5% MRI, and 38.6% urine organic acids. In addition, 39.5% of the participants underwent mitochondrial DNA sequencing, 19% sequencing of nuclear genes, and 11.4% whole-exome sequencing.

Conclusions The diagnostic odyssey of patients with mitochondrial disease is complex and burdensome. It features multiple consultations and tests, and, often, conflicting diagnoses. These reflect disease variety, diagnostic uncertainty, and clinician unfamiliarity. The current survey provides an important benchmark. Its replication at appropriate intervals will assist in tracking changes that may accompany increased popularity of exome testing, more rigorous diagnostic criteria, increased patient-reported outcome activity, and trials for promising therapies.

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