Targeted next-generation sequencing panels in the diagnosis of Charcot-Marie-Tooth disease

Andrea Cortese, MD, PhD, Janel E. Wilcox, MS, CGC, James M. Polke, PhD, et al.

Cite as: Neurology® 2020;94:e51-e61. doi:10.1212/WNL.0000000000008672

Study objective and summary result
This study examined the utility of targeted next-generation sequencing (NGS) panels for achieving a molecular diagnosis of Charcot-Marie-Tooth disease (CMT) and related disorders, and it found that targeted NGS panels can lead to molecular diagnoses in approximately a third of patients who do not carry PMP22 duplications or deletions.

What is known and what this paper adds
Previous studies have validated the utility of targeted NGS panels for detecting point mutations, small insertions and deletions, and larger rearrangements in research settings. This investigation validates the utility of targeted NGS panels in routine clinical practice.

Participants and setting
The investigators prospectively recruited 220 patients through tertiary referral centers in London (n = 120) and Iowa (n = 100) between 2015 and 2017. These patients had been diagnosed with CMT or related disorders and did not carry PMP22 duplications or deletions.

Design, size, and duration
In London, NGS was performed by an accredited laboratory that sequenced 50 CMT-related genes. In Iowa, NGS was performed by accredited commercial companies that sequenced a mean number of 51 (SD, 23) CMT-related genes. Detected mutations were classified according to guidelines from the American College of Medical Genetics. A definite molecular diagnosis was defined as the identification of a pathogenetic or likely pathogenetic mutation.

Primary outcome measures
The primary outcome was the percentage of cases for which molecular diagnoses were achieved.

Main results and the role of chance
Definite molecular diagnoses were achieved in 67 cases (30%). Variants of unknown relevance were identified in 73 patients (33%), including 52 patients (24%) for whom no definite molecular diagnoses were achieved.

Bias, confounding, and other reasons for caution
Some of the present study’s analyses were limited by the cohort’s genetic heterogeneity and the paucities of patients with mutations in specific genes.

Generalizability to other populations
The present study’s reliance on data from London and Iowa may limit the generalizability of the results.

Study funding/potential competing interests
This study was funded by the NIH, the Wellcome Trust, the UK Medical Research Council, Ataxia UK, the Multiple System Atrophy Trust, Muscular Dystrophy UK, and the Muscular Dystrophy Association. The authors report no competing interests. Go to Neurology.org/N for full disclosures.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The corresponding author(s) of the full-length article and the journal editors edited and approved the final version.
Targeted next-generation sequencing panels in the diagnosis of Charcot-Marie-Tooth disease
Andrea Cortese, Janel E. Wilcox, James M. Polke, et al.
Neurology 2020;94;e51-e61 Published Online before print December 11, 2019
DOI 10.1212/WNL.0000000000008672

This information is current as of December 11, 2019

Updated Information & Services
including high resolution figures, can be found at:
http://n.neurology.org/content/94/1/e51.full

References
This article cites 36 articles, 6 of which you can access for free at:
http://n.neurology.org/content/94/1/e51.full#ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
All Genetics
http://n.neurology.org/cgi/collection/all_genetics
All Neuromuscular Disease
http://n.neurology.org/cgi/collection/all_neuromuscular_disease
Peripheral neuropathy
http://n.neurology.org/cgi/collection/peripheral_neuropathy

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints
Information about ordering reprints can be found online:
http://n.neurology.org/subscribers/advertise