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Abstracts

Articles appearing in the February 2018 issue

Familial monophasic acute transverse myelitis due to the pathogenic variant in *VPS37A*

Objective To identify genetic differences among siblings with a family history of idiopathic transverse myelitis (ITM).

Methods We compared whole-exome sequencing (WES) on germline samples from 2 affected sisters with ITM with 3 of their healthy siblings.

Results The 2 sisters with ITM both had acute onset of sensory loss in the legs, weakness, and bowel/bladder dysfunction. The first developed ITM at age 15 years with a clinical nadir of complete paralysis, which slowly recovered over a few years. MRI demonstrated a persistent T2 lesion in the lower thoracic cord. The second developed ITM at age 50 years with a nadir of sensory loss from T6 down and paraparesis in the legs, associated with an MRI lesion at T6. She also made a partial recovery with treatment. Both sisters are homozygous for a missense variant in *VPS37A* (c.700C > A, p.Leu234Ile) identified by WES. We performed targeted sequencing of *VPS37A* in an additional 86 samples from patients with ITM and 175 with other diseases to investigate the p.Leu234Ile variant. We identified another patient with ITM homozygous for the same rare variant. No patients with multiple sclerosis, neuromyelitis optica, other neurologic conditions, or any healthy controls in public databases were homozygous for this variant.

Conclusions A rare missense variant in *VPS37A* may predispose to development of ITM. Further studies are necessary to determine the frequency of this variant in the patient population and the mechanism through which it contributes to the risk of disease.

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Diagnostic utility of exome sequencing in the evaluation of neuromuscular disorders

Objective To evaluate the diagnostic yield and workflow of genome-scale sequencing in patients with neuromuscular disorders (NMDs).

Methods We performed exome sequencing in 93 undiagnosed patients with various NMDs for whom a molecular diagnosis was not yet established. Variants on both targeted and broad diagnostic gene lists were identified. Prior diagnostic tests were extracted from the patients' medical records to evaluate the use of exome sequencing in the context of their prior diagnostic workup.

Results The overall diagnostic yield of exome sequencing in our cohort was 12.9%, with one or more pathogenic or likely pathogenic variants identified in a causative gene associated with the patient's disorder. Targeted gene lists had the same diagnostic yield as a broad NMD gene list in patients with clear neuropathy or myopathy phenotypes, but evaluation of a broader set of disease genes was needed for patients with complex NMD phenotypes. Most patients with NMD had undergone prior testing, but only 10/16 (63%) of these procedures, such as muscle biopsy, were informative in pointing to a final molecular diagnosis.

Conclusions Genome-scale sequencing or analysis of a panel of relevant genes used early in the evaluation of patients with NMDs can provide or clarify a diagnosis and minimize invasive testing in many cases.

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B. Rhead, M. Bäärnhielm, M. Gianfrancesco, et al. 2016;2:e97. doi.org/10.1212/NXG.0000000000000097

A novel *DYNC1H1* mutation causing spinal muscular atrophy with lower extremity predominance

Q. Niu, X. Wang, M. Shi, and Q. Jin. 2015;1:e20. doi.org/10.1212/NXG.0000000000000017

***CHCHD10* variant p.(Gly66Val) causes axonal Charcot-Marie-Tooth disease**

M. Auranen, E. Ylikallio, M. Shcherbii, et al. 2015;1:e1. doi.org/10.1212/NXG.0000000000000003

The Clinical Outcome Study for dysferlinopathy: An international multicenter study

E. Harris, C.L. Bladen, A. Mayhew, et al. 2016;2:e89. doi.org/10.1212/NXG.0000000000000089

Complete callosal agenesis, pontocerebellar hypoplasia, and axonal neuropathy due to AMPD2 loss

A.P.L. Marsh, V. Lukic, K. Pope, et al. 2015;1:e16. doi.org/10.1212/NXG.0000000000000014