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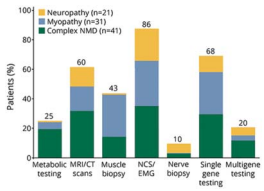
Abstracts

Articles appearing in the February 2018 issue

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 1 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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Alzheimer risk loci and associated neuropathology in a population-based study (Vantaa 85+)

Objective To test the association of distinct neuropathologic features of Alzheimer disease (AD) with risk loci identified in genome-wide association studies.

Methods Vantaa 85+ is a population-based study that includes 601 participants aged ≥85 years, 256 of whom were neuropathologically examined. We analyzed 29 AD risk loci in addition to *APOE* ε4, which was studied separately and used as a covariate. Genotyping was performed using a single nucleotide polymorphism (SNP) array (341 variants) and imputation (6,038 variants). Participants with Consortium to Establish a Registry for Alzheimer Disease (CERAD) (neuritic β-amyloid [Aβ] plaques) scores 0 (n = 65) vs score M + F (n = 171) and Braak (neurofibrillary tangle pathology) stages 0–II (n = 74) vs stages IV–VI (n = 119) and with capillary Aβ (CapAβ, n = 77) vs without (n = 179) were compared. Cerebral amyloid angiopathy (CAA) percentage was analyzed as a continuous variable.

Results Altogether, 24 of the 29 loci were associated (at $p < 0.05$) with 1 or more AD-related neuropathologic features in either SNP array or imputation data. Fifteen loci associated with CERAD score, smallest $p = 0.0002122$, odds ratio (OR) 2.67 (1.58–4.49) at *MEF2C* locus. Fifteen loci associated with Braak stage, smallest $p = 0.004372$, OR 0.31 (0.14–0.69) at *GAB2* locus. Twenty loci associated with CAA, smallest $p = 7.17E-07$, β 14.4 (8.88–20) at *CR1* locus. Fifteen loci associated with CapAβ, smallest $p = 0.002594$, OR 0.54 (0.37–0.81) at *HLA-DRB1* locus. Certain loci associated with specific neuropathologic features. *CASS4*, *CLU*, and *ZCWPW1* associated only with CAA, while *TREM2* and *HLA-DRB5* associated only with CapAβ.

Conclusions AD risk loci differ in their association with neuropathologic features, and we show for the first time distinct risk loci for CAA and CapAβ.

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Neurology 2018;90;735
DOI 10.1212/WNL.0000000000005342