Diagnosis and etiology of congenital muscular dystrophy: We are halfway there.

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Abstract

OBJECTIVE: To evaluate the diagnostic outcomes in a large cohort of congenital muscular dystrophy (CMD) patients using traditional and next generation sequencing (NGS) technologies.

METHODS: A total of 123 CMD patients were investigated using the traditional approaches of histology, immunohistochemical analysis of muscle biopsy, and candidate gene sequencing. Undiagnosed patients available for further testing were investigated using NGS.

RESULTS: Muscle biopsy and immunohistochemical analysis found deficiencies of laminin α2, α-dystroglycan, or collagen VI in 50% of patients. Candidate gene sequencing and chromosomal microarray established a genetic diagnosis in 32% (39 of 123). Of 85 patients presenting in the past 20 years, 28 of 51 who lacked a confirmed genetic diagnosis (55%) consented to NGS studies, leading to confirmed diagnoses in a further 11 patients. Using the combination of approaches, a confirmed genetic diagnosis was achieved in 51% (43 of 85). The diagnoses within the cohort were heterogeneous. Forty-five of 59 probands with confirmed or probable diagnoses had variants in genes known to cause CMD (76%), and 11 of 59 (19%) had variants in genes associated with congenital myopathies, reflecting overlapping features of these conditions. One patient had a congenital myasthenic syndrome, and 2 had microdeletions. Within the cohort, 5 patients had variants in novel (PIGY and GMPPB) or recently published genes (GFPT1 and MICU1), and 7 had variants in TTN or RYR1, large genes that are technically difficult to Sanger sequence.

INTERPRETATION: These data support NGS as a first-line tool for genetic evaluation of patients with a clinical phenotype suggestive of CMD, with muscle biopsy reserved as a second-tier investigation. Ann Neurol 2016;80:101-111.


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