Neuromuscular disease diagnosis: the experience of a reference laboratory in Brazil

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BACKGROUND

Neuromuscular diseases (NMD) are a group of disorders that involve injury or dysfunction of peripheral nerves or muscle. These diseases are usually characterized by degeneration of the skeletal muscles or structural abnormalities of the muscle fiber causing generalized muscle weakness and motor disability. Onset may occur in the neonatal period, childhood, or adult life, pointing to the importance of identifying these diseases' etiology.

Many NMDs have a genetic origin, and around 600 genes related to more than a thousand neuromuscular diseases were described to date. The molecular diagnosis of inherited NMDs is a challenge not only due to their high clinical and genetic heterogeneity but also to the large number and great diversity of genes involved.

We aim to describe genetic findings in molecular analysis of patients with symptoms of NMDs.

MATERIAL AND METHODS

We performed a descriptive, cross-sectional study, with retrospective collection of DNA sequencing results performed in a clinical reference laboratory from Brazil, from 1996 to 2021.

Four gene panels were carried out by Next Generation Sequencing (NGS): mitochondriopathies (159 nuclear genes + 37 mitochondrial genes); muscular dystrophies, myopathies and myasthenic syndrome (80 genes); myopathies and muscular dystrophies (163 nuclear genes + 37 mitochondrial genes) and neuromuscular diseases (82 genes).

Variant classification followed the directives of the American College of Medical Genetics and Genomics (ACMG 2015).

RESULTS

79 patients (40 males/39 females) suspected of having NMDs with age ranging from 2 to 78 years old were evaluated using the gene panels.

Pathogenic variants were detected in 33 patients (41.8%), involving 26 different NMD-relates genes (Table 1).

32 patients carried variants of unknown significance (40.5%), and 1 patient (1.2%) had a pseudodeficiency variant.

Table 1. Pathogenic and probably pathogenic variants

Gene	Chr Location [GRCh37/Hg19]	Variant	Classification
LMNA NM_170707.4	chr1:156115052	c.134A>G;p.(Tyr45Cys)	PP
ACTA1 NM_001100.4	chr1:229568343	c.414C>G;p.(Ile138Met)	PP
	chr1:229568480	c.275_277del;p.(Phe92del)	PP
TTN NM_001256850.1	chr2:179425091	c.80845C>T;p.(Arg26949*)	P
	chr2:179635299	c.8220G>A;p.(Trp2740*)	PP
OPA1 NM_130837.3	chr3:193385074	c.2983+5G>A;p.(?)	PP
DOK7 NM_173660.5	chr4:3494834	c.1124_1127dupTGCC; p.(Ala378Serfs*30)	P
SGCB NM_000232.5	chr4:52895974	c.299T>A;p.(Met100Lys)	PP
WFS1 NM_006005.3	chr4:6302750-6302755	c.1230_1233del; p.(Val412Serfs*29)	P
LAMA2 NM_000426.4	chr6:129663524	c.4348C>T;p.(Arg1450*)	P
	chr6:129486767	c.1255delA;p.(Ile419Leufs*4)	P
	chr6:129601216	c.2461A>C;p.(Thr821Pro)	P
	chr6:129637234	c.3976C>T;p.(Arg1326*)	P
TPM2 NM_003289.3	chr9:35689235	c.145_147del;p.(Lys49del)	P
SURF1 NM_003172.4	chr9:136221583	c.254del;p.(Lys85Serfs*4)	PP
POMT1 NM_001077365.2	chr9: 134390811	c.1176-2A>G;p.(?)	P
POMT2 NM_013382.7	chr14:77769186	c.648C>A;p.(Cys216*)	P
ECHS1 NM_004092.4	chr10:135183486	c.336C>A;p.(Tyr112*)	PP
	chr10:135179506	c.713C>T;p.(Ala238Val)	PP
RAPSN NM_005055.5	chr11:47469631	c.264C>A;p.(Asn88Lys)	PP
PYGM NM_005609.4	chr11:64514268	c.2392T>C;p.(Trp798Arg)	P
ITGA7 NM_001144996.2	chr12:56086711	c.2773C>T;p.(Gln925*)	P
HEXA NM_000520.6	chr15:72645446	c.533G>A;p.(Arg178His)	P
ATP2A1 NM_173201.4	chr16:28899000	c.888dupT;p.(Lys297*)	P
CHRNE NM_000080.4	chr17:4802160	c.1353dupG;p.(Asn452Glufs*4)	PP
	chr17:4805975	c.130dupG;p.(Glu44Glyfs*3)	P
GAA NM_000152.5	chr17:78078341	c.-32-13T>G;p.(?)	P
RYR1 NM_000540.3	chr19:39076592	c.14818G>A;p.(Ala4940Thr)	PP
COL6A1 NM_001848.3	chr21:47409559	c.896G>A;p.(Gly299Glu)	PP
PDHA1 NM_000284.4	chrX:19373831	c.787C>G;p.(Arg263Gly)	PP
DMD NM_004006.3	chrX:32305650	c.6286C>T;p.(Gln2096*)	P
PNPLA2 NM_020376.4	chr11:823728	c.792delG;p.(Leu264Phefs*56)	PP
MT-TL1 NC_012920.1	chrM:3243	m.3243A>G	P

Legend: P: pathogenic; PP: probably pathogenic

CONCLUSIONS

High-throughput sequencing enables the genetic diagnosis of NMD patients, supports evidence-based treatment and the familiar genetic counseling. The identification and classification of these genetic variants are essential to improve the knowledge of the etiology of the NMD diseases.

The authors have no conflict of interest to disclose.

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