NEXT GENERATION SEQUENCING PANEL FOR MUSCULAR DYSTROPHIES AND HEREDITARY MYOPATHIES: DIAGNOSTIC YIELD ON FIFTY-ONE FAMILIES FROM A SINGLE CENTER CROSS-SECTIONAL STUDY

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INTRODUCION

Due to the great clinical and genetic heterogeneity of muscular dystrophies (MD) and hereditary myopathies (HM) next-generation sequencing (NGS) genetic studies might be cost and time-effective diagnostic approaches for these diseases. We aimed 1) to evaluate the diagnostic yield of a NGS panel of 39 genes, and 3) to provide insights about the epidemiological profile of MD/HM in Rio Grande do Sul, Brazil.

METHODS

Index cases from consecutive families with clinical/neurophysiological suspicion of MD/HM were recruited in this single center study. NGS panel of 39 frequent MD/HM related-genes was performed with Ion Torrent-PGM.

RESULTS

Amongst the 51 index cases, we obtained an overall diagnostic yield of 64.7% (33/51), a definitive diagnosis in 39.2% (20/51) and at least a possible diagnosis in other 25.4% (13/51) cases (figure 1).

Diagnostic yield for limb girdle muscular dystrophy (LGMD) was 58.3% (14/24), with 6 LGMD2A (25%); 4 LGMD2B (16.6%) and 1 for each LGMD2D, LGMD2G, LGMD2K and 1 *RYR1*-related disorder (figure 2).

For congenital muscular dystrophy and myopathy the diagnostic yield was 66.6% (10/15), 2 cases of *RYR1*, 1 case of each *LAMA2, COL6A2, NEB, SEPN1* and *POMGNT1*-related disorders.

For muscle diseases with prominent joint contractures, the diagnostic yield was 80% (8/10) (figure 3).

There was no difference in the diagnostic yield of patients with family history/consanguinity from isolated cases.

CONCLUSIONS

A likely molecular diagnosis was obtained in almost two-thirds of index cases with the NGS panel, indicating that this should be a first-tier approach in the investigation for MD/HM. The most frequent types of MD/HM in Southern Brazil were LGMD2A and LGMD2B.

Some perspectives of our study: 1) Evaluate the clinical characteristics (through scales) of these 24 cases with MD/HM, 2) Continue investigations of possible cases with MD/HM in our results, and 3) Establish the genetic diagnoses of another 28 families with MD/HM from Rio Grande do Sul, Brazil.

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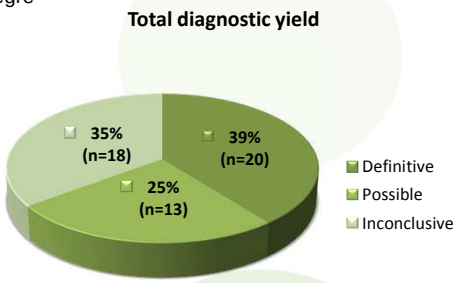

FIGURE 1 – DIAGNOSTIC YIELD OF DM/ HM PANEL ACCORDING TO GENETIC AND CLINICAL CLASSIFICATION OF 51 INDEX CASES.

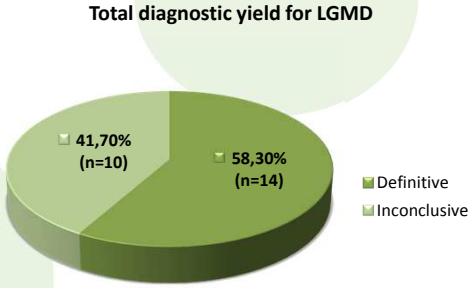

FIGURE 2 – DIAGNOSTIC YIELD FOR LGMD ACCORDING TO GENETIC AND CLINICAL CLASSIFICATION OF OUR 24 I NDEX CASES. IN DEFINITIVE CASES, 6 ARE LGMD2A, 4 LGMD2B AND 1 ARE LGMD2D, LGM2G AND LGMD2K.

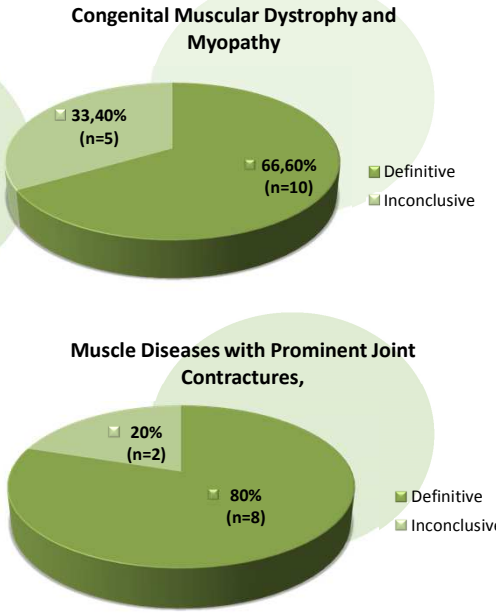

FIGURE 3 – DIAGNOSTIC YIELD FOR CONGENITAL MUSCULAR DYSTROPHY AND MYOPATHY (15 INDEX CASES) AND MUSCLE DISEASES WITH PROMINENT JOINT CONTRACTURES (10 INDEX CASES) ACCORDING TO GENETIC CLASSIFICATION.