POSTER 09

Screening of pathogenic variants of the *DMD* gene in female patients with undetermined muscular dystrophy

MARA MORAIS[1]; ANA GONÇALVES[2]; SANDRA MOTA[1,3]; MANUELA AMORIM[1,3]
1 - Área Científica de Análises Clínicas e Saúde Publica, ESS/IPP, Porto, Portugal2 - Centro de Genética Médica Jacinto Magalhães, Centro Hospitalar do Porto, Porto, Portugal3 - Centro de Investigação em Saúde e Ambiente, ESS/IPP, Porto, Portugal

Introduction: Dystrophinopathy (Duchenne/Becker muscular dystrophy, DMD/BMD), a progressive neuromuscular disease with an X-linked recessive inheritance, is caused by pathogenic variants in the *DMD* gene, including large deletions (68%), duplications (11%), point variants (20%) and others. Although the majority of females heterozygous for these variants are asymptomatic, about 2.5-7.8% may have some symptom manifestations.
Objective: Identify symptomatic carriers of dystrophinopathy.
Methods: In this study, 80 randomly selected female patients with progressive muscular dystrophy of unknown genetic cause, were screened for deletions and duplications in the *DMD*gene, using Multiplex Ligation-dependent Probe Amplification (MLPA) technique. In the positive cases the X-chromosome inactivation (XCI) pattern was studied resorting to the HUMARA assay. Additionally, it was conducted a review of all the manifesting female carriers (n=18), previously characterized in the *Unidade de Genética Molecular do Centro de Genética Médica Jacinto Magalhães (Centro Hospitalar do Porto).*
Results: The present study allowed the identification of 4 new cases of symptomatic female carriers. In the overall analysis of all patients (n=22), 50% of cases had deletions in the *DMD*gene, followed by point variants (27.3%) and duplications (22.7%). Skewed XCI, performed in leukocytes, was observed in 9 of the 18 heterozygous patients.
Conclusions: Symptomatic carriers of dystrophinopathy, although rare, are underdiagnosed and preferentially included in other subtypes of muscular dystrophies. The results obtained corroborate that the skewed XCI can be one of the main mechanisms involved in these DMD/BMD phenotypic expression patients. However, further genetic research is required, namely, systematic XCI analysis in muscle biopsy and patient´s family studies to determine alelism. Due to the high risk of transmission to offspring, referring these patients to genetic counselling is essential.

Keywords: Duchenne/Becker muscular dystrophy; symptomatic female carriers; *DMD* gene; X-chromosome inactivation.