

#### P4.06 Somatic mosaicism in a Duchenne/Becker muscular dystrophy patient

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The most common form of Duchenne and Becker muscular dystrophies causing mutations are large intragenic deletions and duplications that account for 60% to 80% of all cases. The remaining cases are caused by small mutations consisting of nonsense, missense, small insertion-deletions and a wide range of complex changes due to abnormalities of normal splice processing. Genomic based techniques have sometimes limited ability to detect such changes.

The technical approach that we used consisted in: (1) immunohistochemical and western-blot analysis of patient's muscle biopsies against dystrophin and different muscle dystrophy associated proteins, (2) exclusion of exonic deletion and duplication in DMD gene by MLPA technique, (3) muscle biopsy RNA sequencing of total coding region, and (4) further confirmation in targeted genomic DNA. We describe a BMD male patient presenting severe cardiomyopathy and mild skeletal muscle symptoms. The patient was diagnosed by clinical and immunohistochemical criteria, in which further genetic analysis revealed the presence of a nonsense mutation in exon 44 of DMD gene: c.6292C>T, p.Arg2098X.

The mutation was found in apparently heterozygous state and a normal 46, XY karyotype was confirmed. The immunohistochemical analysis of the muscle biopsy with dystrophin antibodies showed clear subpopulations of dystrophin-negative and positive myofibers.

We followed different technical approaches in order to confirm that the mutation was in somatic mosaicism, including: Western blot analysis of the muscle biopsy, Haplotyping with intragenic microsatellites, Taqman allele specific expression assays for quantification of normal versus mutant alleles and Digital PCR (Microfluidics platform, Fluidigm).

DMD somatic mosaicism is probably more common than expected and should be considered when the genotype-phenotype correlations are not concordant.

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#### P4.07 Cardiac involvement in Egyptian Duchenne and Becker muscular dystrophy carriers

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**Objective:** To evaluate the incidence and characteristics of cardiac abnormalities in Duchenne and Becker muscular dystrophy (DMD/BMD) carriers in Egypt **Methods:** 15 DMD and 7 BMD carriers confirmed by multiplex ligation-dependent probe amplification study (MLPA) method were examined by 12-lead electrocardiograph (ECG) and two-dimensional echo-cardiography (Echo). Echo results

were acquired with a Sonos 5500 (Phillips Medical Systems) using standard techniques. **Results:** Three of the DMD carriers were manifesting carriers showing calf muscle hypertrophy and high serum creatine kinase levels, and one had high CK levels of 2000, and three 200–300. None of carriers had cardiac failure clinically. The first manifesting DMD carrier at 16 years had mildly dilated left ventricular diameter of 5.6 cm (normal values: 3.7–5.4 cm), but with normal ejection fraction (EF). The second at 20 years had dilated left ventricle with global hypokinesia and poor systolic function with EF of 45% (normal: 55–77%). The third had normal cardiac function. In 13 of non-manifesting DMD carriers, 1 had ECG abnormalities of (deep Q-wave and increase in Q/R ratios in leads II, III, and V6 were detected with evidence of left ventricular hypertrophy) and left ventricular dilatation but none had decreased EF on echo-cardiography. In 7 of non-manifesting BMD carriers, none had ECG abnormalities and 2 had dilated left ventricular dilatation but none had decreased EF on echo-cardiography. **Conclusion:** Our results confirmed a high incidence of cardiac involvement in DMD and BMD carriers. Careful and regular cardiac follow up is necessary to DMD and BMD carriers.

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#### P4.08 Prevalence of sinus tachycardia in Duchenne muscular dystrophy

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**Background:** Duchenne muscular dystrophy (DMD) is a progressive myopathy resulting from mutations in dystrophin. Myocardial dysfunction and dysrhythmias are frequent causes of death. Sinus tachycardia is commonly reported in the pre-pubertal and adolescent DMD patient, though its natural history has been poorly defined. The objective of this study was twofold: first, to estimate heart rate values for selected age groups of boys with DMD, and, second, to compare heart rate values for patients in the aforementioned age groups with established population averages. **Methods:** Subjects were identified retrospectively in the institutional clinical database. From 1993 to 2009, 365 DMD patients were identified who had 1111 electrocardiograms (ECG's) performed as part of their routine clinical care. Data were analyzed using a one-sample *t*-test for each of six age groups. **Results:** Average heart rates (range) for each group were 1–2 yrs 116 (98–166); 3–4 yrs 108 (89–137); 5–7 yrs 99 (62–135); 8–11 yrs 99 (62–147); 12–15 yrs 100 (50–181); 16+ yrs 101 (58–161). There were statistically significant differences between age group mean heart rates and population averages for the three oldest age groups (8–11 yrs, 12–15 yrs, 16+ yrs) ( $p < 0.001$ ). There was no significant difference between age group mean heart rates and population averages for the three youngest groups (1–2 years, 2–3 years, and 5–7 years). **Conclusions:** We found no difference in resting heart rates of younger DMD patients compared to population norms, suggesting that the presence of significant tachycardia in young DMD patients may warrant additional investigation. In contrast, DMD patients 8 years of age and older demonstrate elevated mean heart rates, and sinus tachycardia is common in older DMD patients. The etiology of this finding is likely complex, as both cardiomyopathy and autonomic dysfunction may contribute to tachycardia in older DMD patients.

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