

dystrophy. This report also shows that BMD may present with a normal CK.

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PI.2

Phenotypic profile of dystrophinopathy patients with deletion of exons 3–7 of the dystrophin gene

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Deletion of exons 3–7 is an out of frame deletion predictive of Duchenne muscular dystrophy (DMD) but is commonly associated with a milder phenotype. An accurate clinical profile of such patients would be of value for prognosis and patient selection for clinical trials. To characterize the clinical phenotype of dystrophinopathy patients with deletion of exons 3–7. IRB approved retrospective case series' review. Patient characteristics: 14 ambulatory males with deletion of exons 3–7. Mean age at last visit – 11.1 yrs (range 5.7–15.8); mean CK (4–10 yr) – 13310 (4269–26,020); FH DMD in 6/14 – mean age of loss of ambulation (LOA) 12.9 yr (10–18) in 5; and deaths at 19–44 yrs. Muscle biopsy (3/14) – decreased dystrophin. MRI pelvic muscle (13/14) – mild to moderate fatty changes. Steroid therapy (daily deflazacort): start mean age 7.1 (3.0–11.1 yr); mean duration 3.9 yr (0.5–12.8); mean dose at last visit 0.5 mg/kg/day (0.2–0.8). Neuromotor function: history of delayed walking >16 months – 2/14 (brothers with hypotonia); 12/14 with onset of motor abnormalities between ages 1.5–5 and 2/14 between ages 6–8; presenting difficulties – toewalking (4/13); slow/abnormal run (8/13); fatigue (1/13); difficulty in rising from the floor – 0/14. Gower's maneuver (from sit to stand, $n=13$) – mean 1.8 s (1.1–2.9); 30 feet run ($n=14$) – 3.79 s (2.8–6.72); 13/14 with ability to jump with both feet and climb up steps with reciprocating pattern; 14/14 with antigravity neck and trunk flexion from supine; 12/14 able to hop on one leg. Cardiopulmonary function: normal 14/14. Neurocognitive function: normal 11/14. Patients with deletion of exons 3–7 who present with mild motor difficulties by age 5 have minimal motor limitations on follow up (on steroid therapy) and normal cardiopulmonary function. This clinical profile of a milder phenotype would have implications for prognosis and clinical trials.

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PI.3

Spectrum of point mutations in Czech DMD/BMD patients and their phenotypic outcome

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Duchenne and milder Becker muscular dystrophies (DMD/BMD) are X-linked recessive neuromuscular diseases, both caused by mutations in the DMD gene. DMD is typically associated with mutations causing premature stop codon creation, while BMD is usually related to in-frame

deletions or duplications. In our study population, excluding 60% of deletions and 5% of duplications detected in DMD gene, we identified 63 different point mutations in 69 DMD/BMD patients and DMD/BMD female carriers. For mutation screening on the RNA level, we used reverse transcription-PCR, protein truncation test, and DNA sequencing. For screening on DNA level, we used PCR and sequencing. We describe patients with a mutation creating a premature termination codon but with a mild BMD phenotype, which present three different ways of rescuing the DMD phenotype. In one patient we detected the insertion of a repetitive sequence AluYa5 in intron 56, which led to skipping of exon 57. On the other hand, we present two patients with mutations deep inside the intron leading to severe DMD phenotype by creating pseudoexon and leading to frame-shift. Among presented mutations, there are 32, which are unique for Czech population. This work was supported by Grants MSMT LC06023 and 2B08060.

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Molecular profile of 307 Portuguese patients with dystrophinopathy, including 39 new variants

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Mutations in the dystrophin gene (*DMD*) give rise to the allelic Duchenne or Becker muscular dystrophies. Besides providing a differential diagnosis for adequate clinical follow-up and management, the molecular characterization of these patients is becoming increasingly important in light of the recent and promising mutation-based therapeutic approaches. Due to the size and complexity of *DMD*, as well as the diversity of mutation types, molecular analysis requires a combination of techniques that enable the detection of gross deletions, duplications and the more subtle point mutations. In the course of our diagnostic service provided on a national basis, a total of 307 patients, representing 282 unrelated families, have been characterized at the molecular level. We identified 174 different mutations, where the distribution according to type was found to be in agreement with that reported in the literature for large cohorts. Also as expected, approximately 1/3 of the cases were shown to be *de novo* occurrences, as ascertained among the "sporadic" cases (25/82). These neo-mutations were comprised by 18% deletions, 6% duplications and 6% point mutations. We describe a total of thirty-nine undocumented variants, three of which were detected in obligate carrier female relatives of deceased patients. These new variants include 9 gross deletions, 8 gross duplications and 22 smaller mutations (deletions, duplications, *delins* rearrangements and nonsense or splice-site substitutions). Comprehensive analysis often involved expression studies at the mRNA level to help delineate breakpoint junctions, to identify altered splicing and ultimately to provide an explanation for apparent exceptions to the reading frame rule. This detailed molecular characterization is also important for the purpose of including our patients in the DMD National Registry, which will be articulated with the TREAT-NMD Global Database.

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