Becker Muscular Dystrophy (BMD) shows a highly variable disease course. The cause of this diversity is mostly unknown. Dystrophin levels in muscle tissue are thought to be an important factor. We investigated the relationship between the amount of dystrophin in muscle biopsies and clinical severity in BMD patients with an exon 45–47 deletion. Thirteen patients with an exon 45–47 deletion were included, ranging in age from 20 to 63 years. Muscle strength was bilaterally measured using the Quantitative Muscle Testing (QMT) system in nine muscle groups: shoulder abduction, elbow flexion/extension, handgrip, hip flexion/extension, knee flexion/extension and ankle flexion. To assess muscle quality, 3T MRI of the lower leg was performed. A muscle biopsy was taken from the anterior tibial muscle. Dystrophin quantification was performed by Western Blot analysis, using two antibodies: DYS1 (rod domain) and AB15277 (C-term). Statistical analysis was performed using Pearson’s correlation test. Dystrophin levels ranged from 15% to 71% compared to healthy control muscle. The correlation between the two antibodies was excellent (R 0.88; p < 0.001). No relationship was present between dystrophin levels and QMT-sum score or fatty infiltration on MRI. In contrast, the QMT-sum score and fatty infiltration on MRI correlated significantly with patients’ age. The current study shows that the dystrophin level in itself does not explain the variation in disease severity in BMD patients with an exon 45–47 deletion. The strong relationship between strength or MRI abnormalities and age suggests that in this subgroup of Becker patients the disease course is determined by the mutation rather than the quantity of the internally deleted dystrophin protein.

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G.P.77

Deletions in the dystrophin gene predict loss of ambulation before 10 years of age in boys with Duchenne muscular dystrophy


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There is considerable variation in the rate of disease progression and response to steroid therapy in males with Duchenne muscular dystrophy (DMD). Genetic influences may explain at least part of this heterogeneity. This retrospective case series explored the relationship between dystrophin gene mutations (DMD) and age at loss of ambulation (LOA). Medical histories (n = 144) were examined from two Australian neuromuscular clinics. Data were collected on clinical characteristics including DMD mutation type and location, age at LOA, anthropometry, lung function and steroid use. The relationship between age at LOA and genetic and clinical characteristics including age at chart review, duration of steroid treatment, and BMI z-score was explored via multiple regression analysis. Significant independent variables were also entered in a logistic regression to predict LOA <10 years of age. The mean ±SD age of the cohort was 11.9 ± 4.0 years, and 51% of boys had lost the ability to walk independently. Mutation type and duration of steroid treatment were significant independent predictors of LOA <10 years in a logistic model explaining 31.2% of the variance in age of LOA. Boys with deletions in the dystrophin gene were six times more likely to stop walking before age 10 compared to boys with duplications, point or unknown mutations. This was reflected in the mean age at LOA in boys with deletions versus other mutations (9.30 ± 1.60 vs 10.97 ± 2.03 years, respectively, p < 0.0005). A longer duration of steroid therapy was associated with a reduction in risk of LOA <10 years. BMI had no relationship with age at LOA. Whilst the negative effects of steroid treatment such as weight gain and decreased bone health need to be considered, early introduction of steroids may provide some functional benefits, especially to boys with a documented deletion in DMD gene.

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G.P.78

Dystrophin isoforms with incomplete β dystroglycan and syntrophin binding domains retain partial function

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Duchenne muscular dystrophy (DMD) is an X-linked, relentlessly progressive muscle wasting disorder resulting from faulty production of the sub sarcolemmal protein, dystrophin. DMD has a predictable course and limited treatment options, with the majority of cases being caused by frame-shifting deletions of one or more of the 79 exons in the dystrophin gene, while deletions that do not disrupt the dystrophin reading frame generally cause the milder allelic disorder, Becker muscular dystrophy (BMD). Antisense oligomer (AO)-mediated splicing manipulation can remove specific exons during transcript processing and overcome DMD-causing dystrophin gene lesions to generate shorter, partially functional BMD-like dystrophin isoforms, and is showing promise as a therapy for DMD. Dystrophin gene structure in BMD patients with less severe phenotypes provides templates for potentially functional dystrophin isoforms. However, such mutations downstream of exon 55 are rare, and the probable consequences of AO-induced exon removal in this region are not known. We report that systemic administration of antisense phosphorodi- amidate morpholino oligomer-cell penetrating peptide conjugates to wild-type C57BL/10ScSn mice can remove dystrophin exons to generate DMD- and BMD-like in vivo models for molecular, physiological and pathology evaluation. Exclusion of single exons and in-frame exon blocks, within the β dystroglycan and syntrophin binding domains, is helping to elucidate the relative importance of these regions to dystrophin function, and provide guidelines for the development of therapeutic exon skipping strategies.

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G.P.79

DMD mutation spectrum in 611 unrelated dystrophinopathy families

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Dystrophinopathies include a spectrum of X-linked myopathic phenotypes caused by mutations in the DMD gene. This gene, located at Xp21, consist in 79 exons expanding 2.4 Mb with a major muscle transcript of 14 Kb. Our centre has performed molecular diagnosis of dystrophinopathy during the last 25 years. The molecular diagnostic strategy during this period has evolved considerably. Nowadays, we use a combination of different techniques. For large gene rearrangements (exonic deletions and duplications) we perform multiplex PCR amplifying 25 exons and two promoters and, MLPA technique screening the 79 exons.