LETTERS TO THE EDITOR

An inherited dystrophin deletion without muscle weakness

Deletions of the dystrophin gene are known to be present in approximately 60 to 70% of Duchenne (DMD) and Becker (BMD) patients. We describe a boy and his grandfather who both have raised creatine kinase levels and an identical deletion including exons 14–18 of the dystrophin gene but no muscle weakness. Muscle histology is normal in the boy.

A previously well 5 year old boy presented with a three year history of occasional muscle cramps in his legs after exercise. On examination he had no calf hypertrophy or muscle weakness and Gower's sign was negative. However, his creatine kinase (CK) was grossly raised at 7854 IU/1 (NR 1–220 IU/l) and a diagnosis of DMD was suspected. Examination by a paediatric neurologist confirmed the diagnosis of DMD. A further CK biopsy was consistent with dystrophin gene defects. A further biopsy showed no evidence of muscle fibre degeneration or regeneration and the faint specific type. There was no evidence of denervation or congenital myopathy. Immunocytochemistry for dystrophin was normal in the patient and his father.

The boy's mother had no muscle related symptoms and a normal CK (101 IU/l) but reported that her father suffered from muscle pains when young. On questioning he remembered having pains in his legs as a child and still had aching of his limbs after exertion. However, he had coped with physically demanding jobs throughout his life. A creatine kinase level in him was also raised at 520 IU/l (NR 1–220 IU/l).

DNA analysis by Southern blotting using standard techniques was carried out using DNA probes specific to dystrophin gene exons. Both the proband and his grandfather showed a deletion with probe 2b–3 spanning exons 14–18 of the dystrophin gene. Exons 13 and 19 were present. Such a deletion would not be expected if the dystrophin gene deleted the reading frame. Western blot analysis of a muscle biopsy from the proband using antibodies against exons 14 and 155–60 which are distal to the deletion showed both of these parts of the dystrophin gene to be present. This is consistent with a deletion which does not disrupt the gene reading frame. Both antibodies detected reduced abundance of dystrophin (>60%) of slightly reduced molecular weight, 20 kDa or 95% of the total.

The site of the deletion in this family, which includes exons 14–18, is unusual, the majority of deletions in DMD BMD patients being in the distal rod domain, exons 45–53. As Western blotting shows the presence of exons distal to the deletion, the deletion must be in frame in this family, as one would predict from the mild phenotype. The normal muscle biopsy is a little surprising in view of the very high creatine kinase levels. Without histological evidence of dystrophy or any clinical muscle weakness it is difficult to label this as even a mild Becker muscular dystrophy.

A family with myalgia and muscle cramps has been reported with nine affected males. The affected men had a non-progressive disease with long resting creatine kinase levels and no muscle weakness but did show some calf muscle hypertrophy. Histologically there were non-specific muscular changes. In that family, molecular analysis showed a dystrophin gene deletion probably involving exons 10–22, which is larger than, but in the deletion in our family.

A further study which attempted to correlate clinical findings with molecular results in BMD patients showed that muscle cramps are a common feature in patients with deletions or duplications in the proximal rod domain (exons 10–44). However, in this series, no patient had a deletion identical to that in our family and, unlike our family, all 14 patients with muscle cramps as a prominent feature had clinical muscle weakness. Families like ours emphasise the importance of molecular analysis in males with non-specific myopathy and raised creatine kinase levels, whether or not there is any family history consistent with X linked inheritance. However, they also show that a real CK and muscle biopsy deletion are not enough to make a confident diagnosis of either DMD or BMD. Muscle biopsy in at least one affected person should be considered unless the clinical course of the condition is clear from other affected family members.

Without the grandfather in our family, the prognosis for the proband would have been difficult to predict. However, as he (the grandfather) has had a non-progressive course with normal muscle function we can be sure that our boy in this family who inherit the dystrophin deletion. It is clear that dystrophin deletions, particularly those in the proximal rod domain, can be associated with normal muscle function and life expectancy.

We are very grateful to Tim Sherratt for performing the Western blotting.

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3. Durrer DT, Blattner P, Harper JF, Spiro AJ, Alter S, Francke U. Intragenic deletions in 25–30, and 55–60 which are distal to the deletion showed both of these parts of the dystrophin gene to be present. This is consistent with a deletion which does not disrupt the gene reading frame. Both antibodies detected reduced abundance of dystrophin (~60%) of slightly reduced molecular weight, 20 kDa or 95% of the total.


The newly recognised skeletal-genital syndrome

I read with great interest the comments of Tebbi \(^1\) on the newly recognised skeletal-genital syndrome (MIM 276820). \(^2\) All nine reported cases (five females and four males) in five unrelated families from Jordan, Brazil, Israel, Kuwait, and Italy\(^1\) showed the characteristic phenotype of the Al-Awadi-Richieri-Costa-Raas-Rothschild limb-pelvis-hypoplasia aplasia syndrome (LPHAS). \(^3\) We recently reviewed the syndrome and discussed inter- and intrafamilial variability of expression of its pleiotropic gene affecting both the skeletal and genital system. \(^4\)

In 1988, Raas-Rothschild \(\text{et al.}^4\) called this syndrome LPHAS and recently Tebbi \(\text{et al.}^1\) proposed a new nomenclature of "limb-pelvis hypoplasia aplasia syndrome" (LPHAS). \(^5\) The first term (LPHAS) ignored all genital anomalies and the second (LPHAS) focused only on the urethra anomalies (40%). Three of the four affected males had inguinal testes (75%), two had a hypoplastic scrotum (50%), and one had hypospadias (25%). Displaced external genitalia was a common feature in both females and males (7, 9, 78%).

I would argue against the nomenclature of Raas-Rothschild \(\text{et al.}^4\) (LPHAS) focusing on the major skeletal anomalies alone and on the nomenclature of Tebbi \(\text{et al.}^1\) (LPHAS) focusing on urethral anomalies (40%). Both ignored the associated genital anomalies (39%) and the displaced external genitalia occurring in seven males and females (table).

Syndromomorphs are invited to enrich the scientific discussion of the best nomenclature for this newly recognised skeletal-genital syndrome.


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Genital anomalies detected in patients with LPHAS

Clinical findings

<table>
<thead>
<tr>
<th>Al-Awadi et al. (1)</th>
<th>Richieri-Costa (1)</th>
<th>Raas-Rothschild et al. (4)</th>
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<tr>
<td>Sex</td>
<td>F</td>
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<tr>
<td>Displaced external genitalia</td>
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<td>Hypospadias</td>
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<td>Hypoplastic scrotum or inguinal testes</td>
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<tr>
<td>Urethral aplasia</td>
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NR = not relevant.

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