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 family and a 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/l (NR 1-220 IU/l) and a diagnosis of DMD was suspected. Examination by a paediatric neurologist confirmed his power, tone, reflexes, and muscle bulk. Two further CK measurements were also raised at 6253 IU/l and 11,800 IU/l (NR 25-195). A fainter line with the biopsy was histologically normal with little variation in fibre size and no evidence of muscle fibre regeneration or degeneration. There was no fibre type differentiation and no evidence of denervation or congenital myopathy. Immunocytochemistry for dystrophin DYS1 and DYS2 were normal.

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 to disrupt the reading frame. Western blot analysis of a muscle biopsy from the proband using antibodies containing 14-18, 19, and 22-25 (which are distal to the deletion) showed both of these parts of the dystrophin gene to be present. This is also 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 very mild Becker muscular dystrophy.

The newely recognised skeletalgenital syndrome

I read with great interest the comments of Tdee’s (1) on the newly recognised skeletalgenital syndrome (MIM 276280). All nine reported cases (five females and four males) in five unrelated families from Jordan, Saudi Arabia, and Italy showed the characteristic phenotype of the Al-Awadi-Richieri-Costa-Raas-Rothschild limb-pelvis-hypoplasia aplasia syndrome (LPHAS). We recently reviewed the syndrome and discussed inter- and intrafarinal variability of expression of its pleiotropic gene affecting both the skeletal and genital systems. In 1988, Raas-Rothschild et al. called this syndrome LPHAS and recently Tdee (1) proposed a new nomenclature of ‘limb, pelvic, hypoplasia—aplasia syndrome’ (LPHAS). The first term (LPHAS) ignored all genital anomalies and the second (LPHAS) focused only on the uterine anomalies (40%). Three of the four affected males had inguinal testes (75%), two had a hypoplastic scrotum (50%), and one had hypogonadism (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 et al (LPHAS) focusing on the major skeletal anomalies alone and on the nomenclature of Tdee (1) (LPHAS) focusing on uterine anomalies (40%). Both ignored the associated genital anomalies (39%) and the displaced external genitalia occurring in seven males and two females.

Syndromologists are invited to enrich the scientific discussion of the best nomenclature for this newly recognised skeletalgenital syndrome.

The newly recognised skeletogenital syndrome.

T I Farag

*J Med Genet* 1994 31: 505
doi: 10.1136/jmg.31.6.505-a