MYH2 mutation in recessive myopathy with external ophthalmoplegia linked to chromosome 17p13.1-p12

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Sir, in 2005, we described a new autosomal recessive myopathy with external ophthalmoplegia in 16 subjects of eight families from a large and highly inbred Arab community near Jerusalem (Lossos et al., 2005). Characteristic clinical features of this disorder include conjugate non-restrictive ocular motility impairment without ptosis, mild facial and limb muscle weakness and scoliosis. The major pathological finding on skeletal muscle biopsy was marked Type 1 fibre predominance. A genome-wide search for areas of homozygosity identified linkage with chromosome 17p13.1-p12 markers defining a critical region of 12 cM encompassing an ordered cluster of six myosin heavy-chain genes. Direct sequencing of the MYH2, reported by that time to be involved in autosomal-dominant myosin heavy-chain (MyHC) IIa myopathy (Martinsson et al., 2000), showed no exonic mutations, and the genetic cause of this disorder remained unknown.

Since then, we have diagnosed six additional similarly affected individuals from the same community (Table 1). The four male and two female subjects were referred for neurological examination because of external ophthalmoplegia (n = 3) or for unrelated reasons (essential tremor, epilepsy or diabetic peripheral neuropathy; n = 1 each) at age 18–45 years. All presented the typical ocular motility limitation in the horizontal and vertical planes, always greatest in the upgaze and often associated with forehead contraction but without ptosis. The distribution of mild [Medical Research Council (MRC) grade 4] facial (n = 6) and limb (n = 4) muscle weakness and atrophy was always symmetrical and relatively homogenous, most prominent proximally in the upper limbs, thus confirming our original description. Given the slow progression of muscular weakness, the age of onset could not be precisely ascertained. However, parents of the two youngest patients described slow eye movements since early childhood. Two patients had slightly elevated creatine kinase level, and one had muscle biopsy reported to show no identifiable alterations but unavailable for our review.

Because of similarities to the recently described recessive myopathy with ophthalmoplegia and absence of Type 2A muscle fibres (Tajsharghi et al., 2010), the entire coding sequence of MYH2 was reanalysed on genomic DNA samples from two affected subjects from the original group of patients. Polymerase chain reaction (PCR) conditions and sequence analysis were performed as described (Tajsharghi et al., 2005). A homozygous single-base deletion, probably missed before by a laboratory error, was disclosed in exon 19 (c.2400delG, GGG4GGT), leading to a reading frame shift and a premature stop codon (p.Phe801SerfsX28). This truncating mutation is likely to result in loss of functional MyHC Ila protein and adds to the list of truncating MYH2 mutations previously described in compound heterozygosity (Tajsharghi et al., 2010).

The same mutation was identified in homozygosity in a previously untested patient and in heterozygosity in his clinically unaffected mother, thus confirming recessive segregation. In addition, the relative expression of different MyHC isoforms was analysed as described (Tajsharghi et al., 2005). A homozgyous single-base deletion, probably missed before by a laboratory error, was disclosed in exon 19 (c.2400delG, GGG4GGT), leading to a reading frame shift and a premature stop codon (p.Phe801SerfsX28). This truncating mutation is likely to result in loss of functional MyHC Ila protein and adds to the list of truncating MYH2 mutations previously described in compound heterozygosity (Tajsharghi et al., 2010).

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truncating effect of the MYH2 mutation. The studies were approved by the national and institutional review boards.

Our findings strongly confirm the evolving MYH2-related clinical phenotype with mild facial and limb myopathy associated with prominent external ophthalmoplegia of early childhood onset and slow progression. The fact that MyHC IIa is expressed in Type 2A muscle fibres and in oculorotatory muscles (Kjellgren et al., 2003) explains the co-occurrence of skeletal myopathy and ophthalmoplegia. Because MyHC IIa is also present in levator palpebrae superioris (Kjellgren et al., 2003), the infrequency of ptosis (Martinsson et al., 2000; Lossos et al., 2005; Tajsharghi et al., 2010) is unclear but may be related to the distinct organization of fibres in this muscle (Kjellgren et al., 2006).

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References


