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Search for mutations in the RYR1 gene in Italian patients with congenital myopathy

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The RYR1 gene encodes the skeletal muscle isoform ryanodine receptor which is fundamental for excitation-contraction coupling and calcium homeostasis of skeletal muscle.

Mutations in RYR1 are associated with malignant hyperthermia (MH), Central core (CCD) and Multiminicore (MMC) myopathies.

CCD is characterized by the presence of amorphous areas (cores) that lack mitochondria and oxidative enzyme activity especially in type I muscle fibres. Inheritance is usually autosomal dominant, although there are some instances of autosomal recessive transmission.

MMC is characterized by multiple, small areas with disorganization of myofibrillar structure and absence of mitochondria. Inheritance is autosomal recessive.

To obtain a more complete molecular characterization of CCD and MMC, we analysed RYR1 by direct sequencing, DH-PLC and MLPA techniques, in 15 Italian patients with clinical and histological diagnosis of CM. 13 variants previously not reported were identified. All the mutations met accepted, consensus criteria for pathogenicity.

Our study expands the spectrum of RYR1 mutations, emphasizes the importance of a complete gene analysis in the Italian population, and proposes further heterogeneity in CM.

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Unusual concurrence of Facio-scapulo-humeral dystrophy and Williams Syndrome in a young boy

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Facioscapulohumeral dystrophy (FSHD) is one of the most common muscular dystrophies, inherited as an autosomal dominant trait; it is characterized by the progressive weakening and loss of skeletal muscles, usually at face, shoulder girdle and upper arms level. The actual incidence may be estimated 1 in 7,500. Infantile FSHD is a more severe and early onset form of FSHD, recently categorized as a subtype of FSHD, with onset in early childhood. There is no generally accepted estimate of its incidence, but it is rare. Both adult and infantile disorders are associated by genetic testing to the deletion of 3.3-kb repeats at the 4q35-qter locus. Patients with the fewest repeats typically present with the most severe symptoms.

Williams syndrome (WS) is a rare genetic disease characterized by a developmental disorder associating a cardiac malformation (most frequently supra valvular aortic stenosis, SVAS) in 75% of cases, psychomotor retardation, a characteristic facial dysmorphism and a specific cognitive and behavioural profile. It is caused by a hemizygous deletion on chromosome 7q11.23, with an incidence of typical forms of 1:20 000 births. However, most cases of WS are not inherited, but occur as random events during the formation of reproductive cells in a parent of an affected individual. Young children with WS have distinctive facial features including broad forehead, short nose with a broad tip, full cheeks, and wide mouth with full lips. We present the case of a boy, 14 year old, affected by both disorders. FSHD was inherited from his mother while the WS was caused by a de novo deletion in chromosome 7. The phenotype deriving from the concurrence of both diseases is described.

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Clinical and electrophysiological feature of 13 Italian patients with oculopharyngeal muscular dystrophy (OPMD)

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Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant (AD) disorder caused by a small expansion of a short polyalanine tract in the poly (A) binding protein nuclear 1 protein (PABPN1). The disease is characterized by the adult-onset of progressive ptosis, dysphagia, and proximal limb weakness. In this study we illustrate clinical features of 13 patients carrying a poly-A expansion, ranging between 12 and 16 repeats. Despite considerable range of PABPN1 expansion we could not detect a linear correlation with phenotype. Most cases (9/13) were familial whereas the remaining were apparently sporadic and there was a moderate female predominance (8:5). Median age at examination was 57 with a mean age at onset of 44 years. Ptosis and dysphagia were prominent symptoms in all cases. Interesting two patients referred only dysphagia as first symptom for several years before developing ptosis. One patient received gastrostomy tube for feeding. Limb weakness was variable and usually proximal. Presence of psychiatric disturbances was also reported in some patients. Electrophysiological studies demonstrated a myopathic pattern in 8 patients whereas nerve conduction velocity studies were normal in all patients, excluding a concomitant nerve involvement which was elsewhere reported. Muscle biopsy analysis (3 patients) showed abundant rimmed vacuoles consistent with previous reports. Our data add new to the clinical characterization of OPMD.