EP.127

Ullrich congenital muscular dystrophy in a boy with 21q22.3 deletion: a revisited diagnosis

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Ullrich congenital muscular dystrophy (UCMD) is among the collagen VI-related muscular dystrophies. Recently, large genomic deletions on one allele involving *COL6A2* or both *COL6A1* and *COL6A2* unmasking a pathogenic mutation on the second nondeleted allele have also been described in the etiology. Case presentation: A 127/12 -year-old boy presented to our clinic at the age of 105/12 years with the main complaints of easy fatigability, muscle weakness and waddling gait. Before his admission to our center, he was evaluated for easy fatigability and waddling gait elsewhere at the age of 15 months, and he was diagnosed ring chromosome 21 from peripheral blood karyotype analysis, however, no further assessment could be performed. On his admission at our center physical examination revealed normal growth with mild dysmorphic facial features, proximal muscle weakness and increased lordotic posture with mild flexion at the knees. He was clinically diagnosed as UCMD. With the use of Affymetrix Cytoscan Optima array platform a 2,202 kb *de novo* deletion at 21q22.3 including *COL6A1* and *COL6A2* was revealed. In addition, genomic DNA sequencing revealed a novel heterozygous mutation at position c.2875G>A (p.Glu959Lys) in the exon 28 of *COL6A2*, predicted as "Damaging" or "Disease causing" by different mutation pathogenicity prediction tools (MutationTaster, PolyPhen2 and SIFT). The mother, heterozygous for the same missense variant in *COL6A2*, was asymptomatic. This patient yet represents another example of the effect of large genomic deletions leading to recessive disorders through unmasking a pathogenic mutation on the second non-deleted allele.

http://dx.doi.org/10.1016/j.nmd.2019.06.585

EP.128

Measuring motor function response to treatment in DOK7 congenital myasthenic syndrome

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DOK7 congenital myasthenic syndrome is a recessively-inherited disorder of neuromuscular transmission. We describe response to salbutamol therapy in fraternal twins who presented at age 5 and 7 years, respectively, with a limb-girdle pattern of weakness. DOK7 congenital myasthenic syndrome was diagnosed in late 2017 and salbutamol treatment (4mg TDS) commenced in the same year. Motor function was assessed using the North Star ambulatory assessment (NSAA) and timed function tests (TFTs), ambulatory capacity using 6 minute walked distance (6MWD) and typical mobility with the functional mobility scale (FMS). Baseline assessments were completed during neuromuscular clinic review five months prior to commencing treatment. Both boys demonstrated significant functional deficits (NSAA 17/34 and 25/34; 6MWD 228 metres and 439 metres; 10 metre walk/run (10MWR) 7.84 secs and 5.75 secs; supine to stand (SS) 7.53 secs and 6.45 secs; 4 stair climb (4SC) 7.31 secs and 4.84 secs; and FMS 5,5,1 and 6,5,5, respectively). Two months after commencement of treatment their TFTs had improved (10MWR 5.87 secs and 4.96 secs; SS 2.96 secs and 3.78 secs; 4SC 3.53 secs and 3.46 secs). Further improvement was seen at seven months of treatment (NSAA 30/34 and 31/34; 6MWD 583 metres and 563 metres; 10MWR 4.38 secs and 3.69 secs; SS 2.58 secs and 2.43 secs; 4SC 1.92 secs and 2.04 secs; and FMS 6,6,6 and 6,6,6, respectively). The weaker of the two, who pre-treatment required a motorised scooter for mobility in community settings, was independently ambulant in all environments. More than 12 months after commencement of salbutamol, both boys continue to make functional gains. In these two cases of DOK7 congenital myasthenic syndrome significant gains in motor function were observed after seven months of salbutamol therapy.

http://dx.doi.org/10.1016/j.nmd.2019.06.586

EP.129

A probable new pathogenic variant in *RYR1* gene? - 3 case reports

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Congenital myopathies represent a group of diseases ascribed as pathogenic variants in over 20 genes. Of these, disorders related to *RYR1* gene are the most frequent, identified in 90% of central core disease patients; however, several histological phenotypes including findings with no specific features have been described. We report here 3 relatives from the same pedigree segregating a variant in *RYR1* gene. A 39-year-old female manifested with distal upper limb weakness which progressed to involve the distal lower limb, proximal upper limb, as well as the face. The symptoms presenting with childhood onset had a slow progression. Creatine kinase(CK) was normal with EMG findings supporting a myopathy. Spirometry showed a restrictive respiratory disturbance. Muscle biopsy showed no specific findings except a type 1 predominance. Her son, 6 years-old, has proximal muscle weakness and facial weakness. CK normal. His brother, 45 years-old, has the same symptom. CK normal. Spirometry showed a restrictive respiratory disturbance. A muscle biopsy was performed showing no specific findings. Her father had the same symptoms with onset during childhood. Clinical exome sequencing revealed a heterozygous probably pathogenic variant in *RYR1* gene: c.12083C>T (p. Ser4028Leu). This variant was found in the literature in 2 cases. The first was a boy, 6 years-old with onset disease at 2 years old. Muscle biopsy showed no specific findings however. The autosomal dominant or de novo cases are considered less severe. The ClinVar database classifies this variant as uncertain significance (VUS), although Invitae database has already reported a family with 3 members affected who segregated the same variant (data not published) Considering the similarities between our family and the missense variants previously reported as pathogenic we support that this variant is better classified as probable pathogenic.

http://dx.doi.org/10.1016/j.nmd.2019.06.587

EP.131

Novel *ACTA1* mutation causes late-onset nemaline myopathy with fuzzy-dark cores

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ACTA1 gene encodes skeletal muscle alpha-actin, the principal actin isoform in adult skeletal muscle, which forms the core of the thin filament of the sarcomere where it interacts with a variety of proteins to produce the force for muscle contraction4. *ACTA1* is implicated in several muscle disorders including nemaline, cores, rod-core or actin aggregate myopathies and fiber-type disproportion. We report clinical, muscle imaging and histopatological data from an Italian family harboring a novel *ACTA1* mutation with peculiar histopathological findings. Affected members showed a late-onset diffuse muscle weakness (facial, axial, proximal and distal) with muscle hypotrophy.