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CASE REPORT

Autosomal dominant Ullrich congenital muscular dystrophy due to a *de novo* mutation in *COL6A3* gene. A case report

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Mutations in the genes encoding collagen VI cause Bethlem myopathy (MIM 158810), Ullrich congenital muscular dystrophy (MIM 254090), and myosclerosis myopathy (MIM #255600). BM is a dominantly inherited disorder, characterised by proximal muscle weakness and joint contractures mainly involving the elbows, ankles, and fingers, which usually follows a relatively mild course. By contrast, UCMD is a severe muscular dystrophy characterized by early onset, rapidly progressive muscle wasting and weakness, proximal joint contractures and distal joint hyperlaxity. Rapid progression usually leads to early death due to respiratory failure. UCMD is usually inherited as an autosomal recessive trait though dominant *de novo* heterozygous variants have recently been reported. We describe a further patient with UCMD classical presentation who showed, at the NGS analysis, the *de novo* variant c.6210+1G > A in the intron 16 of the gene *COL6A3*, known in the literature as pathogenic (VCV0000949S6.5).

Key words: collagen VI disorders, Ullrich congenital muscular dystrophy, UCMD, COL6A3

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Introduction

Collagen VI-related dystrophies (COL6-RDs) represent a continuum of overlapping clinical phenotypes with Bethlem myopathy (BM) at the milder end, Ullrich congenital muscular dystrophy (UCMD) at the more severe end, and a phenotype between UCMD and BM, referred to as intermediate COL6-RD [1-3].

Bethlem myopathy (OMIM #158810), is characterized by a combination of proximal muscle weakness and joint contractures. Hypotonia and delayed motor milestones occur in early childhood; mild hypotonia and weakness may be present congenitally. By adulthood, there is evidence of proximal weakness and contractures of the elbows, Achilles tendons, and long finger flexors. The progression of weakness is slow, and more than two thirds of affected individuals older than age 50 years remain independently ambulatory indoors. Respiratory involvement is not a consistent feature [2]. Ullrich congenital muscular dystrophy (UCMD, OMIM #254090) was originally described by Otto Ullrich in 1930 as ''congen-

ital scleroatonic muscular dystrophy'' characterized by generalized muscle weakness and striking hypermobility of distal joints in conjunction with contractures of more proximal joints and normal intellectual development. Additional findings may include kyphoscoliosis, torticollis, prominent calcanei, follicular hyperkeratosis, excessive scar formation following skin trauma. Respiratory insufficiency develops progressively, and ultimately patients almost invariably need ventilation support[3]. Decreased fetal movements are frequently reported. Some affected children acquire the ability to walk independently; however, progression of the disease results in a loss of ambulation around the age of 10 [3].

Intermediate COL6-RD phenotype is characterized by independent ambulation after the age of 11 and respiratory insufficiency that is later in onset than in UCMD (early 20s). In contrast to individuals with Bethlem muscular dystrophy, those with intermediate COL6-RD typically do not achieve the ability to run, jump, or climb stairs without use of a railing [1-3].

UCMD is considered to be a recessive condition and homozygous or compound heterozygous mutations have been defined in *COL6A2* and *COL6A3* genes. In contrast, the milder disorder Bethlem myopathy shows clear dominant inheritance, caused by heterozygous mutations in *COL6A1, COL6A2* and *COL6A3*. However, there is phenotypic as well as genetic overlap between these two disorders, as patients with Bethlem myopathy not uncommonly may have first symptoms at birth[2], and dominant mutations in COL6A1 were recently identified in a patient with a severe UCMD phenotype [4].

We report a further case of AD-UCMD, confirming that dominant mutations are not as rare as previously believed in patients with UCMD.

Case report

An 11.5-year-boy came to our observation for a clinical picture characterized by early tendon retractions, kyphoscoliosis, respiratory insufficiency (FVC 52%). The symptoms began at the age of 7-9 months, with delay in the acquisition of the motor skills: the child was unable to maintain the sitting position and never acquired autonomous walking. Serum CK values were normal. A muscle biopsy, previously performed at another hospital, showed a myopathic picture with variation in fiber size, increased interstitial connective tissue, and occasional necrotic and regenerating fibers. There was no cardiac involvement after ECG and echocardiogram, nor mental retardation or other intellectual impairments. After the consent of the parents a blood draw was taken for DNA analysis.

Over the years, muscle condition remained stable, while vital capacity progressively deteriorated (Fig. 1).

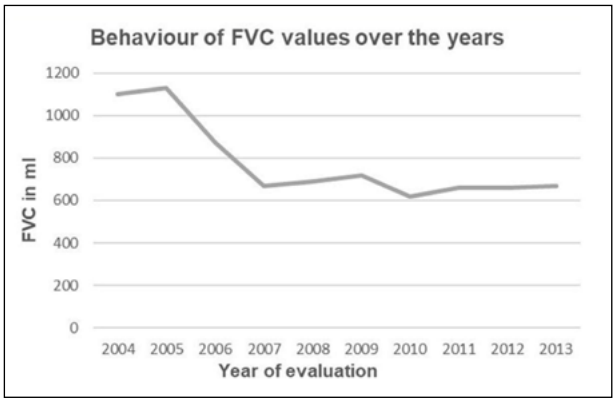

Figure 1. Changes in FVC values over the years.

Although he and his family had been advised several times to have a pulmonological consultation aimed at starting non-invasive assisted ventilation, the patient always refused it. He died at 25.9 years of acute respiratory failure.

Genotyping results

Genomic DNA was extracted from peripheral lymphocytes, by standard procedures. The analysis of *COL6A1* and *COL6A2* genes was negative for mutations. The trio whole exome sequencing, later performed, identified a heterozygous IVS16+1 G > A mutation in the mandatory 5' consensus splice site of intron 16 that accounts for the observed exon skipping. Importantly, the mutation was not present in either of the unaffected parents, indicating that it was a *de novo* mutation in the patient (Fig. 2). Because the patient's cDNA was not available and he refused to perform a skin biopsy, it was impossible to perform RNA RT-PCR from muscle or dermal fibroblasts.

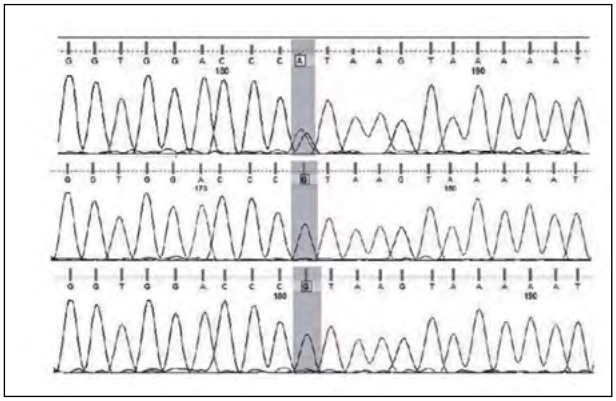

Figure 2. Sequencing of COL6A3 gene in the patient (Top), mother (Center) and father (Bottom). The variation G > A is present only in the patient.

Discussion

The genetics of the collagen VI related disorders is complex. Collagen VI is composed of three different peptide chains encoded by three large genes; the assembly of collagen VI involves a number of different stages. Different mutations may have variable effects on protein assembly, secretion, and its ability to form a functioning extracellular network [5]. In general, heterozygous mutations in the three collagen VI genes *COL6A1, COL6A2* and *COL6A3* cause BM, while homozygous or compound heterozygous mutations in *COL6A2* and *COL6A3* cause UCMD [2,3]. Accordingly, UCMD is considered to be a recessive condition, whilst the milder disorder BM a dominant condition. However, the model was recently questioned as *de novo* dominant collagen VI gene mutations have been found in more than half of severely affected UCMD patients [4-7]. The mutations that often affects the amino acid sequence in the N-terminal region of the triple helical domain before the single cysteine, are either splice site mutations that cause small in frame deletions in the triple-helical domains, or missense changes that alter the obligatory glycine residues of the repetitive Gly-X-Y sequences [7]. In contrast to the total absence or severe deficiency of collagen VI in recessive UCMD, abnormal collagen VI protein is abundantly present in the interstitial connective tissue between muscle fibres in the dominant UCMD patients [8], suggesting that the pathological mechanisms for the dominant and recessive patients are not identical. For instance, the presence of mutant collagen VI in the endomysium seems to alter the muscle extracellular microenvironment, which in turn may influence the cellular activities of the adjacent muscle cells in a manner that differs from the total absence of collagen VI protein in recessive UCMD [8].

The first *de novo* heterozygous deletion of the *COL6A1* gene resulting in the severe phenotype of classical UCMD precluding ambulation, was reported by Pan et al. [4] in 2003. Soon after Lampe et al. [5] reported that 10/26 patients with UCMD they studied, showed a single variation despite a severe presentation, and that 3 of them had the heterozygous variation c.6210+1 G > A splice donor in the intron 16 of the gene *COL6A3*.

Baker et al. [6] found heterozygous in-frame deletions in the N-terminal region of the triple helical domain, chain in 3/5 patients with a clinical diagnosis of UCMD, one of them in alpha3 (VI). The mutations were all located towards the N-terminal end of the 335–336 amino acid triple helical domain. Studies on protein biosynthesis and assembly of Collagen VI showed that these mutations act in a dominant negative fashion and result in severe collagen VI matrix deficiencies [6].

Briñas et al. reported that *de novo* mutations in *COL6A3* are usually located within the TH domains of the chains and that *COL6A3* intron 16 is mutated preferentially, making up 18% of the mutated alleles [7]. Furthermore they detected several exon skipping events due to dominant de novo splice-site mutations in 14/49 patients (28.5%), representing 21% of all mutations. Notably, they observed that different genomic mutations lead to identical consequences both at the mRNA and protein levels. For example, the skipping of *COL6A3* exon 16 can be caused by three different changes affecting the same donor site (c.6210 + 1 G > A, c.6210 +1 G > T, and c.6210 + 5 G > A). Lampe et al. [9] found that > 50% of the *de novo* mutations lead to heterozygous skipping of exon 16 in the alpha3 (VI) chain making this the single most common UCMD mutation mechanism. This was also the most common single exon skipping mutation in a recent series of collagen VI mutations from Japan [10]. In these cases, the severity has been explained as probably due to the proximity of the only cysteine residue encoded by exon 17 of *COL6A3*, which is thought to be involved in the disulfide bonds that assemble dimers and tetramers prior to secretion [11]. Taken together (Leiden Muscular Dystrophy Database; www.dmd.nl; references 5-11) these data indicate that at least as many as 50% of UCMD patients will have dominant mutations.

In conclusion, the patient described here confirms that collagen VI disorders represent a continuous clinical and genetic spectrum from severe to mild phenotypes, and that autosomal dominant UCMD caused by heterozygous *de novo* mutations are not as rare as previously believed.

However, the different patterns of inheritance are of great importance for the impact on genetic counselling of patients and their families.

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Conflict of interest statement

The Authors declare no conflict of interest.

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Authors' contributions

LP: Conceptualization, methodology, data curation, original draft preparation, writing, review and editing and supervision; VN: formal analysis of genetic data, investigation and data collection; EP, AT: validation.

Ethical consideration

The study was conducted in accordance with the Declaration of Helsinki. The approval of the Ethics Committee was not necessary as no particular procedures other than those routinely performed were employed.

Written informed consent was obtained from the parents of the patient for genetic analysis and data publication.

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