Metaphyseal Chondrodysplasia Schmid type - widening the phenotype: Significant variable expression in two familial cases with heterozygous COL10A1 variants

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Abstract

Metaphyseal Chondrodysplasia Schmid Type (SMCD) is a rare dominant form of skeletal dysplasia, caused by heterozygous mutations in the COL10A1 (Collagen Type X alpha 1) gene which codes for α1 chains in type X collagen, and typically results in disproportionate short stature. We report two families with the clinical and radiological diagnosis of SMCD seen in our unit over 4 years. In the first family (A), the proband had a possible pathogenic COL10A1 variant (c.133C>T, p.Pro45Ser). However, his father had the same variant without any obvious signs of SMCD, causing uncertainty whether this mutation was pathogenic. In the second family (B), the proband and her affected father had the same variant. Almost at the same time, a large consanguineous family was reported to have segregation of the variant with SMCD phenotypes in that the homozygosity was related to severer phenotypes and the heterozygosity to milder phenotypes. Hence, we were convinced that the variant was pathogenic. The pathogenic variant (p.Pro45Ser) causes a wide phenotypic spectrum of SMCD and even subclinical features. In this report, we highlight attenuated phenotypes of SMCD, and also discuss the latest therapeutic advances in SMCD and its mechanism of action.

Introduction

Metaphyseal chondrodysplasia encompasses a heterogeneous group of rare skeletal dysplasias. Metaphyseal chondrodysplasia Schmid type (SMCD) is the most common type of the group (others include Jansen and McCusick MCD). SMCD manifests with disproportionate short stature with rhizomelic shortening of the limbs and waddling gait in early childhood1. The classical radiological features include widened growth plates, metaphyseal irregularities, and metaphyseal flaring of the long bones, particularly at the knees and hips. Coxa vara is a common feature. SMCD is an autosomal dominant condition caused by heterozygous mutations of COL10A1 which codes for type X collagen. Increasing availability of molecular testing for genetic disorders has increased the likelihood of detecting variants of unknown pathogenic significance. This report on two families with SMCD due to a pathogenic variant (p.Pro45Ser) highlights the attenuated phenotypes and intrafamilial phenotypic variations in these families, causing uncertainty as to whether the genetic variant was of pathological significance.
Methods

This article is a retrospective report of two families referred to the West Midlands Regional Clinical Genetics Unit, between 2014 to 2018. In both families, the probands showed progressive genu valgum presumably due to a genetic bone disease, and the family histories were notable. The data of the medical history, clinical examination, and sequential growth parameters were retrieved from the clinical records. Additional diagnostic work-up included serum biochemical testing (including serum alkaline phosphatase, calcium, phosphate and vitamin D levels) and radiographic imaging, including the radiographs of the lower limbs and pelvic in both probands, those of the knees and pelvis in the proband’s father in the first family (Family A) and those of the left knee and left hip in the proband’s father in the second family (Family B). A single gene (COL10A1) DNA Sanger sequencing for the probands and follow-up targeted sequencing for the parents was performed. DNA testing was conducted at the Genome Diagnostic lab at the VU University Medical Centre, Amsterdam.

Results

Family A

A 7-year-old boy (P1), the second child of three, born to unrelated Caucasian parents presented with unresolved genu valgum and a waddling gait aged 4 years. He was born at 37 weeks of gestation via normal vaginal delivery. Prenatal imaging had revealed gastroschisis and an umbilical hernia, which were surgically repaired after birth. He had a family history of early-onset hip replacement in his maternal grandmother and great aunt (both at age 52 years), as shown in the pedigree (figure 1). Growth parameters aged 7 were as follows: height 122 cm (50th centile) and OFC (occipito-frontal circumference) 55 cm (97th centile). Weight at age 5 years was 22 kg (>75th centile). His facial features were normal. Psychomotor developmental was normal. He had marked bilateral, asymmetric genu valgum. Both hips abducted to only ~30 degrees. The genu valgum was corrected using a surgical technique of guided growth using an eight plate and screws (image 1.1).

Investigations

Biochemical testing, including ALP (alkaline phosphatase), phosphate and Vitamin D, was normal. Radiographs are described in Image 1.1a-b.

The clinical presentation and radiographic findings suggested SMCD. Sanger sequencing for all exons and surrounding splice sites of COL10A1 revealed a novel heterozygous missense variant c.133C>T (p.Pro45Ser, substitution of serine for proline in a non-collagenous NC2 domain of COL10A1). The proline is highly conserved across species. However, most of the previously described pathogenic COL10A1 variants have been reported in the other non-collagenous NC1 domain. Based on these considerations, the variant was classified as a variant of uncertain clinical
significance (VUS). A DNA analysis for the parents indicated that it was paternally transmitted. However, his father was deemed to be asymptomatic with a normal stature (178cm) and previous radiographic examination was reported as normal (image 1.2a-b). Therefore, this missense variant was considered unlikely to be pathogenic.

However, retrospective radiological assessment for the hip (image 1.2 b, c, d) ascertained subtle ‘cervical’ coxa vara and femoral neck shortening, suggestive of metaphyseal dysplasia.

**Family B**

A 4-year-old female (P2), the second child of three, born to unrelated Caucasian parents, presented with short stature and genu valgum. She was born at 38 weeks following an uneventful pregnancy and normal vaginal delivery. At 3 years 9 months, her height was 96cm (9th centile). She showed normal facial features and normal head size. She showed mild upper-limb rhizomelia and symmetrical progressive genu valgum. She underwent a guided growth surgery at her knees, as shown in image 2.1. Her father and paternal aunt required multiple surgeries for bowed legs and they were 168cm and 150cm tall, respectively, as detailed in the pedigree (figure 2). Her father showed a normal knee joint after genu valgum correction surgery (image 2.2a), but demonstrated shortening of the femoral necks and mild degenerative changes of the hip joint (image 2.2b).

**Investigations**

Biochemical testing including ALP, phosphate and Vitamin D was normal. Radiographs described in image 2.1.
The clinical and radiological features suggested SMCD. COL10A1 testing identified the same variant (paternally inherited) as in family A.

**Discussion**

SMCD is caused by mutations in COL10A1 which codes for α1-chains in type X collagen (structure described in figure 3). It is a network forming collagen, largely expressed in hypertrophic chondrocytes, mainly hypertrophic zones of growth plates and articular-cartilage of long bones. Thus, abnormal type X collagen leads to growth plate defects and possibly defective articular cartilage. To date, 47 pathogenic COL10A1 variants have been reported, 45 within the globular domain (NC1). In this report, both probands with SMCD had a paternally inherited variant, c.133C>T (p.Pro45Ser), substituting a serine residue for a highly conserved proline residue in the NC2 domain. In general, it is not straightforward to make a radiological diagnosis for adults with genetic bone diseases. Nevertheless, meticulous radiological assessment ascertained that the fathers were also affected. Additionally, Ain N et al, recently reported a large consanguineous family with p.Pro45Ser, in which the homozygous state caused a severe form of chondrodysplasia, whilst heterozygous carriers had a mild phenotype of short stature. It is now clear that c.133C>T (p. Pro45Ser) is a pathogenic variant. However, the phenotype of the father in Family A was so mild on clinical and radiological grounds that c.133C>T (p.Pro45Ser) was initially regarded as unlikely to be a pathogenic variant. Height of adult patients with SMCD is generally less than 3.5SD of the mean, although a number of patients with normal height have been reported. In this series both probands were not particularly short. Our report illustrated the wider clinical variability associated with the (p.Pro45Ser) variant and also highlight the large phenotypic spectrum of SMCD, which should be taken in consideration in the interpretation of hitherto uncharacterised molecular findings in COL10A1.

It was intriguing to see premature degenerative disease in older family members of Family A and to a lesser degree in the father of Family B. It is a matter of debate whether this feature should be part of the SMCD phenotype. Interestingly the clinical synopsis of SMCD in the OMIM database specifically mentions ‘no osteoarthritic symptoms’ as a clinical feature. This report stresses the need for careful phenotypic analysis to confirm diagnosis. This is increasingly important with the emergence of potential treatments.

Treatments for SMCD are limited to supportive...
physiotherapy, occupational therapy and surgical correction for lower limb deformities. More recently there have been drug trials looking at the efficacy of Carbamazepine treatment. Carbamazepine (CBZ), is a well-known anti-epileptic drug, is currently in trials for SMCD due to its ability to reduce ER (endoplasmic reticulum) stress (as discussed in Table 1). Mutations in COL10A1 leads to retention of misfolded collagen X within the ER of hypertrophic chondrocytes. Increased ER stress then leads to the unfolded protein response and ultimately disruption of the normal growth plate and bone growth. CBZ efficacy has been demonstrated in SMCD mouse models showing a reduction in severity of phenotypic features. More information can be found on the trial website.

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Conflict of Interest
No conflicts of interests to declare.

References
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