CLINICAL QUIZ (p188) ANSWER

What is the diagnosis?

This patient is diagnosed with Schmid-type metaphyseal chondrodysplasia (MCDS).

A next generation sequencing (NGS) panel test on skeletal dysplasia, performed by Clinical Genetic Service, Department of Health, revealed a heterozygous mutation in the *COL10A1* gene (*COL10A1*:c.1833G>A;p.Trp611*), a known cause of MCDS, which is consistent with the patient's phenotype. This single nucleotide change from G to A at c.1833 alters the codon for tryptophan at position 611 to a premature stop codon, resulting in a mutant mRNA transcript, which could be degraded, or translated into a truncated, and often dysfunctional protein product.

Diagnosis of MCDS is usually made clinically (short stature, bow legs, no extra-skeletal manifestations etc.) and radiographically (metaphyseal changes in the long bones); genetic testing is useful for establishing a definitive diagnosis.

What is Schmid-type metaphyseal chondrodysplasia (MCDS)?

Schmid-type metaphyseal chondrodysplasia is an autosomal dominant skeletal dysplasia characterised by short stature and bowing of long bones, particularly of the lower limbs. Current literature estimated its incidence to be around three to six cases per million of population; however, it has been suggested that this could be an underestimation due to its variable clinical pattern.[1] It is the most common, and relatively mild type of metaphyseal chondrodysplasia, a heterogeneous group of growth plate cartilage disorders. Other features of MCDS include coxa vara, lumbar lordosis, pain and mild hand involvement which improves with age. Spinal involvement is uncommon, but has been observed in a subgroup of patients.[2] Clinically, severity of symptoms varies. Radiographically, metaphyseal abnormalities of long bones are observed; these include widening and irregularity of growth plate (metaphyseal fraying), especially in the proximal and distal femurs.[3]

Diagnosis of MCDS is often made after the age of two, as patients begin to develop skeletal changes with weight bearing, presenting with mild to moderate short stature, bowed limbs and often a waddling gait as they begin to walk. In addition to clinical and radiographic characterisation, molecular genetic testing for *COL10A1* gene is useful to confirm a diagnosis.

What is the differential diagnosis for MCDS?

Bow legs (genu varum) and short stature are characteristic features of other pathologic conditions including rickets, Blount disease and other types of metaphyseal chondrodysplasia.

Bow legs are common deformities in children below the age of two. Physiologic bow legs typically resolve after the age of two, and often do not require medical attention unless there is no improvement beyond that age; deformity is asymmetric or unilateral; intercondylar distance is greater than 2 standard deviations for age; or when short stature is also present. In these cases, pathologic bow legs should be suspected.

MCDS is commonly mistaken for rickets, a bone disorder. There has been a strong perception that most bow legs occur due to vitamin D deficiency rickets; indeed, rickets was first suspected in this patient as well. Although radiologic features of rickets resemble that of MCDS (widening of growth plates with metaphyseal irregularity) (Figure 3), blood test findings are distinctive. Normal levels of 25-hydroxy vitamin D, calcium, phosphate, parathyroid hormone and alkaline phosphatase could rule out the diagnosis of rickets.

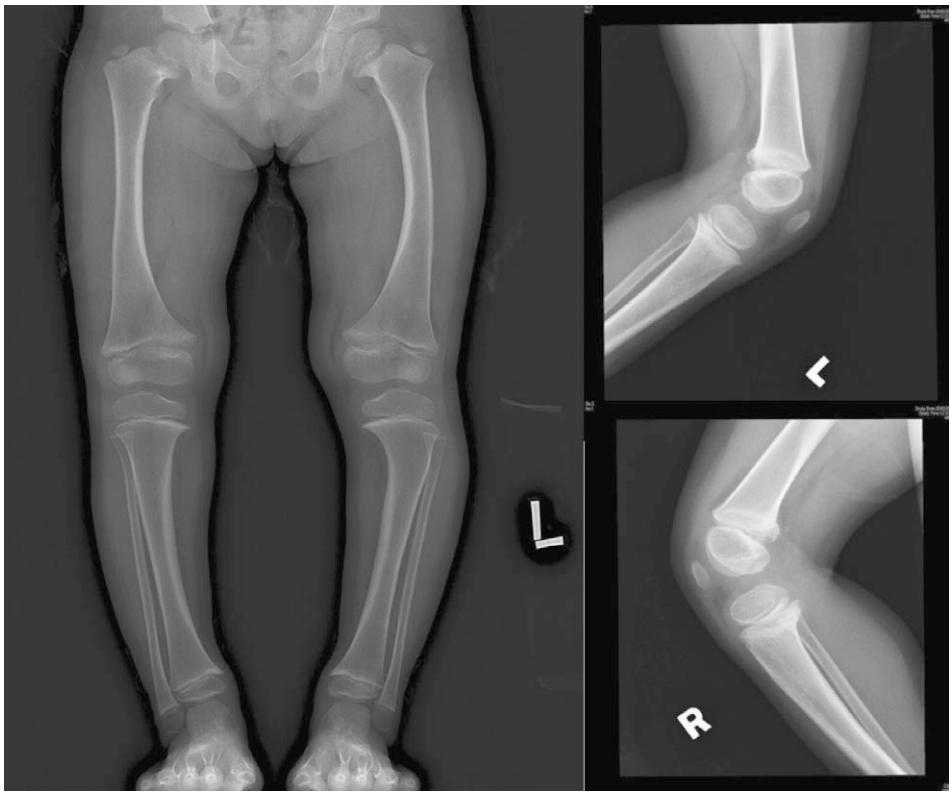

Figure 3 Radiographs of this patient, showing mild bow legs with widening of physis (growth plate) and irregularities at both distal femoral metaphysis, which resembles rickets.

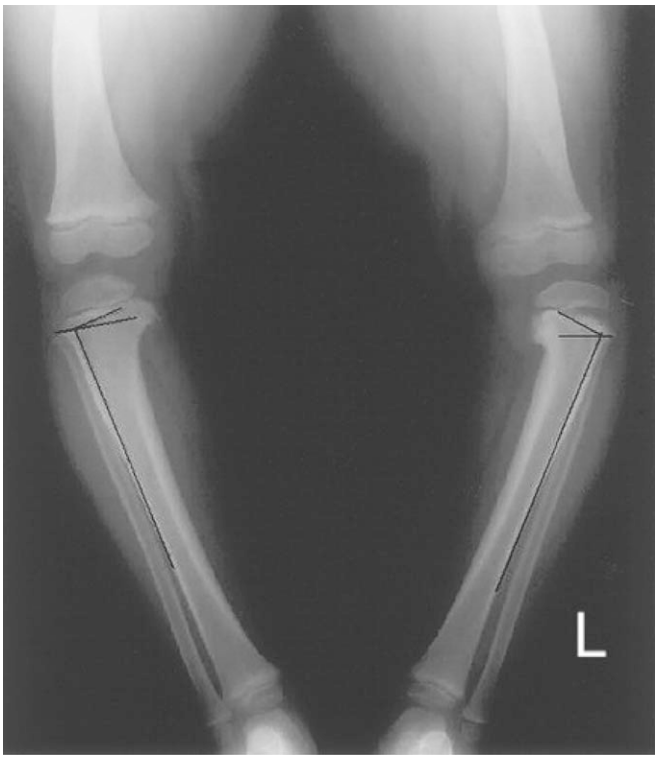

Figure 4 Radiograph of a 23-month-old boy with Blount disease, demonstrating asymmetric depression of proximal tibia. The metaphyseal-diaphyseal angles are also indicated, measured 13 degrees on the right and 26 degrees on the left.[5]

Blount disease is a varus deformity of the proximal tibia in otherwise healthy children. It is a developmental disorder of unclear cause, associated with risk factors such as obesity and early walking.[4] Blount disease was previously suspected in this patient as well. Unlike MCDS, the proximal tibia is primarily affected in Blount disease. Knee radiographs are critical in its diagnosis. While the development of epiphysis is generally preserved in MCDS patients, it is the asymmetric growth of epiphysis that leads to bowing in Blount disease. Metaphyseal-diaphyseal angle can be measured on radiographs, where an angle greater than 16 degrees can support the diagnosis of Blount disease[5] (Figure 4).

Differential diagnosis for MCDS also includes other types of metaphyseal achondrodysplasia, particularly the McKusick type (also known as Cartilage-hair hypoplasia, CHH). They share overlapping radiographic features (metaphyseal changes of the long bones) but distinctive genetic aetiology and clinical presentation. CHH is an autosomal recessive disorder caused by *RMRP* mutations; majority of CHH patients present extra-skeletal manifestations such as poor hair growth and immunodeficiency, which were not detected in this patient. Another type of metaphyseal chondrodysplasia, the Jansen type, caused by *PTH1R* mutations, is the most severe form apparent at birth due to severe short stature and sometimes dysmorphic facial features.[1]

Overall, diagnosis of children with bow legs and short stature requires comprehensive characterisation of clinical and radiographic phenotypes, followed by genetic correlation to effectively establish a definitive diagnosis thus appropriate management.

What is the molecular genetics behind MCDS?

MCDS is caused by mutations in *COL10A1*, a gene encoding type X collagen. Type X collagen is a short chain collagen consisting of three identical a-chains (homotrimer). It is a major extracellular matrix component of hypertrophic chondrocytes within the growth plate cartilage, expressed predominantly by these chondrocytes during endochondral ossification to maintain growth plate structure and function. Accordingly, pathogenic mutations in *COL10A1* affect growth plate function thus long bone growth and development to cause MCDS.

Almost all MCDS-causing mutations (missense, nonsense and frameshift mutations) are located in the NC1 trimerisation domain of *COL10A1* (this patient as well), the region critical for trimer formation and extracellular assembly.[1,6] Different molecular mechanisms have been proposed to account for the clinical variability of MCDS presentation. Heterozygous missense mutations are thought to exert a dominant negative effect (the misfolded mutant chains interfering with the assembly of normal chains, thus disruption of overall collagen network formation) to lead to MCDS.[7] On the other hand, heterozygous nonsense and frameshift mutations, which introduce premature termination signals, could result in complete or incomplete loss of mutant transcripts before protein translation. It has been proposed that complete removal of mutant mRNA transcripts by nonsense-mediated decay results in functional haploinsufficiency (whereby action of the other wild type allele is insufficient to produce a normal phenotype), thus an atypical late clinical presentation of MCDS (after the age of seven). On the other hand, incomplete loss or stability of mutant transcripts, whereby misfolded mutant chains are still produced but retained within the cells, trigger an intracellular stress response and exert the dominant negative effect to account for the typical early clinical presentation and a relatively severe phenotype.[6,8]

What is the management of MCDS?

Currently the management of MCDS is based on individual clinical severity, otherwise symptomatic and supportive. Monitoring and early intervention is particularly important in children to ensure they can reach their growth potential. Physical therapy or orthopaedic treatment may help to correct particular features of MCDS. Orthopaedic surgery is primarily confined to the lower extremities;[1] corrective osteotomies may be indicated for patients with symptomatic

or progressive deformities such as significant coxa vara. While bow legs may improve spontaneously during childhood, permanent or reversible hemiepiphysiodesis, also known as guided growth techniques, can be used to realign angular limb deformity. In particular, temporary guided growth techniques such as the Eight-Plates system (Orthofix, USA) might serve as more gentle and effective alternatives for modulating growth and realignment in MCDS children with bow legs.[1] Regarding short stature, it should be noted growth hormone therapy is not effective to increase final height in MCDS.

Research effort has been ongoing to explore potential treatment of MCDS, and recently, the use of carbamazepine (CBZ). Carbamazepine, commonly used as an anticonvulsant, could stimulate intracellular proteolysis and relieve the intracellular stress caused by the accumulation of misfolded mutant chains within the hypertrophic chondrocytes. As demonstrated in a mouse model, CBZ could effectively reduce the disease severity of MCDS.[8] A clinical trial, MCDS-Therapy (ISRCTN37815869), is underway to ascertain the potential benefit of CBZ in MCDS patients.

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References

1. Al Kaissi A, Ghachem MB, Nabil NM, et al. Schmid's Type of Metaphyseal Chondrodysplasia: Diagnosis and Management. Orthop Surg 2018;10:241-6.
2. Savarirayan R, Cormier-Daire V, Lachman RS, Rimoin DL. Schmid type metaphyseal chondrodysplasia: a spondylometaphyseal dysplasia identical to the "Japanese" type. Pediatr Radiol 2000;30:460-3.
3. Makitie O, Susic M, Ward L, Barclay C, Glorieux FH, Cole WG. Schmid type of metaphyseal chondrodysplasia and COL10A1 mutations-findings in 10 patients. Am J Med Genet A 2005;137A:241-8.
4. Sabharwal S. Blount disease: an update. Orthop Clin North Am 2015;46:37-47.
5. Cheema JI, Grissom LE, Harcke HT. Radiographic characteristics of lower-extremity bowing in children. Radiographics 2003;23:871-80.
6. Makitie O, Susic M, Cole WG. Early-onset metaphyseal chondrodysplasia type Schmid associated with a COL10A1 frame-shift mutation and impaired trimerization of wild-type alpha1(X) protein chains. J Orthop Res 2010;28:1497-501.
7. Bateman JF, Wilson R, Freddi S, Lamande SR, Savarirayan R. Mutations of COL10A1 in Schmid metaphyseal chondrodysplasia. Hum Mutat 2005;25:525-34.
8. Forouhan M, Sonntag S, Boot-Handford RP. Carbamazepine reduces disease severity in a mouse model of metaphyseal chondrodysplasia type Schmid caused by a premature stop codon (Y632X) in the Col10a1 gene. Hum Mol Genet 2018:3840-53.