ELECTRONIC LETTER

Angel shaped phalangeal dysplasia, hip dysplasia, and positional teeth abnormalities are part of the brachydactyly C spectrum associated with CDMP-1 mutations

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In 1967, Bachman described a “hereditary peripheral dysostosis” which affected a mother and her two children.¹ What was later considered as multiple epiphyseal dysplasia combined with phalangeal cone shaped epiphyses² was renamed angel shaped phalangoepiphyseal dysplasia (ASPED) and considered as a genetic bone marker.³ ASPED represents a further variety of multiple epiphyseal dysplasia and is transmitted as an autosomal dominant trait. It is radiologically diagnosed by the characteristic angel shape of the middle phalanges, typical metacarpophalangeal pattern profile, and epiphyseal changes in the hips. The angel shape of the middle phalanges is an isolated bone variation, similar to the non-syndromal, cone shaped epiphyses of type 12.³

Clinical manifestations in ASPED are not restricted to the hands, and the original paper reported on various combinations of angel shaped phalanges, hip dysplasia, and hypodontia.¹ Patients range in stature from short to normal. Osteoarthritis of the hips can be significant, with severe intermittent hip pain. Hyperextensible interphalangeal joints of the fingers have been documented, as well as retarded bone age. Late eruption of deciduous teeth or persistent primary lower incisors have been described.³ Hypodontia was noted in four out of seven patients in Giedion’s cohort, and in 1.6 to 9.6% in the general population.⁴

Brachydactyly type C (BDC) is characterised by shortening of the first metacarpal and of the second, third, and fifth middle phalanges.⁵ Other common hand findings include ulnar deviation of the index finger and polyphalangy. Several reports on BDC emphasise variability of findings such as talipes, shortening of the middle phalanges of the toes, hip dysplasia, and short stature, but have not emphasised the presence of hypodontia or angel shaped epiphyses.^{6,7} CDMP-1 (also known as GDF5) is a secreted signalling molecule that participates in skeletal morphogenesis. CDMP-1 has been detected in the rat dental pulp, and could intervene in tooth development and maintenance.⁸ Heterozygous mutations in CDMP-1 occur in individuals with autosomal dominant BDC.⁶

We report on ASPED in a family with three affected members. Since types of ASP distinct from those observed in ASPED have been reported in BDC,⁹ and since short first metacarpal and hip dysplasia are common in both ASPED and BDC, we performed molecular biological testing and identified a known CDMP-1 mutation. We also report three affected individuals from another family with autosomal dominant BDC secondary to a new CDMP-1 mutation, associated with premature loss of teeth and hip dysplasia.

CLINICAL/RADIOGRAPHICAL DATA

Family A

The propositus (III-3) was referred for abnormal hand radiographs after trauma, being the third child of

Key points summary

- Angel shaped phalangoepiphyseal dysplasia (ASPED) is a specific bone dysplasia characterised by the association of brachydactyly with particular radiological features, abnormal dentition, delayed capital femoral ossification, and early onset degenerative hip arthrosis. It has rarely been described, but angel shaped phalanx (ASP) was identified earlier in multiple epiphyseal dysplasia with bone age retardation and severe coxarthrosis in adult life, considered at that time as cone shaped epiphyses.
- CDMP-1 is a cartilage specific member of the TGFβ superfamily of secreted signalling molecules, functioning as a signal for chondrogenesis, growth, and patterning of the developing vertebrate skeleton. Homozygous and compound heterozygous CDMP-1 mutations cause acromesomelic chondrodysplasia (Grebe and Hunter-Thompson type), and heterozygous mutations can lead to a wide range of phenotypes, from brachydactyly type C (BDC) to no discernable clinical and radiological findings at all.
- In the present study, ASPED was identified in three patients from one family (one adult and three children), and clinical and radiological observations evolving with age are reported. Since radiological findings resembling ASPs had been reported in BDC, molecular analysis of the CDMP-1 gene was performed and one causative mutation was identified in this family. Independently, a new CDMP-1 mutation was identified in three affected individuals presenting typical autosomal dominant BDC, associated with dental anomalies and hip dysplasia in one case.
- It is suggested that ASPED is due to heterozygous mutations in the CDMP-1 gene, and that dental anomalies could represent another associated feature of the CDMP-1 spectrum, in accordance with the expression of this gene in the dental pulp.

non-consanguineous and healthy parents, born at term after a normal pregnancy. She was seen in the genetic clinic at 10.25 years of age. She presented with normal growth parameters. Clinically, the main features were proximally placed thumbs and bilateral short middle phalanges of the second and fifth ray, with fifth finger clinodactyly (fig 2A). Lower limbs appeared normal. Facial appearance, vision, and hearing were normal and school performance was average for age. Odontological examination revealed abnormal enamel,

Figure 1 Pedigree of family A.

delay in tooth eruption, malocclusion of teeth, and several caries. Her brothers III-1 and III-2 were also examined: III-1 was clinically affected. His height was 166 cm at 16 years of age, and he presented with proximally placed thumbs, bilateral short middle phalanges of the second and fifth ray, fifth finger clinodactyly, and similar dental abnormalities (fig 2B). No clinical anomalies were identified in III-2, whose

height was 176 cm at 14 years of age. II-2, the father of the proband, was seen in the clinic at the age of 42 years. He presented with proximally placed thumbs (fig 2C). He did not complain of any joint pain. Dental examination revealed abnormally placed teeth, premature loss of teeth, and multiple caries. According to II-2, his brother (II-1), father (I-2), half brother (II-3), and sister (II-4) were also affected with proximally placed thumbs and dental anomalies, but they were not seen in the clinic.

Full skeletal surveys were obtained for III-1 (aged 10 years), III-3 (aged 6 years), and II-2 (aged 42 years). The major abnormal findings were observed in the hands: radiographs of the hands of III-1 (fig 2 E) and III-3 (fig 2 D) revealed the ASPED aspect of the first metacarpal and middle phalanges of the second and fifth ray, with bilateral accessory epiphyses and fifth finger clinodactyly. These findings were more pronounced on the right side. The foot radiographs revealed ASPED in some phalanges, with cone shaped epiphyses and accessory epiphyses. Radiographs of the hands of II-2 only showed bilateral short first metacarpals (fig 2F). His hips were also abnormal, with bilateral coxarthrosis; no other skeletal abnormalities were identified.

Figure 2 (A) III.3. Note proximally placed thumbs, short middle phalanges of the second and fifth ray with fifth finger clinodactyly. (B) III.1. Note proximally placed thumbs, short middle phalanges of the second and fifth ray, with fifth finger clinodactyly. (C) II.2. Note proximally placed thumbs. (D) and (E) III.3 and III.1. Note ASPED aspect of the first metacarpal and middle phalanges of second and fifth ray, with accessory epiphyses and fifth finger clinodactyly. (F) II.2. Note short first metacarpal.

Figure 3 Pedigree of family B.

Family B

The proband (III-2) was the second child of healthy unrelated parents. The pregnancy had been normal. He was referred after a routine skeletal survey performed for hip osteochondritis, which identified abnormal hand findings. At 9 years of age he presented with growth parameters within the normal range (126 cm in height (-1SD) and 27 kg in weight (-1SD)). Clinical examination revealed hand abnormalities with proximally placed thumbs, short middle phalanges of the second, third, and fifth fingers with bilateral fifth finger clinodactyly (fig 4A). Examination of the feet showed syndactyly of the second and third toes, and short fifth toes. His mother (II-2), aged 41 years, and his sister (III-1), aged 14 years, presented with the same signs in the hands (figs 2B, C). II-2 was short (156 cm) and used a denture

because of total tooth loss before the age of 14 years; III-1 had abnormally placed teeth. These findings were consistent with BDC.

Full skeletal surveys were obtained for III-1 and III-2. The major findings were observed in the hands, and these features were consistent with BDC, with short first metacarpal and shortened middle phalanges of the second, third, and fifth fingers (figs 4D–F). The hips of III-2 were abnormal and dysplastic, but the hips of III-1 did not reveal any abnormalities.

MOLECULAR DATA

Since some clinical and radiological features (short first metacarpal and hip dysplasia) are common to ASPED and BDC, we performed molecular analysis of the CDMP-1 gene in these two families. Genomic DNA was extracted from peripheral blood samples from family members. Mutation detection consisted of PCR amplification of the two coding exons of CDMP-1 with direct sequencing of the amplicons in both directions.¹⁰ We identified a heterozygous CDMP-1 mutation in the affected individuals in both families. In family A, the mutation was identified in III-3, III-1, and II-2; it was an insertion of a C at nucleotide residue 297 of the coding sequence. This insertion produced a shift in the reading frame at codon 99, which resulted in premature termination of the polypeptide five amino acids downstream. This mutation had been reported before, in homozygous patients with Grebe type chondrodysplasia.¹¹ Heterozygous carriers in the latter report did not show any apparent

Figure 4 (A) III-2. Note proximally placed thumb, short middle phalanges of the second, third, and fifth fingers and fifth finger clinodactyly. (B) and (C) II-2 and III-1. Note proximally placed thumb, short middle phalanges of the second, third, and fifth fingers and fifth finger clinodactyly. (D), (E), and (F) Note short first metacarpal and shortened middle phalanges of the second, third, and fifth fingers.

phenotypic abnormalities. In family B, the mutation was identified in III-2, III-1, and II-2; it was an insertion of a C at nucleotide residue 498 of the coding sequence. This insertion produced a shift in the reading frame at codon 166, which resulted in premature termination of the polypeptide 17 amino acids downstream. To our knowledge, this mutation had never been reported in the literature.

DISCUSSION

CDMP-1, also known as GDF5, is mapped on chromosome 20q11.2, and is closely related to the bone morphogenetic proteins. It is a cartilage specific member of the TGF β superfamily of secreted signalling molecules, expressed predominantly at sites of cartilage differentiation in developing limbs, where it may function as a signal for chondrogenesis, growth, and patterning of the developing vertebrate skeleton. Expression of CDMP-1 at the position of future joint spaces also suggests a role in the formation of articulations. In addition, CDMP-1 expression has been reported in the cornea¹² and in the teeth.^[8 13] There is a wide range of phenotypes associated with CDMP-1 mutations, from no discernable clinical and radiographical findings, to classic BDC with or without other skeletal manifestations, isolated short stature, vertebral abnormalities, and developmental dysplasia of the hip.¹⁴ Non-penetrance had been previously described with CDMP-1 heterozygous mutations. Naturally occurring null mutations in mice cause a brachypodism (*bp*) phenotype. In humans, homozygous and compound heterozygous CDMP-1 mutations cause acromesomelic chondrodysplasia (Grebe and Hunter–Thomson types), and demonstrate that the development of appendicular skeletal elements and joint morphogenesis are severely perturbed in the absence of CDMP-1. Heterozygous mutations can lead to haploinsufficiency, producing mild phenotypes,¹⁵ such as autosomal dominant BDC¹⁰ which is characterised by underdevelopment or absence of phalangeal and metacarpal bones. The disorder primarily affects the middle phalanges of the second, third, and fifth fingers and the first metacarpal bone.

ASPED has rarely been reported in the literature,³ and is probably often overlooked. In family A, we screened for CDMP-1 mutation because of clinical and radiographical similarities between ASPED and BDC. We identified a known mutation, previously described in homozygous patients with Grebe type chondrodysplasia; heterozygous carriers did not exhibit any abnormalities. The affected members of family A presented with positional dental abnormalities and late eruption of teeth, but not the hypodontia previously reported in patients with ASPED. Significant severe premature loss of teeth was observed in family B. To our knowledge, no dental findings had been reported before in association with CDMP-1 mutation. Both identified mutations are certainly causative, since they lead to premature termination of the protein. The nucleotide insertion identified in family A had been previously identified in homozygous patients with Grebe syndrome.¹¹

Our findings confirm the broad phenotypic spectrum of CDMP-1 mutations. We therefore propose that ASPED is

another disorder due to CDMP-1 mutation; and that, since CDMP-1 is expressed in the dental pulp, dental abnormalities could represent a new feature within this spectrum.

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