Several reports on BDC emphasise variability of findings such as ulnar deviation of the index finger and polyphalangy. Several 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. 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. Hypodontia was noted in four out of seven patients in Giedion’s cohort, and in 1.6 to 9.6% in the general population.

Brachyactyly type C (BDC) is characterised by shortening of the first metacarpal and of the second, third, and fifth middle phalanges. 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.

Independently, a new CDMP-1 mutation was identified in this family. A combined analysis of the CDMP-1 gene was performed, and one causative mutation was identified in this family.

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.
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 propositus, 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 2D) 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.
Family B

The propositus (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 amplimers in both directions. 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. Heterozygous carriers in the latter report did not show any apparent

Figure 3 Pedigree of family B.

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 TGFβ 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 articulars. In addition, CDMP-1 expression has been reported in the cornea[12] 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 BDC[16] 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, 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 negative 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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**REFERENCES**


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