A new mutation in the SH3BP2 gene showing reduced penetrance in a family affected with cherubism

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Cherubism is a familial benign fibro-osseous disease of the jaws. Mutations in the SH3BP2 gene are identified as the cause of cherubism. In the present study the penetrance of cherubism in a Turkish family is described. Clinical and radiologic examination and DNA analysis were performed in eleven members of the family. Two members had the classic features of cherubism. In 5 family members a point mutation was detected. This specific point mutation has not been described before now. Two of these (1 male and 1 female) showed no evidence of the disease, indicating a reduced penetrance.

Cherubism was first described by Jones in 19331 as a familial multilocular cystic disease of the jaws. In 1938 the term cherubism was used for the first time, because the faces of the patients with more or less symmetrical swollen cheeks resemble the angelic cherubs of Renaissance art. Cherubism is characterized by bilateral expansion of the mandible and/or the maxilla, which becomes noticeable in early childhood and grows progressively larger until puberty. The lesions gradually resolve after puberty.2 Radiologically, cherubism shows bilateral multilocular cystic expansion of the jaws. Displacement or aplasia of teeth and tooth-germs is often seen. The histologic characteristics are indistinguishable from central giant cell granuloma, even though sometimes a characteristic eosinophilic perivascular cuffing is present in cases of cherubism.3,4 Cherubism has an autosomal dominant inheritance and is thought to have a 100% penetrance in males and 50%-70% in females. However, sporadic cases have also been reported. The data on penetrance date back to an early review of 21 affected families5 and are referred to in textbooks on maxillofacial pathology and genetics6,7 as well as in virtually every paper published on cherubism.2,8,9 The expressivity in patients is variable, ranging from lesions bilaterally in only the mandibular rami to lesions involving the entire mandible and maxilla.4

After the mapping of cherubism to 4p16,10,11 Ueki et al.12 identified mutations in the SH3BP2 gene in 12 cherubism families. So far, all the reported mutations are located in exon 9, within a 6–amino acid sequence at amino acid position 415 to 420.8,9,12

In this study we describe the penetrance of cherubism in a Turkish family afflicted with cherubism.

CASE REPORT

Subjects

Eleven members of a family originating from Turkey were clinically, radiologically, and genetically analyzed. The objective criteria for the diagnosis of cherubism were a bilateral swelling of the jaw with expansion, perforation, disruption, or thinness of the bony cortex combined with radiographic findings of (large) bilateral multilocular radioluencies with ir-
regular bony septa and tooth displacement, missing teeth, or root resorption. Routine clinical examination was performed by 2 oral and maxillofacial surgeons. For radiologic examination, panoramic x-rays were made. In patients with signs and symptoms of cherubism, a biopsy of the jaw lesions was taken for histologic examination.

Genetic analysis

DNA was extracted from EDTA blood according to standard procedures using the puregene DNA extraction kit (Gentra Systems, Minneapolis, MN). We analyzed exon 9, in which the mutation hotspot is situated, by direct sequencing. First, polymerase chain reactions (PCR) were performed, using a set of primers flanking the intron/exon boundaries (forward primer: 5'-TGA-CAG-TGA-AAT-GGT-CCT-GCC-3' and reverse primer: 5'-TTG-CTC-AGG-ACG-GTC-TGT-3'). After purifying the PCR products, the sequencing reactions were performed from these purified PCR products using the Big Dye Terminator v.1.1 kit (Applied Biosystems, Warrington, UK) according to the manufacturer’s instructions. Electrophoresis was performed on an ABI377 DNA sequencer (Applied Biosystems). The sequence analyses were performed with Sequencing Analysis 3.5 software of Applied Biosystems.

RESULTS

Two subjects of the family had the classic clinical and radiologic features of cherubism (the proband (III:1) and his cousin (III:6); Fig. 1). Histologic examination showed the microscopic features of central giant cell granuloma. In the proband, the lesions extended to the whole of the mandible and the right side of the maxilla (Fig. 2). His cousin exhibited lesions in the whole of the mandible and maxilla and showed the typical upward-turned eyes (Fig. 3).

In the proband, direct sequence analysis of exon 9 was performed. A point mutation was detected: a C to A transition in exon 9 resulting in a proline to threonine substitution at amino acid position 418 (p.P418T c.1513C > A). The other affected family members (Fig. 1) exhibited the same point mutation.

The proband’s mother (II:4 in Fig. 1) had no clinical symptoms of the disease, but showed a facial appearance consistent with a resolved cherubism. Furthermore, remnants of cherubism in the mandible were seen on the x-ray, including severe displacement of 1 molar. The uncle (II:5 in Fig. 1) and aunt (II:11 in Fig. 1) who carried the mutation demonstrated no clinical or radiologic evidence of cherubism, nor was there any anamnestic indication that they had exhibited signs or symptoms of cherubism in the past. One other family member (II:10 in Fig. 1) did not have any manifestations or anamnestic evidence of cherubism and was not willing to be tested. All the other family members showed no clinical signs and symptoms of cherubism and tested negatively on DNA analysis.

DISCUSSION

The mutation as described here is in a well known mutation hotspot at amino acid number 415 to 420.\textsuperscript{8,9,12} Mutations in pro418 (to leu, arg, or his) are the most frequent described changes in cherubism.\textsuperscript{9,12} However, the specific point mutation (p.pro418thr) described here has not been reported before. It is presumed to be
pathogenic, because it is a substitution of the nonpolar proline by the polar threonine and thus causes a change in polarity. Furthermore, it is in the well known mutation hotspot, which indicates an essential role of this domain of the gene in the development of cherubism.

Up to now, the pathogenesis of cherubism has not been elucidated. It is hypothesized that the development of the lesions in cherubism might be linked to the development of the second and third molars, because these molars are frequently missing or displaced in cherubism. Furthermore, the lesions in cherubism are always located in the jaw, the second molar starts mineralizing at the age of 2 or 3, and the normal odontogenesis stops at adolescence. The onset and regression often seen in cherubism coincide with these sequences in tooth development. However, the question remains in what way the SH2BP3 gene is linked to tooth development and eruption. There are indications that the gene SH3BP2 plays a role in regulating the increased osteoblast and osteoclast activities that are seen in normal tooth eruption. Furthermore, it is suggested that point mutations in the SH3BP2 gene could cause pathologic activation of osteoclasts, presumably by dysfunction of the SH3BP2 gene in the regulatory pathway of osteoclastogenesis. In this process, SH3BP2 has an influence on the regulation of the receptor of parathyroid hormone (PTH) and PTH-
related protein (PThrP). The PThrP mediates a reduction in expression of osteoprotegerin in dental follicle cells, which causes osteoclastogenesis.14-17

In this Turkish family, 5 members were identified as carrying the point mutation, of which 2 did not express any signs or symptoms of cherubism. One of these 2 was male, which is very rare because cherubism is thought to have a 100% penetrance in males.5,6,7 In this male, as in his sister, there was no retrospective evidence or personal memory of any manifestation of cherubism. This means that either he had a mild form of cherubism in his youth that was never diagnosed and healed without any remnants or that he was never afflicted with cherubism. The latter would demonstrate that cherubism does not have a 100% penetrance in males. Incomplete penetrance in males has also been described in a German report on 2 affected families,18 although no DNA analysis on the SH2BP3 gene was performed.

Of the remaining 3 family members identified with the mutation, the proband and his cousin were definitely affected with cherubism. The proband’s mother showed radiologic evidence of an earlier manifestation of cherubism in the mandible. Also, her facial appearance exhibited features consistent with cherubism in the past. Therefore, she has probably suffered from cherubism in her youth, which had dissolved at the start of adulthood.

These findings suggest a variable expressivity of cherubism in these 3 clinically and radiologically affected family members with the same point mutation in the SH3BP2 gene.

In generation II, 4 of the 9 siblings were already deceased at the start of the screening, and a fifth, who exhibited no signs and symptoms of cherubism, refused to be tested. In 3 of the 4 remaining siblings the mutation was identified. In the next line of posterity the incidence was 1 out of 3. This is in line with expectation, cherubism being an autosomal dominant disease with a 50% recurrence risk.

In conclusion, in a Turkish family we found a new amino acid change in the SH3BP2 gene in a known mutation hotspot for cherubism. In 1 male and 1 female the mutation was present without any signs and symptoms of cherubism, either presently or in the past. This could indicate that, contrary to earlier literature, the described mutation does not have a 100% penetrance in males.

We thank C. Maissan and G. B. Salieb-Beugelaar for their excellent technical assistance.

REFERENCES


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