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Call Number:	
Title:	Journal of cranio-maxillo-facial surgery /
ISSN:	1010-5182
Imprint:	Stuttgart ;, New York : Thieme, 1987 9999
Article:	Hyckel; "Cherubism--New hypotheses on pathogenesis ..."
Volume:	33
Number:	1
Date:	2005
Pages:	61-end of article
Verified:	WorldCat Availability: Alternate: Elsevier Science Ltd., The Boulevard, Langford Ln, Kidlington, Oxford OX5 1 GB UK CODEN: JCMSET Desc: v. : Type: Serial, Internet Resource

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Journal of Cranio-Maxillofacial Surgery (2005) 33, 61–68
© 2004 European Association for Cranio-Maxillofacial Surgery
doi:10.1016/j.jcms.2004.07.006, available online at http://www.sciencedirect.com

Cherubism – new hypotheses on pathogenesis and therapeutic consequences

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SUMMARY. Aims: **The hereditary occurrence of cherubism indicates a probable genetic aetiology: a correlation with a mutation in the gene SH3BP2 has been demonstrated. A convincing concept of formal pathogenesis is not yet available. The study was aimed at advancing the understanding of the pathogenesis of cherubism by presenting a case study including genetic findings and an evaluation of the literature.** Results and conclusion: **Because of its association with the development of the second and third molars, cherubism could be defined as a genetically determined alteration of tooth development. In this context, disturbed PTHrP – PTHrP receptor interaction induced by the mutation in SH3BP2 is discussed. The temporal and spatial determination of the clinical symptoms is explained by an interaction of SH3BP2-dependent signal transduction pathways with jaw morphogenesis (e.g. Hox-gene Msx-1). Because of the disease-induced lack of determination of the cap phase of the second and third molar, a spatial compartmentation, which is necessary for normal dental development, does not take place. This leads to dysregulation of mesenchymal bone building tissue areas, and to the development of giant cell granulomas with high osteoclastic activity.**

Because of the genetic determination of cherubism and the associated dedifferentiation of the diseased tissue, a surgical removal should be exclusively restricted to specific indications. Therefore an attitude of wait and see is preferred. © **2004 European Association for Cranio-Maxillofacial Surgery**

Keywords: **Cherubism; Pathogenesis; SH3BP2; MSX1; Giant cell granuloma**

INTRODUCTION

Cherubism – first described by *Jones* (1933) – received its name because of the angel-like appearance of the patients (chubby and upward directed look). The disease is attributed to an osteopathy also involving odontogenic dysplasia of the jaw bones, a form of fibrous dysplasia of bone and a giant cell granuloma (*Burland*, 1962; *Hoppe* et al., 1966). Occasionally, the disease is referred to as cherubism syndrome, since alterations in other bones may occur. It is generally accepted that it is a benign, in most cases hereditary, disease of bone, beginning at the age of 2 or 3 years, progressive in childhood, with a peak at the age of five, and showing spontaneous regression at the end of adolescence.

The diagnosis of cherubism is based on clinical, radiographic and histological findings. The clinical findings are:

- familial occurrence,
- characteristic alterations of the face, with pronounced bilateral involvement of the jaws in early childhood,
- high arched palate and missing second and third molars,
- a cyclical course,
- indolent lymph node swellings,
- spontaneous arrest or regression after adolescence,
- no involvement of the temporomandibular joint.

From a radiographic point of view, a multilocular, cystic, symmetrical expansion of the upper and lower jaws is seen. Computerized tomography shows honeycomb-like lesions of the mandibular cortical bone, with concomitant repair in the mandibular angle area. In the upper jaws, the tuberosity area is affected, with occlusion of the maxillary sinus and elevation of the orbital floor sometimes.

The histology is of limited diagnostic significance. Fibrous hyperplasia and a large number of multinucleated giant cells are noted. Pseudocystic structures are noted especially in the repair phase. The differential diagnosis of cherubism consists of fibrous dysplasia, giant cell granuloma, osteosarcoma, juvenile ossifying fibroma, fibrous osteoma, odontogenic cyst, hyperparathyroidism (*Hoppe* et al., 1966). Therefore, in addition to the typical histological

features, the bilateral involvement of the jaws, as well as the typical course, and the familial occurrence of the disease are required for a diagnosis of cherubism (*Haunfelder*, 1967). Reports on cherubism without a familial occurrence (*Sitzmann*, 1973) or beginning at the age of 10 (*Hoyer* and *Neukam*, 1982; *Opitz* and *Wittstock*, 1990; *Pulse* et al., 2001) or immediately after birth (*Mangion* et al., 1999) should be viewed sceptically. By classification three degrees of severity are distinguished (*Fordyce*, 1978; *Motamedi*, 1998).

The familial occurrence of the disease has been and is still the subject of intense investigation. *Talley* (1952) and *Andersen* and *McClendon* (1962) showed that two-thirds of the families affected had two or three successive generations affected. In seven families, the diseased members affected one line of siblings only. The authors concluded an autosomal dominant inheritance with 100% penetrance in men and 60 – 80% in women.

Mangion et al. (1999) and *Tiziani* et al. (1999) showed that the gene region responsible for cherubism is located on chromosome 4p16.3. The clinically conspicuous disturbance in osteogenesis and a possible relation to tooth development, as well as the location of the gene in an interval between D4S127 and the telomere of 4p, led to the hypothesis that the genes FGFR3 and MSX1, located in this area, are causative for this disease. Finally, in a larger study, *Ueki* et al. (2001) found mutations in the gene for the SH3-binding protein SH3BP2, which is located within the critical area in 12 out of 15 families with cherubism. SH3BP2-dependent signal transduction seems to be involved especially in the regulation of elevated osteoclastic and osteoblastic activities during dentition.

Although the genetic cause of cherubism appears to have been identified, an accepted concept for its formal pathogenesis is not available yet. Therefore, it is the aim of this work to advance the understanding of the aetiology and pathogenesis of cherubism. A case study including molecular genetical findings as well as a synopsis of the literature will be presented.

CLINICAL REPORT

A male patient was referred to this department for the first time at the age of $2\frac{1}{2}$ years. There was swelling at the level of the (maxillary) tuberosity on the right side. During the following 3 years, a swelling became noticeable on both sides, especially in the inter maxilliary region between the jaws. A high arched palate associated with open bite developed (Fig. 1A,B). A non-painful submandibular swelling of lymph nodes existed on both sides. The most prominent swelling was reached at the age of 5. On orthopantomographs in the 3rd and 8th years, pseudo-cystic alteration, mainly of both the ascending rami of the mandible was noted. The condyles were not affected (Fig. 1C). The 2nd and 3rd molars

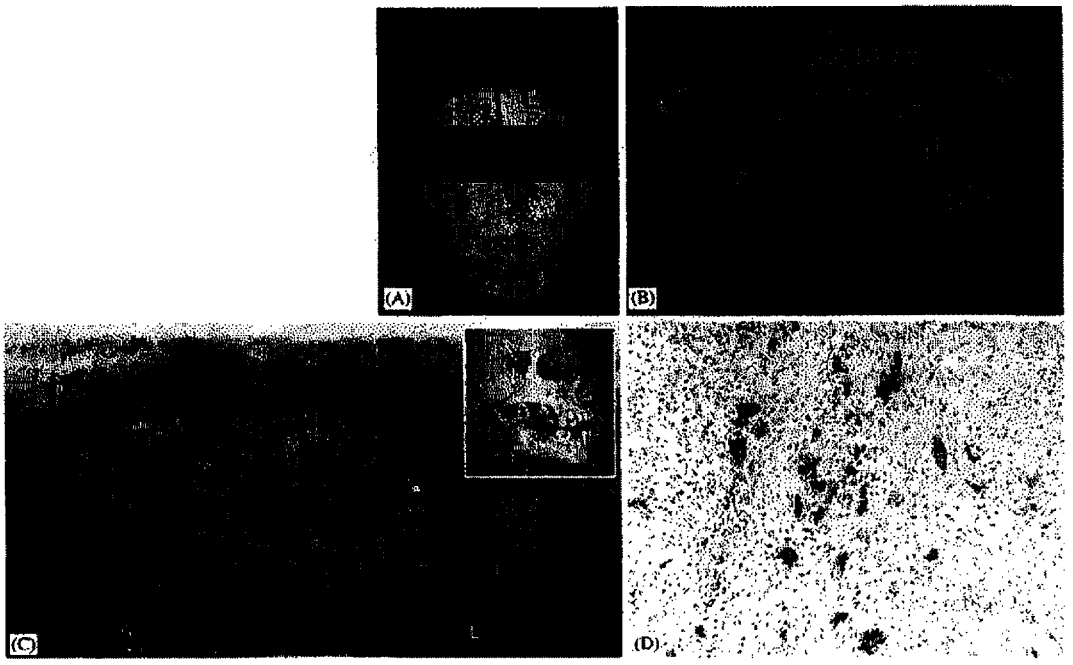

Fig. 1 – A 5-year-old male patient suffering from cherubism: a swelling on both sides, especially of the mandible (A), high arched palate associated with open bite (B); radiograph and CT scan (inset) at the age of 8: extensive pseudo-cystic osteolysis on both sides mainly of the angle of the mandible (C); light microscopy: primarily fibrohistiocytic tissue with multinuclear histiocytic giant cells (D).

never developed. The distal root of the first molar in the left lower jaw was completely resorbed.

To rule out spontaneous fractures, computed tomographic scans were undertaken at ages 5 and 10. CT aspects of skull development of this patient have been published already by *Schleier* et al. (2003). The maxillary sinus was completely occluded on both sides; there was no displacement of the orbital floor and no evidence of a fracture in the mandible. In the ascending ramus and the region of the tuberosity, extensive osteolysis was visible bilaterally (Fig. 1C inset).

Between ages 6 and 10 (annual reviews), the high-arched palate flattened out, and the radio-opacities completely regressed. The patient has been under orthodontic care since the age of 7 years.

At present (aged 12), a tendency for regression was noted, with persistent mandibular swelling and with concurrent growth of the jaws. The open bite was treated successfully by the orthodontists. After establishing the diagnosis based on clinical, radiological, and histological findings, no surgical therapy was performed according to the recommendations of the DÖSAK (German – Austrian – Swiss Registry of Head and Neck Tumours).

FAMILY HISTORY

The father of the patient had suffered familial bilateral giant cell "tumours". In his case, the treatment was conservative. The family history was negative regarding his parents and siblings. The case report of the father was published by *Waurick* (1977). At present, there are no visible pathological changes in the facial profile. On the orthopantomograph only the teeth 43 and 44 were present in the mandible with tooth 44 exhibiting a deformation of the root. The maxilla was edentulous. Both upper and lower jaws were severely atrophic.

HISTOLOGY

Histological processing of tissue samples collected at ages 6 and 11 in connection with primary diagnosis and orthodontic care showed fibrohistiocytic tissue with inclusion of multinuclear histiocytic giant cells. The giant cells were thinly disseminated throughout the fibrous tissue, but did not determine the histological pattern. Immunohistochemical demonstration of tartrate-resistent acid phosphatase (TRAP, antibody clone 26E5; Novocastra Lab. Ltd, UK; Chem Mate™ Kit, Dako, Denmark) revealed the osteoclastic character of these giant cells (Fig. 1D). Histopathology of the specimen obtained from the child at the age of 11, when compared with the specimen at age 6, showed a distinct regression of the tumour. The pseudo-cystic changes are now predominant.

CYTOGENETIC AND MOLECULAR GENETIC FINDINGS/CHROMOSOME ANALYSIS

Cytogenetic and molecular genetic studies were performed using chromosome preparations obtained from cultured peripheral lymphocytes. Chromosome preparations as well as GTG (*G-bands by trypsin using Giemsa*) and CBG (*C-bands by barium hydroxide using Giemsa*) banding were performed according to standard methods described by *Verma* and *Babu* (1995). In each chromosome preparation, 15 metaphase plates were evaluated. Analysis of the chromosomes revealed a male karyotype (46, XY, 1qh+) in both father and son, without any pathological finding.

FLUORESCENCE IN SITU HYBRIDISATION (FISH)

Fluorescence in situ hybridisation (Fish) was performed according to *Liehr* et al. (1995). For specific demonstration of the chromosome region 4p16.3, the LSI WHS Wolf-Hirschhorn microdeletion probe (LSI WHS region SpectrumOrange/CEP 4 SpectrumGreen, control probe, alpha satellite DNA) was used. As the result of the evaluation of 25 metaphase plates, a deletion in the WHS region 4p16.3 was not evident in father or son (normal karyotype ish 4p16.3 (WHS × 2)).

QUANTITATIVE AND QUALITATIVE ANALYSIS OF MSX-1 EXPRESSION IN PERIPHERAL BLOOD, TOOTH BUD, AND TOOTH FOLLICLE AS WELL AS IN THE GIANT CELL GRANULOMA

For demonstration of expression of the Msx-1 gene in the patient, total RNA was extracted from peripheral blood using the Total RNA Kit (Qiagen, Hilden, Germany). It was transcribed into cDNA and Msx-1 expression was analysed by means of polymerase chain reaction (PCR) using primers based on the gene bank sequence of Msx-1/Hox-7 (Acc. No. M97676). As control for cDNA integrity as well as for semi-quantitative estimation of Msx-1 expression, beta-actin cDNA was also amplified. PCR analysis revealed that cells from peripheral blood of the patient expressed Msx-1. Msx-1 mRNA could also be demonstrated in the control sample (father of the patient). The tissue samples available for examination, namely, from tooth bud, tooth follicle, and giant cell granuloma, were incubated in RNA lysis buffer (Qiagen, Hilden, Germany) overnight on ice, in order to obtain optimal digestion of the samples. RT-PCR revealed a low level of Msx-1 mRNA in all samples examined; hence there was no evidence for a lack of expression of Msx-1.

SEQUENCING THE SH3BP2 GENE

DNA was prepared from blood samples of father and son. As all mutations known so far were localized in exon 9 of the *SH3BP2* gene, only this exon was sequenced. Sequencing was performed using the ABI Prism-BigDye-Terminator Cycle Sequencing Ready Reaction Kit and exon 9 specific PCR primers on the sequencing machine ABI 3700 (both from Applied Biosystem, USA) as recommended by the manufacturer.

The heterozygous mutation 13369C>A (exchange of cytosine (C) by adenine (A) at position 13369) could be demonstrated in exon 9 of the SH3BP2 gene of both patients. This mutation causes incorporation of the amino acid histidine (CAC) instead of proline (CCC) at amino acid position 418 of the protein.

DISCUSSION

Cherubism as a result of a disturbance in dental development

Although *Jones* assumed as early as 1965 that cherubism was an odontogenic lesion, where the growth pressure exerted by dental germs, or exaggerated deciduous tooth resorption were supposed to play a role, a directly odontogenic cause is currently considered as unlikely. *Burkhardt* and *Berthold* (1986) have examined the tissue taken from a boy afflicted with cherubism using light and electron microscopy and immunohistology. They found a close relationship with giant cell granuloma of the jaws.

Because cherubism is a location-stable phenomenon found only in the jaws with multiple occurrences, a structure-associated process is a very likely link to the pathogenic mechanism. Conspicuous in this respect is the regular development of giant cell granuloma in all quadrants of both jaws in the area of the molars. In cherubism patients, the second and third molars are also missing. In addition, the cyclic course of the disease is closely linked to the normal development of the second and third molars: The incidence is coincident with the beginning of second molar mineralization (at the age of two or three). Spontaneous regression during adolescence is at the normal conclusion of molar odontogenesis. Furthermore the eponymous symptom of cherubism, the skyward directed gaze, can be explained by excessive tissue formation in association with molar development: The dental germs of the second molars are located rather high in the tuberosities at the age of 2–3 years. Looking at developmental biology, further facts with relevance to understanding cherubism are clear. Thus, the second and third molars are the only dental germs not completely developed at birth. Furthermore, the histological alterations in cherubism only affect structures of the first branchial arch. Considering both the temporal and spatial associations of the clinical course of cherubism with development of the second and third molars, it may be justified to speculate that the underlying genetic defect of cherubism is disturbing normal development of these teeth and is dysregulating the associated bone formation.

What are the relations between SH3BP2 and dental development?

The patient presented here fulfils the classical and very stringent diagnostic criteria of cherubism with respect to inheritance, physiognomy, radiography, histology and clinical course. In this respect, the finding of a heterozygous mutation in exon 9 of the SH3BP2 gene matches the earlier results of *Ueki* et al. (2001). Their hypothesis that cherubism originates from this genetical alteration was confirmed in the case presented. SH3BP2 was originally described as a tumour suppressor gene with respect to bladder cancer. To date, it is known as a regulator protein of the c-abl oncogene (*Bell* et al., 1997). Because of its specific domain structure, it is thought to have a role in signal transduction.

So far, however, there is no idea of how SH3BP2 interferes with regulation of dental development. An explanation of such regulatory action can perhaps be deduced from the genesis of giant cell granuloma, which occurs in other diseases, too, and is important for differential diagnosis. In this respect, true giant cell tumours must be differentiated as well as the so-called brown tumours found in hyperparathyroidism (*Van Damme* and *Mooren*, 1994). The latter appear to be induced by a dysregulation of parathormone signal transduction. It may be assumed that the giant cell granuloma-like proliferation in cherubism originates from a similar disturbance in this signal transduction pathway. In fact, it is possible to conclude from a small number of published results of an influence of SH3BP2 on the regulation of the receptor for parathyroid hormone (PTH) and PTH-related protein (PTHrP): SH3BP2 interacts with the chaperone protein 14-3-3 (*Foucault* et al., 2003), which recently was described as a regulatory protein of the type I PTH/PTHrP receptor (*Tazawa* et al., 2003). Current investigations suggest that the PTHrP – PTHrP receptor interaction is of fundamental importance for the spatio-temporal organisation of bone cells and their osteoclastic function in normal development of the tooth germ and the surrounding alveolar bone, as well as in the dentition (*Philbrick* et al., 1998, *Wysolmerski* et al., 2001, *Mekaapiruk* et al., 2002, *Kitahara* et al., 2002).

Moreover, the formation of signal transduction protein complexes, or the regulation of non-receptor tyrosin kinases (src, abl) through the src-homology sequences SH2 and SH3 are a fundamental component of eukaryote signal transduction. Increasingly, adaptor proteins are described (e.g. RIN1, 14-3-3), which can, through an SH-based interaction, also serve as a linker to Ras-dependent signal transduction pathways (*Han* et al., 1997; *Wang* et al., 2002;

Tzivion et al., 2001). Also a direct influence of a mutation-induced disturbance in SH3BP2 interaction on fibroblast growth factor (FGF)/FGF receptor-dependent regulatory mechanisms in tooth development (via NF-kappaB and Msx-1, see below) has to be considered (*Romashkova* and *Makarov*, 1999; *Bushdid* et al., 2001).

What is the cause of the temporal and spatial determination of clinical symptoms in cherubism?

When assuming a causal genetic defect, the question arises why and how the clinical alterations found in cherubism are temporarily and spatially limited and are subject to regression. It may be hypothesized that SH3BP2-dependent signal transduction chains interact with regulatory pathways temporarily determining jaw morphogenesis – especially in the molar area.

Pattern formation in a developing organism (e.g. segmentation, positioning and formation of limbs) is regulated by a group of temporarily active development controlling genes, the homeotic selector genes. In mammals, the group of Hox-genes is well characterized. Besides its role in limb positioning, Hox-7 (synonym Msx-1) particularly appears to be involved in the regulation of mesenchymal – epithelial interaction in craniofacial morphogenesis – especially concerning structures of the first branchial arch (*Chen* et al., 1996). Thus, mutations in the Hox-7 gene, can lead to selective agenesis of the second and third molar, or to hypodontia and clefting of lip, alveolus and palate (Wolf-Hirschhorn-syndrome, WHS; Witkop-syndrome; *Vastardis* et al., 1996; *Hu* et al., 1998). Comparable deficiencies can be observed also in Msx-1 deficient mice (*Satokata* and *Maas*, 1994). In fact, the co-location of chromosomal aberrations in 4p16.3 and the Hox-7/Msx-1 gene – originally connected with cherubism – leads to the opinion that this gene may indeed play a central role in early tooth development. Hox-7/Msx-1 regulates the interaction of tooth forming epithelium and mesenchyme during development of the dental germ by interaction with mediators of the BMP-, FGF-, Hh- and Wnt-families as well as the homeobox genes Dlx-1 and Dlx-2 (*Bei* and *Maas*, 1998).

Since in the patient described here, neither mutations in the Hox-7/Msx-1 gene nor deletions in the WHS region in 4p16.3 could be detected, it should be possible to conclude that there is some influence of the SH3BP2 mutation on Hox-7/Msx-1-dependent regulation of tooth development, finally leading to formation of a giant cell granuloma. An interaction of interest has been described between PTHrP and Hh proteins (*Iwamoto* et al., 1999). Furthermore, a direct dependence of PTH receptor signalling on Msx expression has been reported (*Satokata* et al., 2000).

Disturbances of the complex interactions in these signalling pathways could principally lead to a complete failure of the transition from germ to cap stage, and thus to a general deficit in tooth development (for review see *Jernvall* and *Thesleff*, 2000). Postnatal development of the second and third molars requires a re-activation of embryonic mechanisms, which involve Msx-1. The complete embryonic tooth development in cherubism can, on the one hand, be explained by a specific role of Msx-1 for molar development and, on the other hand, by a possible intrauterine maternal substitution of missing regulatory factors. Thus, the clinical characteristics of the disease can be well explained as generated by a dysregulation of Msx-1-dependent molar morphogenesis. With the ontogenetically determined end of molar development at adolescence, the genetically determined differentiation programme reaches a halt, and so does the disease.

How can the formation of a giant cell granuloma with osteolytic activity, root resorption and lymph node swelling be explained?

The formation of a cap stage is an essential prerequisite for the sequential and reciprocal interaction of tissue, which depends on an increasing spatial compartmentation. In the absence of this compartmentation, a dysregulation of mesenchymal, bone forming tissue will occur adjacent to dental germs. This compartmentation appears to be especially important for the regulation of Msx-1 expression via endogenous Msx-1 antisense transcripts. A decrease in Msx-1-antisense RNA leads to an overexpression of Msx-1 and consequently to a decreased expression of Cbfa1 and a downregulation of osteocalcin RNA (*Blin-Wakkach* et al., 2001). If a genetically determined postnatal upregulation of Msx-1 is presumed in the context of molar development, and if transition to the cap stage is lacking (thus lacking compartmentation), a non-physiological expression of Msx-1 in the bone mesenchyme can lead to insufficient Cbfa1 expression with a failure of osteoblastic differentiation. Since there is proliferation pressure, this leads to the formation of undifferentiated new tissues (granuloma).

Because of decreased expression of osteoprotegerin, there is osteoclast activation, which manifests itself histologically by TRAP positive giant cells. This in turn leads to cortical lesions and root resorption. The lymph node swelling can be explained by the high osteoclastic resorptive activity.

Some recent findings regarding Msx-1 expression in giant cell granuloma (made in this laboratory) suggest that the development of giant cell granuloma could be linked to dysregulation of Msx-1: The expression rate was of the same order as for dental germs.

The genetic information for Msx-1 is switched off at the end of molar development, leading to normalization of Cbfa1 and, thus, osteocalcin production. During the second growth period (adolescence), deficits in normal bone development are compensated for virtually completely.

Suggestions for therapy in cherubism

Recommended therapy ranges from radical surgical removal to an attitude of wait and see, the latter being preferred today especially in 'classical' cases. Radical surgery is obsolete when the disease occurs in all four quadrants. Poor results have also been reported for curettage, but only in early childhood (*Caffey* and *Williams*, 1951; *Thompson*, 1959): A tendency to relapse was reported for such early intervention. This is easy to understand regarding the high growth potential and a lack of complete removal of the pathological tissue. Likewise, a modelling osteotomy, as in the case of fibrous dysplasia, is not indicated as the secondary process for repairing the bone is again disrupted. The proposal of *Jones* (1965), however, makes sense. A curettage in the beginning of the resorptive phase was successful in his hands. Attempts to control this disease with radiotherapy have to be rejected completely (*Völkel*, 1957). *Mangion* et al. (1999) even reported an osteosarcoma in the irradiated area.

CONCLUSIONS

Fig. 2 gives an overview on the concept for formal pathogenesis of cherubism presented in this paper. Because of its association with the development of the second and third molar, cherubism may be defined as a genetically determined alteration of tooth germ development. A disturbed PTHrP – PTHrP receptor interaction due to the mutation in SH3BP2 leads to interaction with Hox gene Msx-1 activity. Thus the temporal and spatial termination of the clinical symptoms is explained by SH3BP2-dependent signal transduction pathways interfering with jaw morphogenesis (e.g. Hox-gene Msx-1). The cap stage of the

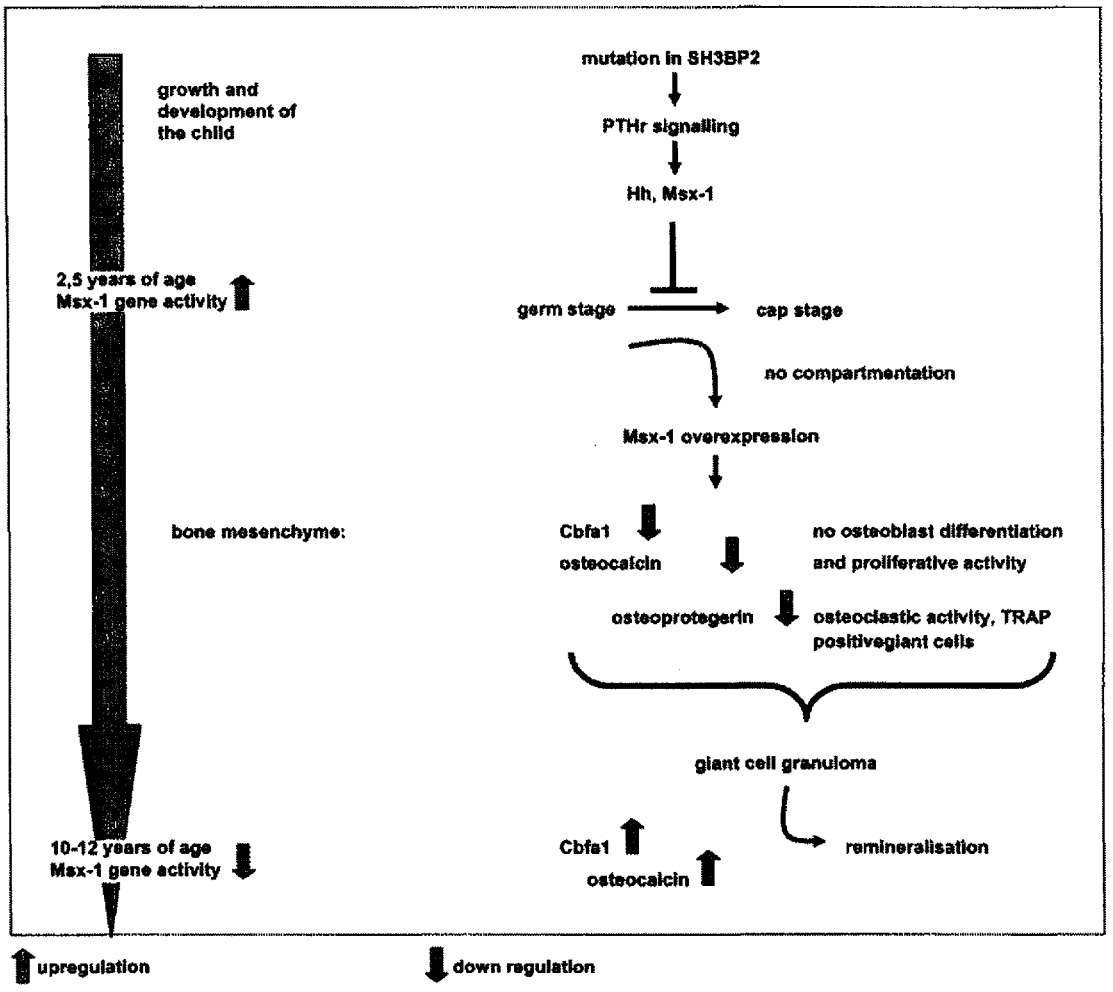

Fig. 2 – Schematic presentation of the proposed molecular pathogenesis of cherubism.

second and third molars, a spatial compartmentation does not take place, being necessary for normal dental development. This leads to dysregulation of mesenchymal bone formation, and to the development of giant cell granulomas containing osteoclasts.

Because of the genetically determined course of cherubism any surgical removal should be exclusively restricted to specific indications – e.g. deterioration of visual acuity. An attitude of wait and see is preferred. A pharmacological modulation of bone metabolism could be a therapeutic option in the future if the hypothesis presented can be proven.

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Paper received 15 October 2003
Accepted 29 July 2004