GENEReviews

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Cherubism

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Summary

Disease characteristics. Cherubism is characterized by painless bilateral, symmetrical enlargement of the mandible and/or maxilla resulting from replacement of bone with multilocular cysts composed of fibrotic stromal cells and osteoclast-like cells. The phenotype ranges from no clinical manifestations to severe mandibular and maxillary overgrowth with respiratory, vision, speech, and swallowing problems. Onset is typically between ages two and five years. Other bones are usually not affected and the affected person is otherwise normal. The jaw lesions progress slowly until puberty when they stabilize and then regress. Dental abnormalities include congenitally missing teeth, premature exfoliation of the deciduous teeth, and displacement of permanent teeth by the jaw lesions. By age 30 years, facial abnormalities are no longer apparent; residual jaw deformity is rare.

Diagnosis/testing. Diagnosis depends on typical clinical findings and radiographic findings of well-defined, often extensive bilateral multilocular areas of diminished density in the mandible and/or maxilla. *SH3BP2* is the only gene currently known to be associated with cherubism. Sequence analysis of exon 9 detects all missense mutations identified to date. Molecular genetic testing is clinically available.

Management. *Treatment of manifestations:* care by a craniofacial team in a major pediatric medical center; surgery (curettage with or without bone grafting) as needed between ages five to 15 years for disfiguring enlargement of jaws or locally aggressive lesions; orthodontic treatment; ophthalmologic treatment for displacement of the globe or vision loss. *Prevention of secondary complications:* Early orthodontia and/or jaw reconstruction may reduce risk for upper airway obstruction, obstructive sleep apnea, tooth displacement. *Surveillance:* long-term follow-up with clinical, radiographic, dental, orthodontic, ophthalmologic evaluations. *Testing of relatives at risk:* When the disease-causing mutation in the family is known, molecular

testing can be used to identify mildly affected relatives who may benefit from early intervention; otherwise use clinical and radiographic evaluations to identify relatives at risk. *Other:* Results of studies using calcitonin are not promising.

Genetic counseling. Cherubism is inherited in an autosomal dominant manner. The proportion of cases caused by *de novo* mutations is unknown because of variable expressivity and reduced penetrance. Each child of an individual with cherubism has a 50% chance of inheriting the mutation. Prenatal diagnosis for pregnancies at increased risk is possible when the *SH3BP2* disease-causing mutation has been identified in the family.

Diagnosis

Clinical Diagnosis

Diagnosis of cherubism is made on the presence of clinical findings and radiographic and histologic manifestations and is confirmed with molecular genetic testing of *SH3BP2*.

No clinical diagnostic criteria have been established. However, the diagnosis is suspected in individuals based on the following:

- **Clinical findings**
  - Usual age of onset between two and five years
  - Painless bilateral, symmetrical enlargement of the mandible and/or maxilla including choronoids and condyles. Other cranial bones are usually unaffected.
  - Slow progression of the jaw lesions up to adolescence and spontaneous regression typically starting after puberty and extending into the twenties
  - Upturned tilting of eyeballs (in advanced stages); rim of sclera visible beneath iris
  - Dental abnormalities: congenitally missing second and third molars; premature exfoliation of the deciduous teeth and displacement of permanent teeth secondary to the jaw lesions
- **Radiographic manifestations** in the mandible and/or maxilla: well-defined bilateral multilocular areas of diminished density, very often extensive, with few irregular bony septa.
- **Histologic manifestations** of lesions in the mandible and/or maxilla: non-neoplastic fibrotic lesions that contain numerous multinuclear giant cells and occasionally cysts. Increase in osteoid and newly formed bone matrix is observed in the periphery.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. *SH3BP2* is the only gene currently known to be associated with cherubism.

Other loci. Failure to identify *SH3BP2* mutations in 20% of affected individuals suggests possible genetic heterogeneity [Ueki et al 2001].

Clinical testing

- **Sequence analysis.** Sequence analysis of exon 9 of *SH3BP2* detects an estimated 80% of mutations [Ueki et al 2001]. Sequencing of the remaining exons of *SH3BP2* is performed on individuals who lack mutations in exon 9.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Cherubism

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis	*SH3BP2* sequence variants in exon 9	~80% [2]	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, and/or test method
2. Ueki et al 2001

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

- **Molecular genetic testing** to confirm the diagnosis in a proband with the suggestive clinical findings and typical radiologic and/or histologic manifestations (see Clinical Diagnosis)
- **Prenatal diagnosis/ preimplantation genetic diagnosis (PGD)** for at-risk pregnancies

  Note: Prenatal diagnosis/PGD require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *SH3BP2*.

Clinical Description

Natural History

Individuals with cherubism are normal at birth. Usually, cherubism manifests in early childhood (age 2-5 years) and progresses until puberty when it begins to stabilize and starts to regress. By age 30 years, the facial abnormalities are not usually recognizable and residual deformity of the jaws is rare [Von Wowern 2000].

Cherubism is an isolated benign condition, in which the affected person is otherwise mentally and physically normal.

The symptoms and signs of cherubism are related to the severity of the condition, and range from clinically unrecognized features to severely deformed mandibular and maxillary overgrowth with respiratory, speech and swallowing complications [Kozakiewicz et al 2001]. Massive enlargement of the jaws is not uncommon and can also be associated with severe pain [Battaglia et al 2000, Timosca et al 2000, Silva et al 2002, Gomes et al 2005, Wang et al 2006].

In some studies,males were found to be more commonly and severely affected than females [Von Wowern 2000].

Involvement of cranial bones. The disease starts with rapid bone degradation, usually restricted to the mandibular and maxillary regions, and leads to multiple symmetrical cystic changes. These cysts are filled with fibrous tissue mass that consists of stromal cells and osteoclast-like cells, resulting in the typical facial phenotype [Ozkan et al 2003].

Dental. In most affected persons, teeth are displaced, unerupted, unformed, or absent or may appear to be floating in cystlike spaces. Malocclusion, premature exfoliation of deciduous teeth, and root resorption have also been reported [Kozakiewicz et al 2001].

Orbital and ophthalmologic. In rare instances, enlargement of the maxilla and penetration of the stromal mass into the orbital floor can cause lower lid retraction, proptosis, diploia, globe displacement, and/or visual loss as a result of optic atrophy [Carroll & Sullivan 2001, Font et al 2003].

Respiratory problems. Respiratory problems can include obstructive sleep apnea and upper airway obstruction caused by backward displacement of the tongue [Battaglia et al 2000, Ladhani et al 2003].

Genotype-Phenotype Correlations

No genotype/phenotype correlations have been described for cherubism.

Penetrance

Penetrance is close to 100% in males and 50%-75% in females [Anderson & McClendon 1962, Peters 1979].

Anticipation

Anticipation has not been described in cherubism.

Nomenclature

Cherubism was first described as "familial multilocular cystic disease of the jaws" by Jones in 1933; however, shortly thereafter he renamed the condition cherubism because of the resemblance of affected individuals to the cherubs in Renaissance art.

Prevalence

Prevalence is unknown. Variability of the cherubism phenotype may result in underdiagnosis of the condition.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Noonan-like/multiple giant-cell lesion syndrome. Noonan-like/multiple giant-cell lesion syndrome is a rare condition, with phenotypic overlap with Noonan syndrome and cherubism [Lee et al 2005]. It is characterized by dysmorphic features, developmental delay, short stature, pulmonary stenosis, and giant-cell lesions of bones and soft tissues. The giant-cell lesions are frequently found in the jaws and therefore persons with mild Noonan-like/multiple giant-cell lesion syndrome can be misdiagnosed with cherubism [Jafarov et al 2005]. Mutations in *PTPN11* have been described in both familial and simplex cases (i.e., a single occurrence in a family) of Noonan-like/multiple giant-cell lesion syndrome.

Central giant-cell granuloma. Central giant-cell granuloma is a rare benign lesion that usually occurs in the mandible and maxilla. The lesions can lead to facial deformity and displacement of the teeth. The condition occurs in children and young adults, with a higher frequency in females. Histologically, central giant-cell granuloma cannot be separated from cherubism. The two conditions can be distinguished by radiologic findings because the majority of lesions in cases of central giant-cell granuloma are unilocular, whereas in cherubism the lesions are usually multilocular [De Lange & Van den Akker 2005]. No mutations in the *SH3BP2* gene have been identified in individuals with aggressive central giant-cell granuloma [de Lange et al 2006]. The etiology of central giant-cell granuloma is unknown.

Fibrous dysplasia. Fibrous dysplasia of the jaw is characterized by benign giant-cell lesions localized asymmetrically in maxilla rather than mandible. The condition usually presents in childhood and is progressive until after adolescence [Zenn & Zuniga 2001]. Cherubism can be distinguished from fibrous dysplasia on a clinical basis.

Hyperparathyroidism. Brown tumors are rare benign giant-cell lesions that arise as a result of parathyroid hormone effects on bone tissue in persons with hyperparathyroidism. Brown tumors can occur in both the maxilla and mandible [Lessa et al 2005]. The age of onset is usually in adulthood. Hyperparathyroidism can be distinguished from cherubism with biochemical investigations, since serum concentrations of calcium, parathyroid hormone, and alkaline phosphatase are elevated in hyperthyroidism [Silva et al 2002].

Other. Cherubism is also part of Ramon syndrome, which is characterized by short stature, mental retardation, and gingival fibromatosis.

Cherubism has also been reported in association with neurofibromatosis type 1 [Martinez-Tello et al 2005, van Capelle et al 2006], fragile X syndrome, and in a single case of coronal and sagittal craniosynostosis, which is likely to be a coincidental association [Stiller et al 2000].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with cherubism:

- Radiology assessment to determine facial bone involvement
- Orthodontic assessment
- Ophthalmologic examination
- Assessment of family history and natural course

Treatment of Manifestations

Treatment protocols for cherubism are not well established since both ends of the spectrum, mild clinically unrecognized cases, and severe cases with extensive bone loss are seen. Given that cherubism is considered to be a self-limited condition that improves over time, treatment should be tailored to the individual's needs. Depending on the severity, surgery may be needed for functional and esthetic concerns.

- **Children with cherubism** should be referred to a craniofacial clinic with pediatric experience for evaluation. A craniofacial clinic associated with a major pediatric medical center usually includes a surgical team, medical geneticist, dentist, orthodontic specialist, ophthalmologist, and social worker.
- **Surgical interventions** include curettage with or without bone grafting [Kozakiewicz et al 2001, Lannon & Earley 2001]. Liposuction has also been used successfully to

re-contour the jaws. Surgical interventions are likely to be done between ages five to 15 years in individuals with disfiguring enlargement of jaws or locally aggressive lesions associated with complications.

- **Orthodontic treatment** is commonly required as the jaw distortion leads to permanent dental abnormalities including a malocclusive bite, premature loss of deciduous teeth, and widely-spaced, misplaced, unerupted, or absent permanent teeth.
- **Ophthalmologic treatment** is necessary in rare individuals in whom orbital manifestations such as lower lid retraction, proptosis, diploia, globe displacement, and visual loss caused by optic atrophy are present.

Prevention of Secondary Complications

Early treatment (i.e., orthodontic and surgical reconstruction of the jaw) may reduce the risk for secondary complications such as upper airway obstruction, obstructive sleep apnea, and tooth displacement.

Surveillance

Generally, long-term follow-up including clinical, radiographic, dental, orthodontic, and ophthalmologic evaluations is indicated [Silva et al 2006].

Testing of Relatives at Risk

At-risk relatives should have clinical and radiographic evaluations given that manifestations may not be evident in all affected individuals. When the disease-causing mutation is known in the proband, molecular testing can be used to evaluate relatives at risk for the disorder. This may allow mildly affected relatives to benefit from early surveillance and intervention.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

A mouse model for cherubism demonstrated that increased cytokine tumor necrosis factor α (TNF-α) production by myeloid cells is causative [Ueki et al 2007]. If TNF-α were found to be pathogenic in humans, anti-TNF therapies could provide new treatment options for cherubism.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Results in the two reports to date on the use of calcitonin in the treatment of cherubism have not been promising [Hart et al 2000, Lannon & Earley 2001].

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Cherubism is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with cherubism have an affected parent.
- A proband with cherubism may have the disorder as the result of a new gene mutation and no previous family history of cherubism will exist. The proportion of cases caused by *de novo* mutations is unknown since variable expressivity and reduced penetrance are observed in cherubism.
- If the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include physical examination and molecular genetic testing for the identified *SH3BP2* mutation in the proband. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of failure by health care professionals to recognize the syndrome and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Note: Although some individuals diagnosed with cherubism have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected and/or the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, the risk to sibs is low, but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. Each child of an individual with cherubism has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members may be at risk.

Related Genetic Counseling Issues

See Testing of Relatives at Risk for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novof* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The *SH3BP2* disease-causing mutation must be identified in the family before prenatal testing can be performed.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Note: It is the policy of *GeneReviews* to include clinical uses of testing available from laboratories listed in the GeneTests Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Cherubism

Gene Symbol	Chromosomal Locus	Protein Name
SH3BP2	4p16.3	SH3 domain-binding protein 2

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Cherubism

118400	CHERUBISM
602104	SH3 DOMAIN-BINDING PROTEIN 2; SH3BP2

Table C. Genomic Databases for Cherubism

Gene Symbol	Entrez Gene	HGMD
SH3BP2	6452 (MIM No. 602104)	SH3BP2

For a description of the genomic databases listed, click here.

Normal allelic variants: The *SH3BP2* transcript spans approximately 2.4 kb and comprises 13 exons. The gene was identified in a search for candidate tumor suppressor genes [Bell et al 1997].

Pathologic allelic variants: Ueki et al (2001) first described missense mutations in the *SH3BP2* gene in cherubism. All 11 missense mutations identified to date are in exon 9 and affect four amino acids within a six-amino acid sequence [Ueki et al 2001, Lo et al 2003, Lietman et al 2006].

Normal gene product: *SH3BP2* encodes the adaptor protein SH3-domain binding protein 2. It is required in several intracellular protein tyrosine kinase-dependent signaling pathways during hematopoietic cell differentiation and function [Foucault et al 2005]. *SH3BP2* positively regulates the activity of the transcription factor NFAT, which is involved in osteoclastogenesis [Lietman et al 2006].

Abnormal gene product: Cherubism results from presumed gain-of-function mutations in *SH3BP2* [Lietman et al 2006]. In a recent study, a knock-in mouse model was created with the most common human *SH3BP2* mutation. This mutation was shown to activate TNF-α expression in myeloid cells, leading to both bone loss and inflammation [Ueki et al 2007].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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www.aboutfaceinternational.org

Children's Craniofacial Association
13140 Coit Road Suite 307
Dallas TX 75240
Phone: 800-535-3643; 214-570-9099
Fax: 214-570-8811
Email: contactCCA@ccakids.com
www.ccakids.com

Let's Face It
PO Box 29972

Bellingham WA 98228-1972
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Email: letsfaceit@faceit.org
www.faceit.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

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Chapter Notes

Revision History

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