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The Gene for Cherubism Maps to Chromosome 4p16.3

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Summary

Cherubism is a rare familial disease of childhood characterized by proliferative lesions within the mandible and maxilla that lead to prominence of the lower face and an appearance reminiscent of the cherubs portrayed in Renaissance art. Resolution of these bony abnormalities is often observed after puberty. Many cases are inherited in an autosomal dominant fashion, although several cases without a family history have been reported. Using two families with clinically, radiologically, and/or histologically proved cherubism, we have performed a genomewide linkage search and have localized the gene to chromosome 4p16.3, with a maximum multipoint LOD score of 5.64. Both families showed evidence of linkage to this locus. Critical meiotic recombinants place the gene in a 3-cM interval between *D4S127* and 4p-telomere. Within this region a strong candidate is the gene for fibroblast growth factor receptor 3 (*FGFR3*); mutations in this gene have been implicated in a diverse set of disorders of bone development.

Introduction

Cherubism (MIM 118400) is a rare, painless disfiguring disease primarily affecting bones of the jaw (first described by Jones [1933, 1938], with many subsequent reports, including those by Peters [1979], Riefkohl et al. [1985], Zachariades et al. [1985], Zohar et al. [1989], Kaugars et al. [1992], Marck and Kudrick [1992], Vaillant et al. [1993], Penfold et al. [1993], Hitomi et al. [1996], Valiathan and Prathanth [1997], and Southgate et al. [1998]). The mandible and maxilla are usually bilaterally enlarged, producing a full, round lower contour of the face. The skin over the cheeks is stretched and pulls down the lower eyelids. As a consequence, a thin line of sclera is exposed beneath the iris and the eyes appear to be raised heavenward in a manner reminiscent of a the cherubs in Renaissance paintings (fig. 1).

Radiologically, cherubism is characterized by multilocular radiolucent areas that may be unilateral (Arnott 1978; Reade et al. 1984) (fig. 1). The disease is usually restricted to the mandibular and maxillary regions, although, occasionally, radiological abnormalities have been observed in the ribs. Histopathological evaluation of the lesions shows proliferating fibrous connective tissue containing numerous multinucleated giant cells, which are osteoclasts (Southgate et al. 1998). The clinical and histological features of cherubism may sometimes present problems in diagnostic distinction from giant-cell tumor, giant-cell granuloma, ossifying fibroma, fibrous dysplasia of the jaw, and Paget disease of bone (Kerley and Schow 1981; Flanagan et al. 1988; Zohar et al. 1989; Kaugars et al. 1992; Penfold et al. 1993; Whitaker and Singh 1995).

Affected individuals are normal at birth. Usually, the disease manifests in early childhood (at age 2–5 years) and becomes more marked until puberty, at which time the bony lesions begin to regress. However, the distortion of the jaw during childhood leads to permanent dental abnormalities. Other complications, such as visual disturbance (due to lesions within the orbital bones) and deafness, have also been reported but are relatively rare (Hawes 1989; Marck and Kudrick 1992).

Cherubism is a familial disease in which the trait is transmitted in an autosomal dominant fashion (Peters 1979; Zohar et al. 1989; Southgate et al. 1998), although several sporadic cases have been described (Kaugars et al. 1992; Ayoub and El-Mofty 1993). The penetrance is high (Peters 1979), but the precise estimate will depend on whether clinical or radiological diag-

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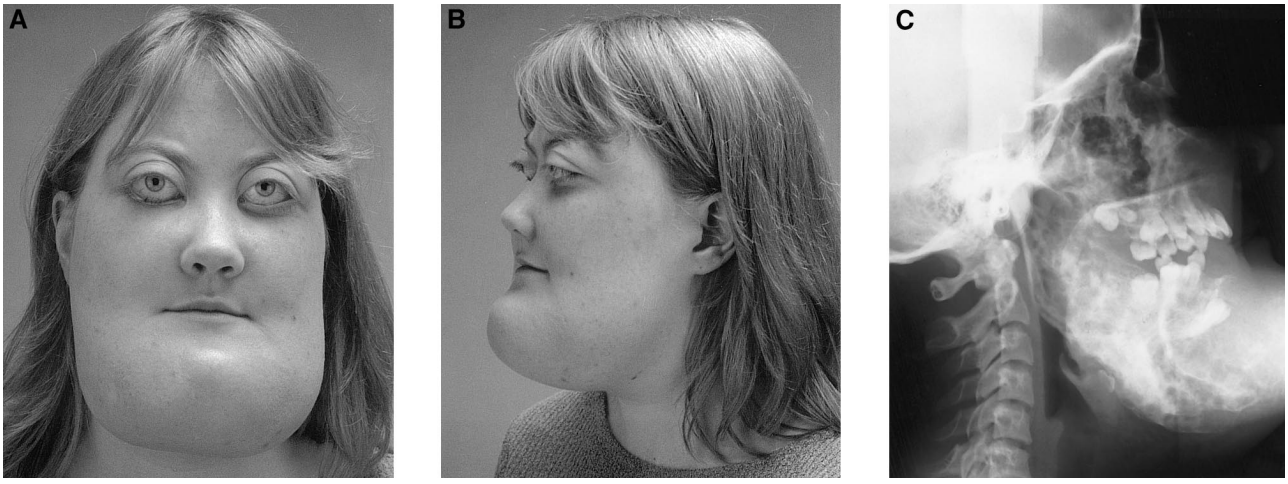

Figure 1 Photographs and x-ray of 19-year-old girl with cherubism who is from family CH1. *A,* Anterior-posterior view, demonstrating characteristic facial disfigurement of cherubism, including visible sclera below iris because of overgrowth of maxilla. *B,* lateral view, emphasizing protruding mandible and proptosis of eyes. *C,* X-ray, showing that pathology is restricted to bones of skull that are formed by endochondrial ossification.

nostic criteria are used. Males are more commonly and more severely affected than females. Cherubism has been associated with other genetic disorders, including a number of cases both of a Noonan-like syndrome (known as the "Noonan-like/multiple giant-cell lesion syndrome") (MIM 163955; Cohen et al. 1974; Dunlap et al. 1989; Cohen and Gorlin 1991; Betts et al. 1993) typified by short stature; low–normal intelligence; ocular hypertelorism; prominent posterorly angulated ears; giant-cell lesions of the bones, joints, and soft tissues; pectus excavatum; and pulmonic stenosis) and of Ramon syndrome (MIM 266270; Ramon et al. 1967; Pina-Neto et al. 1986), which is typified by short stature, mental retardation, epilepsy, gingival fibromatosis, and hypertrichosis. Cherubism has also been described in an individual with fragile-X mental retardation (Quan et al. 1995).

The gene underlying cherubism has not been mapped. We have therefore obtained samples from two large families with the disease and have performed a genomewide linkage search.

Subjects and Methods

Families were interviewed and samples were collected with full informed consent of the patients involved. The studies were performed with the approval of the Research Ethics Committee of St. Mary's NHS Trust, London.

DNAs were extracted from peripheral venous blood samples by conventional methods. Polymorphic microsatellite markers, predominantly from the Généthon set, were PCR amplified (with one primer of each pair either radio- or fluorescently labeled) and were electrophoresed through 4.5% denaturing polyacrylamide gels on either an ABI377 DNA sequencer or a conventional gel rig, as appropriate.

Two-point and multipoint linkage analyses were performed by the MLINK suite of programs. A model was employed in which disease alleles were given a frequency of .0001, the penetrance was set at 90%, and no sporadic cases were allowed. Because of the variable severity of the disease, strict diagnostic criteria were employed in the assignment of disease status. The assignment of affected status required evidence of a characteristic radiological appearance (mandibular and/or maxillary multilocular radiolucency) and/or typical histological appearance in a biopsy. Individuals were classified as "likely" to be affected if they had clinical features of the disease (as indicated by information obtained from childhood photographs or from the reports of family members) in the absence of histological or radiological confirmation. Linkage analyses were performed, classifying "likely" affected cases as unknown. Patients thought, on the basis of pedigree information, to be obligate gene carriers, and for whom histological or radiological confirmation was not available or who were clinically normal, were classified as affected for the purposes of linkage. Allele frequencies were determined from 24 unrelated chromosomes in families CH1 and CH2.

Results

Families with Cherubism

Two families were used in a genomewide linkage search for the cherubism gene (fig. 2). Details of the

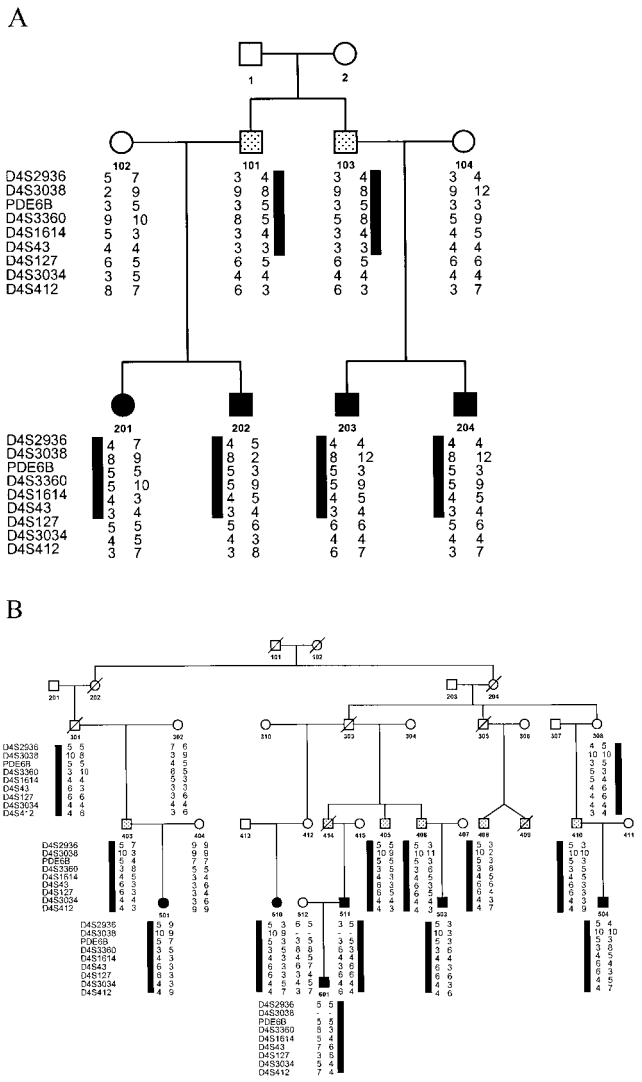

Figure 2 Pedigrees of cherubism families CH1 (A) and CH2 (B). Blackened symbols denote that individual is definitely affected, on the basis of confirmation by radiology or histology; stippled symbols denote that individual is likely affected, on the basis of clinical information, but with no confirmation by radiology or histology; unfilled symbols denote unaffected individuals and obligate gene carriers for whom information is not available or who were phenotypically normal.

clinical status of individuals within these families are summarized in table 1. Three cases (403, 408, 409) in family CH2 were known to have been treated with radiotherapy during childhood, to mitigate the effects of the disease. Of these cases, one (409) subsequently developed an osteosarcoma of the jaw, in the area which had been irradiated, and died. None of the affected individuals in family CH1 was treated by radiotherapy.

Genetic-Linkage Analysis

A framework genomic-linkage map of polymorphic microsatellite markers spaced at 15–20-cM intervals was used to perform the genomewide search. Initial evidence of linkage to cherubism was obtained by use of *D4S412*, for which an LOD score of 3.57 was obtained at a recombination fraction (θ) of .05 (table 2). Subsequently, LOD scores obtained by use of additional markers analyzed in the vicinity of *D4S412* confirmed linkage to this region, in both families. The highest two-point LOD score obtained was 5.06 at $\theta = 0$ from *D4S3360*. With *D4S3360* and *D4S2936*, maximum three-point LOD scores of 1.16 and 4.48 (total 5.64) were obtained from families CH1 and CH2. Linkage was confirmed by a haplotype of marker alleles segregating with the disease in both pedigrees (fig. 2). The two individuals (405 and 408) in family CH2 previously designated as "likely" affecteds (table 1) carried the haplotype linked to the disease in this family. When these were included as def-

initely affected cases in the linkage analysis, the maximum total two-point LOD score was 6.01 at $\theta = 0$ from *D4S3360*, and, with *D4S3360* and *D4S2936*, a three-point LOD score of 5.51 was obtained from family CH2 (total LOD score, from both families, was 6.67). Three individuals who previously had been phenotypically classified as "unaffected," who were not obligate gene carriers, and who had a 50% chance of inheriting the linked haplotype, did not inherit it, suggesting that the penetrance of the disease is relatively high, as assumed in the model (data not shown, to preserve confidentiality).

The marker order and the sex-averaged genetic distances within this interval from the Généthon map are 4pter–*D4S2936*, *D4S3038*–1.8 cM–*D4S1614*–1.9 cM–*D4S3034*, *D4S412*. On the basis of both additional information from the Genetic Location Database and mapping data from this study, we have inferred the following marker order: 4pter–*D4S2936*, *D4S3038*–*PDE6B*–*D4S3360*–*D4S1614*–*D4S43*–*D4S127*–*D4S3034*, *D4S412*. Critical meiotic recombinants in family CH2 place the gene between *D4S127* and 4p-telomere. *D4S127* is physically located within band 4p16.3, the terminal cytogenetic band on the short arm of chromosome 4. All published polymorphic short tandem repeats located within the region of linkage defined by the recombinant at *D4S127* in family CH2 have been analysed in families CH1 and CH2 and in five additional families with cherubism. There is no clear evidence of a segregating haplotype common to more than one family with cherubism.

Table 2

Total Two-Point LOD Scores for Cherubism Families CH1 and CH2 at Values of Theta from Markers on Chromosome 4p

	LOD Score at θ =								
Marker	0	.05	.1	.15	.2	.25	.3	.35	.4
D4S2936	4.05	3.61	3.17	2.72	2.26	1.81	1.37	.95	.57
D4S3038	3.18	2.83	2.48	2.12	1.76	1.41	1.06	.74	.44
PDE6B	2.51	2.18	1.86	1.55	1.25	.97	.72	.49	.29
D4S3360	5.06	4.55	4.03	3.5	2.95	2.40	1.86	1.32	.82
D4S1614	2.86	2.53	2.20	1.86	1.54	1.22	.92	.64	.38
D4S43	2.62	2.29	1.96	1.64	1.33	1.03	.76	.52	.31
D4S127	−2.27	.76	.82	.77	.67	.55	.44	.32	.21
D4S3034	.91	.79	.67	.56	.45	.35	.26	.18	.11
D4S412	.66	3.57	3.36	3.03	2.63	2.20	1.75	1.30	.85

Discussion

We have provided strong evidence for the localization of the gene for cherubism to chromosome 4p16.3, between *D4S127* and 4p-telomere, an interval of ~3 cM. Both families analyzed show linkage to this region, so, on the basis of this small series, there is no evidence for

Table 1

Clinical Information and Disease Status for Families CH1 and CH2

Individual	Information on Disease Status[a]	Disease Status
CH1-101	Photo, PMH	Obligate carrier, likely affected
CH1-103	Photo, PMH	Obligate carrier, likely affected
CH1-201	Clinical, radiology, histology	Definitely affected
CH1-202	Clinical, radiology	Definitely affected
CH1-203	Clinical, radiology	Definitely affected
CH1-204	Clinical, radiology	Definitely affected
CH2-202	No information, DNA unavailable	Obligate carrier
CH2-204	No information, DNA unavailable	Obligate carrier
CH2-301	No evidence of cherubism	Obligate carrier
CH2-303	No information, DNA unavailable	Obligate carrier
CH2-308	No evidence of cherubism	Obligate carrier
CH2-403	PMH, radiotherapy	Obligate carrier, likely affected
CH2-405	PMH	Likely affected
CH2-406	PMH	Obligate carrier, likely affected
CH2-408	Radiotherapy, photo	Likely affected
CH2-409	Radiotherapy, photo	Likely affected
CH2-410	PMH	Obligate carrier, likely affected
CH2-412	No information, DNA unavailable	Obligate carrier
CH2-414	PMH	Obligate carrier, likely affected
CH2-501	Clinical, histology, radiology	Definitely affected
CH2-503	Clinical, histology, radiology	Definitely affected
CH2-504	Histology	Definitely affected
CH2-510	Radiology	Definitely affected
CH2-511	Clinical, radiology	Definitely affected
CH2-601	Clinical, radiology	Definitely affected

[a] Photo = suggestive childhood photograph; Clinical = clinical examination during childhood; PMH = patient told in the past by medical professional he or she was affected.

genetic heterogeneity. These families have classic cherubism, on the basis of strict, objective clinical criteria. In this form, the disease is restricted to the bony tissues of the lower face. However, aspects of the cherubism phenotype are present in other diseases. For example, some features of cherubism have been reported in association with a Noonan-like syndrome (Dunlap et al. 1989; Betts et al. 1993). The classic form of Noonan syndrome has previously been mapped to chromosome 12. If cases of the Noonan-like/multiple giant-cell lesion syndrome are due to the Noonan syndrome gene on chromosome 12, the genetic basis of this form of cherubism must be different from that of the classic cherubism present in families CH1 and CH2. There are no published data pertaining to this issue. However, it is also possible that Noonan syndrome with cherubism either is allelic with respect to the cherubism gene on chromosome 4 (perhaps as a result of a contiguous-gene syndrome) or is due to an entirely different gene. Cherubism has also been reported as part of Ramon syndrome (Ramon et al. 1967; Pina-Neto et al. 1986), which has not yet been genetically mapped. However, the published pedigrees are consistent with autosomal recessive inheritance. If this interpretation is correct, the genetic basis of Ramon syndrome is also likely to differ from that of classic cherubism, which is clearly due to an autosomal dominant trait. It is therefore possible that the bony lesions that characterize cherubism constitute a phenotypic picture common to a number of disease processes that arise from multiple, distinct, initiating pathogenetic events, and it would not be surprising if genetic heterogeneity in classic cherubism is ultimately encountered.

Within the currently defined interval there is one major plausible candidate for the cherubism gene, fibroblast growth factor receptor 3 (*FGFR3*) (MIM 134934). FGFR3 is composed of three glycosylated extracellular immunoglobulin-like domains, a transmembrane domain, an intracellular kinase domain that is split, and a carboxyl terminus. Mutations in *FGFR3* are known to cause a remarkably diverse set of diseases associated with disordered growth of cartilage and bone. Achondroplasia is predominantly due to a single mutation in the transmembrane domain (Rousseau et al. 1994; Shiang et al. 1994). Hypochondroplasia is attributable to missense mutations in the tyrosine kinase domain (Bellus et al. 1995). Thanatophoric dysplasia type 1 is caused by missense mutations which create cysteine residues in the linker region between between immunoglobulin domains 2 and 3 (Tavormina et al. 1995), thanatophoric dysplasia type 2 by a mutation in the kinase domain (Tavormina et al. 1995). Crouzon syndrome in association with acanthosis nigricans is caused by missense mutations within the transmembrane domain (Meyers et al. 1995). A mutation in the extracellular domain causes non-syndromic craniosynostosis (Muenke et al. 1997). Many of these mutations constitutively activate the kinase activity of FGFR3, which, in turn, is believed to inhibit normal development of cartilage. By contrast, homozygous disruption of *FGFR3* in mice results in both deafness and bony abnormalities associated with overgrowth of long bones (Colvin et al. 1996; Deng et al. 1996). A further candidate for cherubism is *MSX1* (also known as "Hox7"; MIM 142983). A mutation in *MSX1* is responsible for an autosomal dominant syndrome of agenesis of second premolars and third molars (MIM 106600; Vastardis et al. 1996), and mice rendered homozygous for a nonfunctioning *MSX1* gene show cleft palate with other facial and dental abnormalities (Satokata and Maas 1994). On the basis of published genetic and physical maps, *MSX1* is located centromeric to the currently defined cherubism region, but minor changes in the map order would include it. A polymorphic microsatellite marker located within *MSX1* was not informative in family CH2 (data not shown).

It is interesting that the pedigrees in both families show some clinical evidence of anticipation. This is particularly intriguing in family CH2, in which at least two branches (301, 403, and 501 and 308, 410, and 504) provide reasonable evidence for progressive worsening of the phenotype over three generations. However, in view of the age-dependent phenotype in this disease, it is difficult to assess this formally. There have been no previous reports of anticipation in cherubism, and this observation may represent a bias of ascertainment of the younger—and thus obviously affected—individuals.

Although an increased risk of frank neoplastic change associated with cherubism has been alluded to in the published literature (Caballero Herrera et al. 1998), this is clearly rare. Of three individuals in our series of families who were known to have been treated with radiotherapy to mitigate the effects of the disease, one developed an osteosarcoma of the mandible. It is highly likely that the radiation treatment was causally implicated in the development of this tumor. Whether the presence of cherubism increased the likelihood of neoplastic change in response to the radiation dose is less clear. However, it is plausible, given the proliferative nature of the disease, the rarity of osteosarcoma (even after irradiation), and the fact that other diseases characterized by bone remodeling (such as Paget disease or fibrous dysplasia) are also associated with an elevated risk of osteosarcoma. Indeed, the existence of unilateral and asymmetric cases of cherubism, the localized nature of the changes within bone even when it is bilateral, and the histological similarity to other presumed neoplastic conditions (such as giant-cell tumor) suggest that the proliferative lesions of cherubism may themselves constitute multiple neoplastic clones. On the other hand, a striking feature of the disease is its resolution after pu-

berty, which is more suggestive (although not definitive) of a hyperplastic than of an autonomous neoplastic process. Although we currently have no insight into the mechanism of action of the cherubism gene, it should now be possible to evaluate some of these hypotheses further—for example, by examinination of biopsy samples from the bony lesions of cherubism for evidence of loss of heterozygosity on chromosome 4p, and ultimately by structural and functional analyses of the cherubism gene itself.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Généthon map, http://waldo.wi.mit.edu/ftp/distribution/human_STS_releases/july97/genmap/Chr4.genmap (for genetic map)

Genetic Location Database, http://cedar.genetics.soton.ac.uk/public_html/ (for physical and genetic marker maps)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for Cherubism [MIM 118400], Noonan-like syndrome [MIM 163955], Ramon syndrome [MIM 266270], *FGFR3* [MIM 134934], *MSX1* [MIM 142983], autosomal dominant syndrome of agenesis of second premolars and third molars [MIM 106600])

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