SH3BP2 Gene Analysis in Cherubism

Disorder also known as: CRBM; Familial benign giant-cell tumor of the jaw; Familial multilocular cystic disease of the jaw

Clinical Features:
Cherubism is a rare genetic disorder of the jaw characterized by bilateral, symmetrical enlargement of the mandible and/or maxilla resulting from rapid bone degradation followed by extensive bone remodeling with multilocular benign cysts. As a consequence, the skin is stretched over the classically swollen cheeks, pulling the lower eyelids down and exposing a line of sclera so that the eyes appear to be "raised heavenward." This facial appearance of the upwardly turning eyes and swollen cheeks has been described as resembling the faces of cherubs found in Renaissance art. The variable cherubism phenotype can range from absence of any clinical features to severe mandibular and maxillary overgrowth causing respiratory, vision, speech, and swallowing concerns. Typical age of onset is 2 to 5 years, with the jaw lesions progressing gradually until puberty when the swelling spontaneously stabilizes and then regresses. Residual radiographic changes can last into the fourth decade. Associated dental abnormalities may include congenitally missing teeth, premature loss of the deciduous teeth, and displacement of the permanent teeth by jaw lesions. While the disease is usually restricted to the jaw, rare cases of radiological abnormalities of the ribs have been reported.

The differential diagnosis for Cherubism includes Noonan-like/Multiple giant-cell lesion syndrome, Central giant-cell granuloma, Fibrous dysplasia of the jaw, and Hyperparathyroidism. Pathogenic variants in the PTPN11 gene have been described in association with both familial and isolated Noonan-like/Multiple giant-cell lesion syndrome. Full gene sequencing of the PTPN11 gene is available at GeneDx. Cherubism can be distinguished from the other conditions on the basis of clinical, radiologic, and biochemical evaluation. Finally, Cherubism has been reported as one of the clinical features of Ramon syndrome (characterized by short stature, mental retardation, and gingival fibromatosis)[1], and also can be associated with Neurofibromatosis Type 1.[2,3]

Inheritance Pattern/Genetics:
Autosomal dominant; penetrance is reportedly almost 100% in males and 50-70% in females.[4,5]

Test Methods:
Bi-directional sequencing analysis is limited to exon 9 of the SH3BP2 gene, where all variants have been reported to date. Variants found in the first person of a family to be tested are

confirmed by repeat analysis using sequencing, restriction fragment analysis, or other appropriate method.

Test Sensitivity:

In one study, SH3BP2 variants were identified in patients with clinically diagnosed cherubism in 12 out of 15 (80%) families. Eight of the 12 families with an identifiable variant had an amino acid change affecting the Proline 418 residue in exon 9.[7] In addition to this study, several case reports of SH3BP2-associated cherubism have been published.[6, 8-11] The sequencing approach used by GeneDx will identify >99% of existing variants located in exon 9 of the SH3BP2 gene.

References:

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