

PTCH1 Gene Analysis in Gorlin Syndrome

DISORDER ALSO KNOWN AS

Basal cell nevus syndrome (BCNS); Nevoid basal cell carcinoma syndrome (NBCCS); Multiple basal cell nevi, odontogenic keratocysts, and skeletal anomalies; Gorlin-Goltz syndrome.

CLINICAL FEATURES

Gorlin syndrome is characterized by multiple basal cell carcinomas (BCC), jaw keratocysts, palmar and plantar pits, and calcification of the falx cerebri. BCCs in Gorlin syndrome typically begin to develop in the late teens to early adulthood, but diagnoses in childhood have been reported.^{1,2} Most affected individuals will develop several carcinomas over their lifetime; however, approximately 10% of individuals with Gorlin syndrome will not develop BCC.¹ Many skeletal anomalies occur in association with this disorder, including malformations of the spine and vertebrae. Other congenital malformations, such as cleft lip and/or palate and polydactyly, are present in about 5% of affected patients. Approximately 60% of affected individuals have a characteristic facial appearance with macrocephaly, frontal bossing, coarse facial features, and facial milia. In addition to the increased risk for skin cancer (BCC), individuals with Gorlin syndrome are at elevated risk for pediatric medulloblastoma (5%), cardiac fibromas (2%), and ovarian fibromas in women (20%).¹

INHERITANCE PATTERN

Gorlin syndrome is inherited in an autosomal dominant manner. Approximately 30% of cases are *de novo* (new).^{9,19}

TEST METHODS

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of *PTCH1* are PCR amplified and capillary sequencing is performed. Bidirectional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing or another appropriate method is used to confirm all variants with clinical or uncertain significance. If present, apparently homozygous variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. All sequence alterations are described according to the Human Genome Variation Society (HGVS) nomenclature guidelines. Concurrent deletion/duplication testing is performed using either exon-level array CGH or MLPA. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat aCGH analysis. Data analysis is performed using gene-specific filtering. The array is designed to detect most single-exon deletions and duplications. Array CGH alterations are reported according to the International System for Human Cytogenetic Nomenclature (ISCN) guidelines. Benign and likely benign variants, if present, are not reported but are available upon request.

TEST SENSITIVITY

The clinical sensitivity of sequencing and deletion/duplication analysis *PTCH1* depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with features suggestive of Gorlin syndrome as outlined above. Sequencing and deletion/duplication analysis are expected to identify pathogenic variants in approximately 60% of individuals with Gorlin syndrome, with large deletions accounting for approximately 15% of these variants.⁵⁻⁸

DNA sequencing will detect nucleotide substitutions and small insertions and deletions, while array CGH will detect exon-level deletions and duplications. These methods are expected to be greater than 99% sensitive in detecting pathogenic variants identifiable by sequencing or array CGH.

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