

## 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:**

The classic diagnostic triad for Gorlin syndrome includes: multiple basal cell carcinomas (BCC) of the skin that develop at an early age and may number in the hundreds to thousands over a lifetime; odontogenic keratocysts of the jaw; and palmar and plantar pits. Calcification of the falx cerebri (visible on skull x-ray) is present in the majority of affected individuals by age 20. Many skeletal anomalies occur in association with the disorder, including malformations of the spine and vertebrae. Other congenital malformations are present in about 5% of affected patients, most notably cleft lip and/or palate and polydactyly. Approximately 60% of affected individuals have a characteristic facial appearance with macrocephaly, frontal bossing, coarse facial features, and facial milia. Sebaceous and dermoid cysts are common. With the exception of macrocephaly, many of these features become pronounced around puberty. In addition to the extremely high risk for skin cancer (BCC), individuals are at increased risk for pediatric medulloblastoma (5% of affected patients), cardiac fibromas (2%), and ovarian fibromas in women (20%).

### **Inheritance Pattern/Genetics:**

Autosomal dominant with high penetrance; 30-50% of cases result from de novo variants.

### **Test Methods:**

Using genomic DNA of a submitted blood specimen, bi-directional sequencing analysis of exons 1-23 and the splice sites of the PTCH1 gene is performed. Concurrently, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed to evaluate for a deletion or duplication of one or more exons of this gene. A mutation/deletion is confirmed by repeat analysis using sequencing, restriction fragment analysis, qPCR or another appropriate method.

### **Test Sensitivity:**

Approximately 60% of patients with a diagnosis of Gorlin syndrome are found by sequencing to have a variant in the PTCH1 gene.<sup>1</sup> Of the 40% of patients in whom no variant is found by sequencing, 30% will be found to have a full or partial deletion involving the PTCH1 gene. The combination of sequencing and deletion testing thus gives a sensitivity of approximately 72% for the identification of a variant in a patient with the syndrome.<sup>4</sup> Gene copy number analysis by ExonArrayDx enables detection of a complete PTCH1 deletion as well as a partial gene deletion involving one or more exon of the PTCH1 gene.

The vast majority of germline variants in the PTCH1 gene cause premature termination of protein translation (nonsense, splice site or frameshift variants), and are concentrated in the two large extracellular loops: the large intracellular loop and the N-terminus. Missense variants also have been published but there is no clear evidence of a genotype-phenotype relationship at this time.<sup>2,3</sup> Recently, genomic deletions including PTCH1 alone or together with neighboring genes ranging in size from between 165kb to 11Mb have been identified in a few patients with Gorlin syndrome.<sup>4</sup>

## References:

1. Klein, R. et al., Clinical testing for the nevoid basal cell carcinoma syndrome in a DNA diagnostic laboratory. *Genet Med.* 7: 611-19, 2005.
2. Wicking, C. et al., Most Germ-Line Mutations in the Nevoid Basal Cell Carcinoma Syndrome Lead to a Premature Termination of the PATCHED Protein, and No Genotype-Phenotype Correlations Are Evident. *Am J Hum Genet.* 60: 21-26, 1997
3. Lindström, E. et al., PTCH Mutations: Distribution and Analyses. *Hum Mutat.* 27: 215-19, 2006
4. Benhamed S and Bale S. Gorlin Syndrome: A substantial proportion of previously "missing" mutations are large PTCH deletions. ASHG Abstract presented 2008.