

## GPC3 Gene Analysis in Simpson-Golabi-Behmel Syndrome (SGBS)

**Disorder also known as:** Golabi-Rosen Syndrome; Simpson Dysmorphia Syndrome; X-linked Dysplasia Gigantism Syndrome

### **Clinical Features:**

Simpson-Golabi-Behmel Syndrome (SGBS) is an X-linked disorder characterized by pre- and postnatal overgrowth and distinctive facial features. Macrosomia and macrocephaly are typically noted on prenatal ultrasound or at birth and continue throughout development. The facial features are described as “coarse” and may include hypertelorism, downslanting palpebral fissures, epicanthal folds, macrostomia, macroglossia, a wide nasal bridge, ear pits or tags, and a central groove of lower lip and/or tongue. The risk for congenital anomalies is increased, including cleft lip/palate, congenital heart disease, diaphragmatic hernia, umbilical hernia, cystic hygroma, renal dysplasia, cryptorchidism, and hypospadias. Other common findings may include hypotonia, fingernail hypoplasia, interdigital webbing, polydactyly, supernumerary nipples, pectus excavatum, and skeletal anomalies. As with other overgrowth syndromes, hypoglycemia may occur in the neonatal period, and hepatomegaly has been described.<sup>1</sup> The risk for embryonal tumors is increased but is not well established. Previous cases of Wilms tumor, hepatoblastoma, adrenal neuroblastoma, gonadoblastoma, and hepatocellular carcinoma have been published.<sup>2</sup> Some individuals with SGBS have normal intelligence, while others exhibit mental retardation that may range from mild to severe. Even among individuals with normal intelligence, speech delay occurs frequently and may be secondary to macroglossia and malocclusion.<sup>3</sup>

### **Genetics:**

SGBS is caused by pathogenic variants of the *GPC3* gene located at Xq26. The gene has eight coding exons and encodes the glypican-3 protein, which is a heparan sulfate proteoglycan that plays a role in cell growth and cell division.<sup>4</sup> SGBS is caused by loss-of-function variants and deletions in *GPC3*. Variants and deletions are scattered throughout the gene, and no specific “hot spot” has been identified; however, the majority of point variants are identified in exon 3, as it accounts for about 40% of the coding region of the gene.<sup>5</sup>

Pathogenic variants in *GPC3* are inherited in an X-linked manner and most affected individuals are male. Heterozygous females may exhibit variable clinical features of SGBS.

### **Test Methods:**

Using genomic DNA from a submitted blood specimen, bi-directional sequence analysis of the complete coding region (exons 1-8) and the exon/intron splice junctions of the *GPC3* gene is performed. Because sequencing cannot identify large deletions in females, targeted array

CGH analysis with exon-level resolution (ExonArrayDx) is available to evaluate for a deletion of one or more exons of this gene. Any variant identified is confirmed by repeat analysis using sequencing, restriction fragment analysis, or other methods as appropriate.

### Test Sensitivity:

The sensitivity of genetic testing in males with a clinical diagnosis of SGBS is not well established. Three small studies have performed both sequencing and deletion analysis of the *GPC3* gene. Combining data from these studies, 20/36 (~56%) males with a clinical diagnosis of SGBS had an identifiable variant in the *GPC3* gene, including 8/36 (22%) large deletions and 12/36 (33%) point variants identified by sequencing.<sup>5,6,7</sup> Several additional studies have evaluated for large deletions only using PCR and/or Southern blot, and partial deletions of the *GPC3* gene were identified in 28-70% of males with a diagnosis of SGBS.<sup>8,9,10</sup>

### References:

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