PreventionGenetics
Disease prevention through genetic testing

CLIA #: 52D1027685 ● CAP #: 7185561
AU ID: 1407125 ● NPI: 1114140571
3700 Downwind Drive
Marshfield, WI 54449 USA
Phone: 715-387-0484 Fax: 715-384-3661

Simpson-Golabi-Behmel Syndrome via *GPC3* Gene Sequencing (Test #563)

Brief Description of Clinical Features: Simpson-Golabi-Behmel syndrome (SGBS, OMIM 312870) is characterized clinically by pre- and postnatal overgrowth, distinct craniofacial and skeletal findings, and variable mental retardation. Craniofacial findings include macrocephaly, down slanting palpebral fissures, ocular hypertelorism, epicanthal folds, broad and flat nasal bridge with short nose, low-set and posteriorly rotated ears, and large mouth and tongue. Skeletal and limb abnormalities include postaxial polydactyly of hands, syndactyly of the second and third fingers and toes, short and webbed neck, fusion of vertebrae, and pectus excavatum. Language delay is common and mental retardation varies from mild to severe, although individuals with normal intelligence have been reported. Structural CNS findings, including agenesis of the corpus callosum and Chiari malformation and hydrocephalus, have been reported (Young et al. *Ped Neurol* 34:139-142, 2006). Other findings include cardiac conduction defects, supernumerary nipples, and increased risk of embryonal tumors (Li et al. *Am J Med Genet* 102:161-168, 2001). Female carriers may exhibit some features of SGBS (see below) and skewed X inactivation has been reported to correlate with clinical features in females (Yano et al. *Clin Genet* doi:10.1111, 2010).

Genetics: Simpson-Golabi-Behmel syndrome is inherited as an X linked recessive disorder with marked inter- and intra-familial variable expression. Mutations in the *GPC3* gene (OMIM 300037) were found to cause SGBS (Pilia et al. *Nat Genet* 12:241-247, 1996) and, to date, are the only known cause of this disorder. Penetrance in males is thought to be complete (James et al. *GeneReviews*, 2006). Penetrance in female carriers is unknown, although carriers can manifest some clinical features (Golabi and Rosen *Am J Med Genet* 17:345-348, 1984; Rodriguez-Criado *Am J Med Genet* 138A:272-277, 2005). Nearly fifty *GPC3* mutations have been reported. The great majority of these mutations are deletions of one or more exons. Other mutation types include missense, nonsense and splicing defects that presumably result in loss of function. Gonadal mosaicism has been documented for *GPC3* mutations (Pilia et al. 1996; Romanelli et al. *Clin Genet* 72:384-386, 2007).

Description of This Particular Test: The putative extracellular proteoglycan, glypican-3, is coded by exons 1-8 of the *GPC3* gene located on chromosome Xq26. Testing is accomplished by amplifying each coding exon and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. This test will not reliably detect partial *GPC3* gene deletions.

Reference Sequences: **Genomic: NC_000023.10** **mRNA: NM_004484.3**
Protein: NP_004475.1 **mRNA and Protein: CCDS 14638.1**

Indication for Testing: A child with pre- and post-natal overgrowth and characteristic craniofacial and skeletal features.

Sensitivity of test: Because most causative *GPC3* mutations are deletions of single or multiple exons, clinical sensitivity of *GPC3* sequencing is expected to be low. For example, Li et al. (2001) failed to identify any individuals with point mutations among a group of 45 patients. Seven patients in this study were found to have deletions. In another study, however, six individuals were found to have *GPC3* point mutations among a cohort of 25 patients (Veugelers et al. *Hum Mol Genet* 9:1321-1328, 2000). Of these 25 patients, ten had a clinical diagnosis of SGBS and the remaining were diagnosed with other overgrowth syndromes, or were classified as undiagnosed overgrowth.

Turnaround Time: Maximum of 40 days although many tests are completed in 2-3 weeks.
Specimen Requirements: See page 4 of Requisition Form.

Price: **Sequencing of *GPC3* Gene** **Exons 1-8** **$ 690**

CPT Codes:

Sample Ascertainment	83890	$ 30	DNA Isolation	83891	$ 40
Amplification x11	83898	$ 190	Sequencing x11	83904	$ 280
Separation	83894	$ 40	Interpretation/Report	83912	$ 110

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Contact: Thomas L. Winder, PhD, FACMG, tom.winder@preventiongenetics.com, www.preventiongenetics.com