THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Goldberg-Shprintzen megacolon syndrome: Mutation Analysis of *KIAA1279*

Clinical Features:

Goldberg-Shprintzen megacolon syndrome (GOSHS, OMIM #609460) is a multiple malformation disorder characterized by Hirschsprung megacolon, microcephaly, hypertelorism, submucous cleft palate, short stature, and learning problems (1). Some reported patients also have iris coloboma, and bilateral generalized polymicrogyria malformation of the cerebral cortex (2, 3). The distinctive facial features include sparse scalp hair, synophyrs, arched eyebrows, hypertelorism, ptosis, large ears and prominent nose (4).

Differential Diagnosis:

- Mowat-Wilson syndrome (OMIM # 235730), has phenotypic overlap with GOSHS but is a genetically distinct disorder caused by mutations in the *ZEB2* gene (5). Distinctive features of Mowat-Wilson syndrome include epilepsy, cortical malformations and agenesis of the corpus callosum which have not been well characterized in patients with GOSHS.
- Despite some resemblance to GOSHS, Shprintzen-Goldberg craniosynostosis syndrome (SGS, OMIM #182212) tends to associate with craniofacial or skeletal abnormalities, and at least in some cases, mutations in the *FBN1* gene have been reported in affected individuals (6).
- Velocardiofacial syndrome (VCFS, OMIM #192430) (VCFS) is caused by a 1.5- to 3.0-Mb deletion of chromosome 22q11.2. It is associated with a highly variable phenotype, including frequent features such as cleft palate, cardiac anomalies, typical facies, learning disabilities, and lack of or underdeveloped thymus and parathyroid glands (7).

Molecular Genetics:

Mutations in the *KIAA1279* gene (OMIM #609367) have been identified in patients with GOSHS and homozygous nonsense mutations have been reported in 10 affected individuals in two families [3]. The *KIAA1279* gene maps to 10q22.1 and is likely important in both enteric and central nervous system development as it is highly expressed in heart, brain, reproductive, spinal cord regions. It has 7 exons, spanning 28 kb, with 2 tetratricopeptide repeats (TPR).

Inheritance:

GOSHS is inherited in an autosomal recessive condition. Parents of an affected child are likely carriers. Recurrence risk for carrier parents is 25%.

Test methods:

We offer full gene sequencing of all 7 coding exons and intron/exon boundaries by direct sequencing of amplification products in both the forward and reverse directions. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

KIAA1279 sequencing and deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81404, 81405
Turn-around time:	4 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Goldberg RB, Shprintzen RJ. Hirschsprung megacolon and cleft palate in two sibs. J Craniofac Genet Dev Biol 1981: 1: 185-189.
2. Brooks AS, Bertoli-Avella AM, Burzynski GM et al. Homozygous nonsense mutations in KIAA1279 are associated with malformations of the central and enteric nervous systems. Am J Hum Genet 2005: 77: 120-126.
3. Hurst JA, Markiewicz M, Kumar D et al. Unknown syndrome: Hirschsprung's disease, microcephaly, and iris coloboma: a new syndrome of defective neuronal migration. J Med Genet 1988: 25: 494-497.
4. Murphy HR, Carver MJ, Brooks AS et al. Two brothers with Goldberg-Shprintzen syndrome. Clin Dysmorphol 2006: 15: 165-169.
5. Dastot-Le Moal F, Wilson M, Mowat D et al. ZFHX1B mutations in patients with Mowat-Wilson syndrome. Hum Mutat 2007: 28: 313-321.
6. Sood S, Eldadah ZA, Krause WL et al. Mutation in fibrillin-1 and the Marfanoid-craniosynostosis (Shprintzen-Goldberg) syndrome. Nat Genet 1996: 12: 209-211.
7. Bassett AS, Chow EW, Husted J et al. Clinical features of 78 adults with 22q11 Deletion Syndrome. Am J Med Genet A 2005: 138: 307-313.

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