THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Schinzel-Giedion Syndrome: Mutation analysis of *SETBP1*

Clinical Features:

Patients with Schinzel-Giedion syndrome (SGS) [OMIM #269150] have characteristic facial features, midface retraction, skull anomalies abnormal genitalia, and cardiac and renal malformations. SGS is a lethal condition, as most patients die in infancy of respiratory failure or infections. Most patients have profound developmental delay. Characteristic facial features include large fontanelles, prominent forehead, hypertelorism, shortened and retracted midface, macroglossia, and a short neck. Failure to thrive, seizures, vision and hearing problems are also very common. Patients with SGS also have an increased risk for tumors, particularly neuroepithelial neoplasia (1).

Lehman (2008) reviewed 46 reported cases of SGS and proposed the following diagnostic criteria:

Mandatory features: Developmental delay
Facial phenotype
- prominent forehead
- midface retraction
- short upturned nose

Plus, either: Hydronephrosis
Skeletal features (at least 2 of following):
- Sclerotic skull base,
- Wide occipital synchondrosis
- Increased cortical density or thickness
- Broad ribs (at least 2)

These diagnostic criteria yield 100% sensitivity for the 46 reviewed cases of SGS (1).

Molecular Genetics:

Mutations of the *SETBP1* [OMIM #611060] gene were identified in four patients with SGS by whole exome sequencing (2). Additional sequencing of the *SETBP1* gene in individuals with SGS identified mutations in 8/9. All 13 patients in this study met Lehman's above diagnostic criteria (2). *SETBP1* has 6 coding exons and all mutations reported to date have been *de novo* missense mutations within a stretch of 11 base pairs in exon 4 (2, 3).

Inheritance:

SETBP1 mutations are inherited in an autosomal dominant pattern. Most cases appear to be *de novo*. Germline mosaicism is hypothesized to explain rare sibling occurences; recurrence risk for unaffected parents of an isolated case is approximately 1-5%. Recurrence risk for affected individuals and carrier parents is 50%.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of *SETBP1* is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. 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.

SETBP1 sequencing and deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81403, 81404
Turn-around time:	4 weeks

Note: The sensitivity of our assay may be reduced when DNA is extracted by an outside laboratory.

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. Lehman AM, McFadden D, Pugash D et al. Schinzel-Giedion syndrome: report of splenopancreatic fusion and proposed diagnostic criteria. Am J Med Genet A 2008: 146A: 1299-1306.
2. Hoischen A, van Bon BW, Gilissen C et al. De novo mutations of SETBP1 cause Schinzel-Giedion syndrome. Nat Genet 2010: 42: 483-485.
3. Suphapeetiporn K, Srichomthong C, Shotelersuk V. SETBP1 mutations in two Thai patients with Schinzel-Giedion syndrome. Clin Genet 2011: 79: 391-393.

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