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SETBP1 analysis for Schinzel-Giedion Syndrome

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:

We offer mutation analysis of all coding exons and intron/exon boundaries of *SETBP1* by direct sequencing of amplification products in both the forward and reverse directions. Deletion/duplication analysis is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

SETBP1 sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1675
CPT codes:	81404
Turn-around time:	4 - 6 weeks

SETBP1 deletion/duplication analysis

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

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

Testing for a known mutation in additional family members by sequence analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$390
CPT codes:	81403
Turn-around time:	3-4 weeks

Prenatal testing for a known mutation by sequence analysis

Sample specifications:	2 T25 flasks of cultured cells from amniocentesis or CVS or 10 mL of amniotic fluid
Cost:	$540
CPT codes:	81403
Turn-around time:	1-2 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.

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.