THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Genetic Testing for Rubinstein Taybi Syndrome

Clinical Features:

Patients with Rubinstein-Taybi syndrome (RSTS) [OMIM #180849] have characteristic facial features, short stature, broad (often angulated) thumbs and great toes, and moderate to severe mental retardation. Facial features include arched eyebrows, down-slanting palpebral fissures, a beaked nose with long columella, high arched palate, and grimacing smile. Many patients with RSTS develop obesity in childhood or adolescence. Other features include eye findings, undescended testes, urinary tract anomalies, and congenital heart defects. Patients with RSTS also have an increased risk for tumors including meningioma, pilomatrixoma, rhabdomyosarcoma, pheochromocytoma, and leukemia (1).

Molecular Genetics:

Mutations of the *CREBBP* (CREB binding protein) [OMIM #600140] gene have been identified in a majority of patients with RSTS (2). *CREBBP* encodes a co-activator in cyclic-AMP-regulated gene expression and has 31 coding exons. Approximately 10-20% of patients with RSTS have deletions involving the *CREBBP* gene. These deletions may be as small as single exon or include the entire *CREBBP* gene along with other nearby genes (1). Intragenic deletions/duplications will not be detected by FISH or genomic CGH analysis. In addition, 30-50% of patients with RSTS have mutations in the *CREBBP* gene (3, 4). Nonsense, missense, frameshift and splicing mutations have all been identified in the *CREBBP* gene (4).

Mutations of the *EP300* (E1A binding protein, 300-KD) [OMIM #602700] gene have been identified in approximately 3% of patients with RSTS (1, 5). *EP300* encodes a histone acetyltransferase that is important in the process of cell proliferation and differentiation and has 31 coding exons. Only nonsense mutations, frameshift and interstitial deletions have been identified in the *EP300* gene to date.

Mutations in either gene are associated with the classic facial features, mental retardation and other abnormalities typically associated with RSTS (5).

Inheritance:

RSTS is an autosomal dominant condition that occurs in 1 in 125,000 live births. Most cases appear to be *de novo*. Recurrence risk for unaffected parents of an isolated case is approximately 0.1%. Individuals with RSTS rarely reproduce. Recurrence risk for affected individuals is theoretically 50%.

Additional Resources:

Rubinstein-Taybi Parent Group
PO Box 146
Smith Center KS 66967
Phone: 888-447-2989; 785-697-2984
Fax: 785-697-2985
Email: lbaxter@ruraltel.net

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *CREBBP* and *EP300* genes 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.

We also offer deletion/duplication analysis of the *CREBBP and EP300* genes by MLPA or oligonucleotide array-CGH to identify deletions/duplications of one or more exons. 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. This testing will also detect the 16p13.3 microdeletion. The sensitivity of our deletion/duplication assay may be reduced when DNA is extracted by an outside laboratory. For best results, please provide a fresh blood sample for this testing.

CREBBP sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81407
Turn-around time:	4 weeks

CREBBP deletion/duplication testing

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81406
Turn-around time:	4 weeks

EP300 sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81407
Turn-around time:	4 weeks

EBP deletion/duplication testing

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81406
Turn-around time:	4 weeks

Comprehensive Rubenstein-Taybi Syndrome Panel (sequencing and del/dup of *CREBBP* and *EP300*)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$2500
CPT codes:	81406, 81407
Turn-around time:	8 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. Stevens C. Rubinstein-Taybi Syndrome. In: Pagon R, Bird T, Dolan C, eds. GeneReviews [Internet]. Seattle: University of Washington, 2002.
2. Petrij F, Giles RH, Dauwerse HG et al. Rubinstein-Taybi syndrome caused by mutations in the transcriptional co-activator CBP. Nature 1995: 376: 348-351.
3. Bartsch O, Schmidt S, Richter M et al. DNA sequencing of CREBBP demonstrates mutations in 56% of patients with Rubinstein-Taybi syndrome (RSTS) and in another patient with incomplete RSTS. Hum Genet 2005: 117: 485-493.
4. Roelfsema JH, White SJ, Ariyürek Y et al. Genetic heterogeneity in Rubinstein-Taybi syndrome: mutations in both the CBP and EP300 genes cause disease. Am J Hum Genet 2005: 76: 572-580.
5. Bartholdi D, Roelfsema JH, Papadia F et al. Genetic heterogeneity in Rubinstein-Taybi syndrome: delineation of the phenotype of the first patients carrying mutations in EP300. J Med Genet 2007: 44: 327-333.

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