

The University of Chicago Genetic Services Laboratories



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CREBBP analysis 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. Characteristic 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].

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%.

Molecular Genetics:

Mutations of the *CREBBP* (CREB binding protein) [OMIM #600140] gene have been identified in patients with RSTS [2]. Approximately 10% of patients with RSTS have 16p13.3 microdeletions involving the *CREBBP* gene [1], 30-50% of patients with RSTS have mutations in the *CREBBP* gene [3,4], and approximately 10-20% of patients with RSTS have intragenic deletions or duplications involving one or more exons of *CREBBP* [3]. *CREBBP* encodes a co-activator in cyclic-AMP-regulated gene expression. *CREBBP* has 31 coding exons. These intragenic deletions/duplications will not be detected by FISH or CGH analysis. Microdeletions, interstitial deletions, rearrangements, nonsense, missense, frameshift and splicing mutations have all been identified in the *CREBBP* gene [3].

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:

We offer full gene sequencing of the entire coding region for *CREBBP*. We also offer deletion/duplication analysis of the *CREBBP* gene by MLPA to identify deletions/duplications of one or more exons. 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 deletion/duplication testing

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$350
CPT codes:	83891, 83900, 83912
Turn-around time:	4 weeks

CREBBP mutation analysis (sequencing)

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: \$2400
CPT codes: 83891, 83898 x 9, 83904 x 9, 83912
Turn-around time: 10 weeks

Targeted analysis for a known sequence change in additional family members

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: \$390
CPT codes: 83891, 83898 x 2, 83894, 83912
Turn-around time: 3-4 weeks

Prenatal testing for a known mutation

Sample specifications: 2 T25 flasks of cultured cells from amnio or CVS or 10ml of amniotic fluid
Cost: \$590
CPT codes: 83891, 83898 x 2, 83894, 83912, 99051
Turn-around time: 1-2 weeks

Molecular Diagnostics Laboratory Faculty and Staff:

Soma Das, Ph.D. Director ABMG Certified Molecular Geneticist	Eden Haverfield, Ph.D. Assistant Director ABMG Eligible Molecular Geneticist
Melissa Dempsey, M.S. Assistant Director, Clinical Services and Education ABGC Certified Genetic Counselor	Chris Tan, M.S. ABGC Eligible Genetic Counselor
William B. Dobyns, M.D. Clinical Advisor ABMG Certified Clinical Geneticist	Darrel J. Waggoner, M.D. Clinical Advisor ABMG Certified Clinical Geneticist

References:

1. Stevens CA. Rubinstein-Taybi syndrome (2006) GeneReviews. www.genetests.com
2. Petrij F, et al. Rubinstein-Taybi syndrome caused by mutations in the transcriptional co-activator CBP (1995) Nature 376: 348-351.
3. Roelfsema JH, et al. Genetic heterogeneity in Rubinstein-Taybi syndrome: mutations in both the *CBP* and *EP300* gene cause disease (2005) Am J Hum Genet 76: 572-580.
4. Bartsch O, et al. DNA sequencing of *CREBBP* demonstrates mutations in 56% of patients with Rubinstein-Taybi syndrome (RSTS) and in another patient with incomplete RSTS (2005) Hum Genet 117: 485-493.

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