Rubinstein-Taybi and Related Syndromes Gene Panel

GenesTested:

CREBBP	*EP300*	*HNRNPH1*	*HNRNPH2*
SIN3A	*SIN3B*	*SRCAP*	

Description:

The Rubinstein-Taybi and Related Syndromes Gene Panel utilizes exome sequencing technology to analyze 7 genes involved with the following genetic syndromes:

Rubinstein-Taybi syndrome is a rare genetic syndrome characterized by characteristic facial features, broad angulated thumbs and great toes, failure to thrive in infancy, developmental delay, short stature, hearing loss, ocular differences, congenital heart defects, genitourinary abnormalities, recurrent infections, and constipation. Intellectual disability is variable and not present in every individual with Rubinstein-Taybi syndrome. Rubinstein-Taybi syndrome is caused by heterozygous pathogenic variants in *CREBBP* (type 1) or *EP300* (type 2), both of which function as histone acetyltransferases. Rubinstein-Taybi syndrome is autosomal dominant and frequently *de novo*.

Floating-Harbor syndrome is a rare genetic syndrome characterized by characteristic facial features, broad fingertips, short thumbs, prominent joints, low birth weight, short stature, delayed bone age in early childhood, clinodactyly, developmental delay, variable intellectual disability, conductive hearing loss, seizures, and genitourinary abnormalities. Floating-Harbor syndrome is an autosomal dominant condition caused by heterozygous pathogenic variants in *SRCAP* that are frequently *de novo*.

Witteveen-Kolk syndrome is a genetic syndrome characterized by developmental delay, intellectual disability, and distinctive facial features including small pointed chin. Witteveen-Kolk syndrome is autosomal dominant and caused by heterozygous pathogenic variants in *SIN3A*.

SIN3B-related intellectual disability syndrome is a genetic syndrome characterized by developmental delay, intellectual disability, variable autism spectrum disorder, growth restriction, and congenital anomalies. This condition is autosomal dominant and caused by heterozygous pathogenic variants in *SIN3B*.

HNRNPH1-related syndromic intellectual disability is a rare genetic syndrome characterized by intellectual disability, characteristic facial features, and congenital anomalies. This condition is autosomal dominant and caused by heterozygous pathogenic variants in *HNRNPH1*.

X-linked Syndromic Intellectual Developmental Disorder, Bain Type is a rare genetic syndrome characterized by developmental delay, intellectual disability, language impairment, motor difficulties, hypotonia, failure to thrive, and musculoskeletal differences including thumb hypoplasia. This condition is X-linked caused by pathogenic variants in *HNRNPH2*.

Indications:

- Confirmation of a clinical diagnosis of Rubinstein-Taybi syndrome, Floating Harbor syndrome, or related syndrome
- Broad thumbs and great toes
- Characteristic facial features
- Short stature
- Developmental delay
- Other features concerning for Rubinstein-Taybi syndrome or related disorder

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Genetic Conditions Commonly Associated with Rubinstein-Taybi and Related Syndromes

Gene	Inheritance	Condition
CREBBP	AD	Rubinstein-Taybi syndrome 1; Menke-Hennekam syndrome 1
EP300	AD	Rubinstein-Taybi syndrome 2; Menke-Hennekam syndrome 2
HNRNPH1	AD	HNRNPH1-related syndromic intellectual disability
HNRNPH2	XLD	Intellectual developmental disorder, X-linked, syndromic, Bain type
SIN3A	AD	Witteveen-Kolk syndrome
SIN3B	AD	SIN3B-related syndromic intellectual disability
SRCAP	AD	Floating-Harbor syndrome; Developmental delay, hypotonia, musculoskeletal defects, and behavioral abnormalities

Note: Rubinstein-Taybi and Related Syndromes Gene Panel cases with negative or uncertain findings can be reflexed to Whole Exome Sequencing (WES). A separate test order and a signed consent form is required for all WES testing. In addition, including biological parental samples is strongly encouraged to assist with the analysis of WES and to increase test yield. Reflex to WES orders can either be placed simultaneously or separately. Separate reflex to WES orders are subject to review prior to the initiation of testing. Please see our website at www.cincinnatichildrens.org/exome to obtain a WES test requisition and consent form.

What is Reported?

Variants that will be discussed in detail in the report:

- Pathogenic/likely pathogenic variants: Variants that are known to be pathogenic or for which the laboratory has sufficient evidence suggesting pathogenicity

Variants that will be listed in the report:

- Variants of uncertain clinical significance

What is not reported:

- Variants in genes not included in the predefined gene list
- Variants where there is currently no evidence of association with the disease and that are identified in healthy individuals (benign or likely benign variants)
- Variants that predict an increased risk of diseases, but do not cause a disease by themselves (risk alleles).

Methodology:

Rubinstein-Taybi and Related Syndromes Gene Panel uses the Human Comprehensive Exome kit from Twist Bioscience to capture the exonic regions of genes from the genomic DNA. Targeted regions are sequenced using an Illumina sequencing system with paired-end reads. Sequence reads are alignedwith paired-end reads. Sequence reads are aligned to the human reference genome (GRCh37/hg19 Build). Variants within exons and flanking sequences are identified and evaluated by a validated in-house developed bioinformatics analysis pipeline that includes the usage of GATK and Fabric Genomic Analysis platform. Data quality is assessed to confirm it has a minimum coverage of 20X for >95% coverage of 20X for >95% of targets of interest. The detection of copy number variations (deletions/ duplications) within the *CREBBP* and *EP300* genes is done by multiplex ligation-dependent probe amplification (MLPA) analysis.

Technical Limitations:

- Pathogenic variants may be present in a portion of the genes not covered by this test or in regions with suboptimal data due to homologous issue, poly-nucleotides, or nucleotide repeats, and there-fore may not be identified. Thus, the absence of identified pathogenic variants does not exclude the possibility of a genetic etiology for the patient's symptoms.
- Certain types of mutations are not detected. Only single base pair changes or small insertions or deletions of DNA are detected by next-generation sequencing. Large deletions, duplications, or complex rearrangements, low level mosaicism and many epigenetic defects may not be detected by this test.

Regions of Homology:
No significant regions of homology have been identified for gene regions targeted by this panel during test validation.

Low coverage (<20X) regions:
No specific regions of low coverage (<20X) of genes included in this panel were detected during test validation. For specific patient cases, low coverage of the targeted regions may be detected.

Please note: *Targeted deletion and duplication analysis of CREBBP and EP300 by MLPA is part of this test. MLPA has been validated for blood samples only. Other sample types may not yield MLPA results. Deletion and duplication analysis of the other genes on this panel is not available clinically.*

Turn-Around Time:

56 days (8 weeks)

Specimen:

The following specimens are accepted for this assay:

- 3 mls whole blood in a lavender top (EDTA) tube
- Saliva in an Oragene saliva kit. Please call 513-636-4474 for a free saliva collection kit.
- 10 mcg of high quality DNA extracted in a CLIA certified lab
- 25 mL amniotic fluid or two (2) T25 flasks grown to confluence

Label the tube/container(s) with the patient's name, birth date, and date of collection.

CPT Codes:

- 81405, 81406 (x2)

Shipping Instructions:

Please enclose test requisition with sample. **All information must be completed before sample can be processed.**

Place samples in Styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Saturday.

Ship to:

Genetics and Genomics Diagnostic Laboratory
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474

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