CREBBP Gene Analysis in Rubinstein-Taybi Syndrome (RSTS)

Disorder also known as: RTS; Rubinstein Syndrome; Broad thumb-hallux syndrome

Clinical Features:
Rubinstein-Taybi Syndrome is a congenital disorder characterized by broad thumbs and great toes, typical facies (microcephaly, small mouth, short upper and pouting lower lip, downslanting palpebral fissures, heavy eyebrows, long lashes, beaked nose, and high narrow palate), micrognathia, hirsutism, and low anterior hairline. Patients exhibit growth retardation, psychomotor developmental delay and cognitive disability. Ocular problems (including strabismus, cataract, glaucoma), congenital heart defects, feeding problems, hemangiomas, keloid formation, finger pads, increased risk of tumors (particularly of tissues derived from the neural crest), abnormalities of the patella, and seizures are seen in varying percentage of affected individuals.

Pathophysiology:
The CREBBP gene codes for CREB-binding protein, a transcriptional coactivator that participates in basic functions of the cell, including growth and differentiation, and DNA repair. Another gene, EP300, shares homology with CREBBP, and also serves as a transcriptional coactivator. Pathogenic variants in either gene can lead to RSTS. Studies suggest that abnormal dosage of CREBBP is the underlying mechanism for RSTS. Other genes are likely to play a role in the pathogenesis of RSTS, but they have not yet been identified.

Genetics:
Autosomal dominant. The majority of cases occur sporadically.

Test Methods:
Analysis of the CREBBP gene is offered in two tiers, as studies suggest a higher frequency of pathogenic variants in particular domains encoded by certain exons. Tier 1 includes targeted array CGH analysis with exon-level resolution (ExonArrayDx) to evaluate for a deletion or duplication of one or more exons, and sequencing of exons 1-5, 8, 18, and 20-31. Tier 1 is expected to identify the vast majority of deletions/duplications and a significant majority of CREBBP variants. Tier 2 analysis encompasses the remaining exons of the CREBBP gene. Both tiers of the CREBBP analysis are expected to identify >99% of deletions and small intragenic variants, if they exist. Any variant is confirmed by repeat analysis using sequencing, restriction fragment analysis, qPCR or another appropriate method.

Test Sensitivity:

Germline variants involving the CREBBP gene have been found in 50%-77% of patients with RSTS [4,5,6] depending on the methods used. The combination of ExonArrayDx for deletion/duplication identification and full sequencing of all coding exons and intron/exon boundaries of the CREBBP gene is expected to identify pathogenic variants in at least 77% of patients clinically diagnosed with RSTS.

References:

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7. Thienpont B et Al., (2010) J Med Genet 47: 155-161.