RSK2 (RPS6KA3) Gene Analysis in Coffin-Lowry Syndrome

Clinical Features:
Coffin-Lowry syndrome is typically characterized by intellectual disability in males. Intellectual disability usually ranges from severe-to-profound, although less affected individuals have been reported. Patients with Coffin-Lowry present with typical facial features (progressive development of coarse facies with prominent chin and ears, and heavy brow; down-slanting palpebral fissues and epicanthal folds, hypodontia and other dental anomalies, and a narrow high palate). Additionally, a consistent feature is large, puffy, soft hands with fingers tapering distally, small fingernails, and small forearms. Skeletal anomalies include kyphoscoliosis, lordosis, and pectus carinatum or excavatum. Patients are usually short with delayed bone age, and joints are hyperextensible. Patients are hypotonic and may have “drop attacks”. Sensorineural hearing loss has been described. Complications due to cardiac abnormalities can result in early death. Heterozygous females may exhibit mild to severe features of the disorder.

Inheritance Pattern:
X-linked recessive

Test Methods:
Bi-directional sequence analysis of the RSK2 (RPS6AK3) gene is offered in two tiers, as evidence suggests a higher frequency of pathogenic variants occurring in certain exons. Tier 1 includes analysis of exons 4-7, 9, 11, 14, 17, 18, and 22, and is expected to identify ~70% of RSK2 variant. Tier 2 analysis of the remaining 12 exons of the RSK2 gene (exons 1, 2, 3, 8, 10, 12, 13, 15, 16, 19, 20, and 21) is expected to identify ~30% of existing variants. Alternatively, full sequencing of the RSK2 gene can be ordered. Targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available to evaluate for a deletion or duplication of one or more exons of this gene. Pathogenic variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:
Sensitivity data are available for only two non-sequencing methods of RSK2 mutation detection: single-strand confirmation polymorphism (SSCP) analysis and cell function assays. Previous studies using SSCP alone have identified pathogenic variants in the RSK2 gene 34-36% of patients with a suspected clinical diagnosis of Coffin-Lowry syndrome.[1,2] The results of SSCP combined with cell function assays in a limited number of patients indicate that approximately 50% of individuals with a suspected clinical diagnosis of Coffin-Lowry syndrome have an identifiable mutation in the RSK2 gene.[2,3] It is expected that complete bidirectional

sequencing of all exons and the intron-exon boundaries of the RSK2 gene (as performed at GeneDx) has a greater sensitivity than either of these two methods.

References:

1. Delaunoy et al., (2001) *Hum Mutat* 17:103-116.
2. Delaunoy et al., (2006) *Clin Genet* 70:161-166.
3. Zeniou et al., (2002) *Am J Hum Genet.* 70:1421-1433.
4. Hanauer et al., (2002) *J Med Genet*. 39: 705-713, 2002.