PORCN Gene Analysis in Focal Dermal Hypoplasia

Disorder also known as: Goltz Syndrome; Goltz-Gorlin Syndrome

Clinical Features:
Goltz Syndrome, or Focal Dermal Hypoplasia (FDH) is, by definition, an ectodermal dysplasia syndrome due to the involvement of skin (focal hypoplasia/atrophy of skin with herniation of fat into the dermal layer, and pigmentary abnormalities often following the lines of Blaschko); hair (sparse, brittle, patchy); teeth (hypo/oligodontia, enamel hypoplasia/pitting, abnormal shape); nails (dystrophic/absent); and eyes (coloboma, micro/anophthalmia, aniridia). In addition, the disorder shares some features of Ectrodactyly-Ectodermal Dysplasia-Clefting syndrome (a disorder caused by variant of a different gene, TP63/TP73L), as most individuals have digital anomalies (syndactyly, brachydactyly, oligodactyly, ectrodactyly, polydactyly) and some have cleft lip/palate. In addition to the ectodermal component of the syndrome, limb anomalies (osteopathia striata), short stature, breast anomalies, and facial dysmorphism may occur. Approximately 15% of affected individuals have mental retardation. It is possible that contiguous gene deletion involving the PORCN gene is responsible for those cases with a more complex phenotype. Variant affecting only a specific isoform of the protein is hypothesized to cause phenotypic effects restricted to the tissue(s) in which that isoform is expressed.

Genetics:
X-linked dominant. Ninety percent of affected individuals are female. Males with FDH and some females are mosaic. Variants in 95% of females and all males appear to have arisen de novo.[1,5] X-inactivation is highly skewed in the non-familial cases.

Test Methods:
This comprehensive test includes bi-directional sequence analysis of all coding exons and their intron-exon boundaries. In addition, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed concurrently to evaluate for a deletion or duplication of one or more exons of this gene. A variant/deletion is confirmed by repeat analysis using sequencing, restriction fragment analysis, quantitative PCR or oligo-array comparative genome hybridization (GenomeDx), as appropriate.

Test Sensitivity:
Based on the current published literature, approximately 75% of individuals FDH have variants detectable by sequence analysis while about 11% of patients were identified to have large deletions detected by array CGH, qPCR or other quantitative method.[6] Cases with a very low level of mosaicism of the variant are more difficult to identify, and could be missed. It may be

necessary to test DNA derived from more than one tissue in these cases (e.g. blood and cultured fibroblasts).

References:

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