Keratin Gene Analysis in Pachyonychia Congenita and Steatocystoma multiplex

Disorder also known as:
Jadassohn-Lewandowsky Syndrome; Jackson-Lawler Syndrome

Clinical Features:
Pachyonychia congenita (PC) is characterized by thickened and friable finger and toe nails often apparent at birth or soon after. There are painful plaques of callus-like hyperkeratosis (keratoderma) on palms and soles with underlying blisters, hyperhidrosis and some individuals may have spiny follicular hyperkeratosis elsewhere on the body. Patients who also have natal teeth, alopecia and epidermoid cysts were previously described as having PC type 2. Patients with oral leukoplakia (a finding absent in PC type 2) were previously described as having PC type 1. However, recent genotype/phenotype correlation reports favor the more general nomenclature of pachyonychia congenita (PC) due to high phenotypic overlap between the subtypes. Heterozygous variants in five keratin genes have been associated with PC: KRT16, KRT6A, KRT17, KRT6B, and KRT6C. Patients with KRT6C variants typically have callus-like palmoplantar keratoderma with little or no nail dystrophy.

In steatocystoma multiplex, multiple round or oval sebaceous (epidermoid) cysts develop, widely distributed over the back, anterior trunk, arms, scrotum, and thighs. Thickened nail plates, focal palmoplantar keratoderma and natal teeth are variable features.

Inheritance Pattern/Genetics:
Autosomal dominant

Test Methods:
Using genomic DNA obtained from submitted biological material, bi-directional sequence analysis of select exons (hotspot regions) is performed in the KRT16, KRT6A, KRT17, KRT6B, and KRT6C genes. In steatocystoma multiplex, select exons in only KRT17 are screened. If no variant is identified by hotspot analysis, sequence analysis of the entire coding region of the gene(s) is available. If a variant is identified, the result will be confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:
Analysis of the variantal hotspots in the KRT16, 6A, 17, 6B, and 6C genes (specifically the sequence regions coding for the ends of the rod domains of the respective keratin proteins) is expected to identify the vast majority of variants in pachyonychia congenita (PC). Some patients with the clinical diagnosis of PC have been found to have a variant in the GJB6 gene

(usually associated with Clouston syndrome). Analysis of the GJB6 gene should be considered in those patients with PC in whom no keratin gene variant has been identified; testing is available as a separate test (see information material for GJB6 testing in 'Clouston syndrome').

Most variants in keratin genes associated with PC are missense variants or small in-frame deletions that affect the ends of the rod domains of the keratin proteins and affect stability of keratin intermediate filaments.

References:

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