Ichthyosis Follicularis with Atrichia and Photophobia (IFAP) / Keratosis Follicularis Spinulosa Decalvans (KFSD) (MBTPS2)

Clinical Features:
Two clinical disorders, Ichthyosis Follicularis with Atrichia and Photophobia (IFAP) with or without BRESK/BRESHECK syndrome, and Keratosis Follicularis Spinulosa Decalvans (KFSD), have been associated with variants in the MBTPS2 gene.

IFAP syndrome is characterized by the triad of follicular ichthyosis, total or subtotal atrichia, and photophobia to variable degree. Congenital atrichia is most prevalent and most affected boys have total atrichia at birth. A subgroup of patients has been described with lamellar rather than follicular ichthyosis. Less common features include nail dystrophy, growth and psychomotor retardation, aganglionic megacolon, and seizures. Female carriers may show features of the disorder, including a linear pattern of follicular ichthyosis, mild atrophoderma, hypotrichosis, and hypohidrosis.[1] Some individuals may have additional features, which constitute BRESK/BRESHECK syndrome. These features include brain anomalies, intellectual disability, ectodermal dysplasia, skeletal deformities, ear or eye anomalies, and renal anomalies, with or without Hirschprung disease and cleft palate or cryptorchidism.[2]

KFSD is a disorder affecting the skin and eyes. In affected men, the skin findings include inflammatory hyperkeratotic follicular papules or pustules on the scalp, eyebrows and elsewhere on the integument. This process leads to progressive scaring alopecia. Eye findings include photophobia and corneal dystrophy. Other findings include hyperkeratosis of the elbows, knees, and palms and soles. KFSD can be distinguished from IFAP due to the nature of alopecia, which is progressive and scaring in KFSD, and congenital and non-scarring in IFAP. Carrier females are usually less severely affected.[3]

Inheritance Pattern/Genetics:
X-linked

Test Sensitivity:
Only a few large-scale studies of patients with IFAP with or without BRESK/BRESCHEK and KFSD have been published to date. One study reported distinct variants in MBTPS2 in three multi-generational families with IFAP with typical X-linked inheritance, and in three smaller unrelated families. Minor intra-familial phenotypic variability between affected males was noted; however, the severity between different families varied greatly. Female carriers in all reported families were either phenotypically normal or showed mild features.[1] Another study of IFAP in a large Chinese family identified a missense variant, and affected individuals showed a broad phenotypic spectrum.[5] In one study of nine families with a clinical diagnosis of KFSD,

the same variant was identified in three families (26 cases). In the remaining six small families, there was not a clear X-linked mode of inheritance.[3]

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

References:

1. Oeffner et al., (2009). Am J Hum Genet 84: 459-467.
2. Naiki et al., (2011). Am J Med Genet Part A 158A: 97-102.
3. Aten et al., (2010). Hum Mutat 31(10): 1125-1133.
4. Oeffner et al., (2011). Exp Dermatol 20: 445-456.
5. Tang et al., (2011). J Am Acad Dermatol 64 (4): 716-722.