IKBKG (NEMO) Gene Analysis in Incontinentia Pigmenti / Hypohidrotic Ectodermal Dysplasia with Immune Deficiency (HED-ID)

Disorder also known as: Incontinentia pigmenti, familial male-lethal type, Bloch-Sulzberger syndrome, Incontinentia pigmenti Type II, HED-ID, ecotdermal dysplasia, anhidrotic with immune deficiency, EDA-ID, Hyper-IgM immunodeficiency X-linked with ectodermal dysplasia, XHM-ED

Clinical Features:
Incontinentia Pigmenti (IP) is an X-linked dominant disorder of the skin, hair, teeth, and nails that progresses through four distinct stages and occurs in 1 in 50,000 newborns. Stage 1 is characterized by blisters or bullous eruptions on the extremities and trunk, and is typically evident at birth or within the first few postnatal months. Stage 2 is defined by a hypertrophic rash on the extremities and trunk and has been described as wart-like. This stage can last for several months or even years. Stage 3 develops with the appearance of brown hyperpigmentation along the lines of Blaschko. This is the most conspicuous sign of IP and manifests at about six months of age and lasts into adulthood. State 4 is marked by hypopigmentation of skin regions that are affected in previous stages. Affected female individuals can also suffer from retinal detachment and blindness, alopecia, conical or absent teeth, and mental retardation. Male fetuses with an inherited IP variant usually do not survive gestation because this disorder causes is lethal in males.

Hypohidrotic ectodermal dysplasia with immune deficiency (HED-ID) is a disorder that is allelic to IP. Affected males exhibit hypotrichosis with fine, sparse, and light-colored scalp and body hair. Patients show a decreased ability to sweat, which often leads to severe heat intolerance. In addition, hypodontia and conical or peg shaped teeth are also observed in affected individuals. Facial features are characterized by dark pigmented skin around the eyes, a saddle nose, and full lips. Defects in secretions from the lacrimal, meibomian, and other secretory glands result in thick nasal secretion and cerumen. Absent or accessory nipples are not uncommon. These patients also present with recurrent infections of the digestive tract, respiratory tract, and skin infections that may result in hospitalizations.

Genetics:
Incontinentia pigmenti (IP) is an X-linked dominant disorder. Hypohidrotic ectodermal dysplasia with immune deficiency is an X-linked recessive disorder and is therefore typically seen in males. Approximately 80% of IP cases are due to variants in the IKBKG gene in Xq28 that encodes the I-kappa-B kinase gamma subunit protein (IKK-gamma). In this X-linked disorder, females individuals demonstrate a phenotype and affected male fetuses typically terminate spontaneously during pregnancy. HED-ID is also due to variants in the IKBKG gene. This

disorder is X-linked recessive affecting male children. The widely expressed IKK-gamma protein binds the IKK-alpha and IKK-beta proteins to activate the NF-kappa-B complex, which protects cells from apoptosis triggered by tumor necrosis factor alpha. The IKBKG gene has a complex structure, with the existence of a highly homologous but nonfunctional second copy of the gene located distal to the functional copy.

Test Methods:

In females whose clinical indication is IP, long-range PCR analysis will first be used to detect the common deletion of exons 4-10 using genomic DNA obtained from the submitted biological material. In females whose clinical indication is IP and who are negative for the common deletion, bi-directional sequence of the entire coding region and splice junctions of the IKBKG gene (exons 2-10) is obtained and analyzed. In patients whose clinical indication is hypohidrotic ectodermal dysplasia with immune deficiency, bi-directional sequence of the entire coding region and splice junctions of the IKBKG gene (exons 2-10) is obtained and analyzed. 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:

In one study of 357 unrelated patients with IP, DNA sequencing and Southern blot analysis identified IKBKG variants in 78% of these individuals.[1] About 90% of the patients with an identified variant harbored the common IP deletion. In one study 12 patients (3 of whom were deceased and not tested) from 8 unrelated families with a diagnosis of EDA-ID DNA sequencing analysis identified an IKBKG variant in 9 all patients.[3] In another study of 4 unrelated families with a diagnosis of HED-ID DNA sequencing analysis identified an IKBKG variant in each family.[5] Therefore, IKBKG variants have been identified in approximately 100% of tested individuals with HED-ID.

Variant Spectrum:

More than 50 distinct variants have been reported in the IKBKG gene for IP. These variants include nonsense, small deletions, small insertions, a few missense, and two large deletions. Approximately 90% of affected females with IP who test positive for a variant in the IKBKG gene carry the common deletion of exons 4-10 of the IKBKG gene.[1] More than 25 distinct variants have been reported in the IKBKG gene for HED-ID. The vast majority of these variants (approximately 52%) are missense variants. A splice site, a small deletion, 3 small insertions, 3 nonsense variants, and a large insertion have also been reported. Most variants in HED-ID are found in exon 10 if IKBKG.

References:

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