ABC12 Gene Analysis in Harlequin Ichthyosis, Congenital Ichthyosiform Erythroderma and Lamellar Ichthyosis

Disorder also known as: HI, harlequin fetus, Lamellar ichthyosis type 2

Clinical Features:
Harlequin ichthyosis (HI) and lamellar ichthyosis (LI) are different types of congenital recessive ichthyosis. Harlequin ichthyosis is the most severe form of ichthyosis and life-threatening. Infants are usually born prematurely and are encased in a thick, hard, armor-like covering that severely restricts movements. The taut cast cracks and forms large, diamond-shaped, adherent plates, which are separated by broad, deep, and intense red fissures. The taut skin results in deformation of facial features, such as out-turning of eyelids (ectropium) and lips (eclabium), rudimentary development of nose and ears, and microcephaly. Hands and feet are swollen and covered by a mitten-like casing. Malformations of inner organs are not uncommon. The postnatal period is usually complicated by respiratory distress, dehydration, electrolyte imbalance, temperature instability, feeding problems and bacterial infections, often with fatal consequences. In recent years, an increasing number of patients with prolonged survival have been reported. After shedding the armor-like cast, these survivors developed clinical features of severe non-bullous congenital ichthyosiform erythroderma (CIE) with generalized fine, whitish scale and intense redness. Alopecia, thickening of the skin on palms and soles, and heat intolerance are common. In lamellar ichthyosis, babies are born with a taut, translucent collodion membrane that encases the body and may cause ectropium and eclabium. After the membrane is shed, patients develop white or brown, plate-like scale with no or little redness over the entire body.

Genetics:
Harlequin ichthyosis is a very rare autosomal recessive disorder; affected individuals in consanguineous as well as non-consanguineous families have been reported. HI is caused by mutations of the ABCA12 gene on chromosome 2q34\(^1\)-\(^2\). The gene product encoded by ABCA12 belongs to a subfamily of ATP binding cassette (ABC) transporters responsible for the energy-dependent transport of lipid substrates. Lack of this protein leads to a profound defect in epidermal lipids and destroys the barrier function of the skin. Patients with HI surviving the neonatal period often develop clinical features of severe congenital ichthyosiform erythroderma (CIE) and ABCA12 mutations have been reported in these patients as well\(^3\). Lamellar ichthyosis is genetically heterogeneous and in most cases associated with pathogenic variants in the TGM1 gene on chromosome 14q11.2. However, other gene loci were reported. Mutations in the ABCA12 gene have been identified in 9 LI families from Northern Africa\(^4\).

Test Methods:
Bi-directional sequence analysis of the ABCA12 gene in HI and LI are offered as separate tests. For testing in HI, all 53 exons and corresponding splice junctions of the ABCA12 gene will be obtained and analyzed. For testing in LI, analysis includes 5 selected exons (exons 28-
32) of the ABCA12 gene and their splice sites, where all reported mutations associated with LI have been found. 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 and Variant Spectrum:**
According to a literature review by Akiyama (2010), a total of 56 pathogenic variants in the ABCA12 gene have been reported in 66 unrelated families worldwide to date. The patients from these 66 families were diagnosed with HI (n=48), LI (n=9) and CIE (n=8). Among the 48 HI families, 100% (48/48) had variants identified in the ABCA12 gene\(^2,5-6\). Pathogenic variants are private and scattered across the gene, although mutation 7322delC in exon 49 is more common in the Pakistani/Indian population due to a founder effect\(^6\). About two-third of variants are nonsense changes and small insertions/deletions resulting in premature termination of gene translation. Less common are splice site defects. Partial gene deletions including one or more exons (up to 35 exons) have been observed\(^1\).

In patients with LI, TGM1 pathogenic variants account for the majority of cases and should be ruled out first. Of those LI patients who do not harbor TGM1 variants, missense variants of the ABCA12 gene have been reported in individuals of Northern African decent (Morocco, Mali, Algeria)\(^4\). The variants cluster within 5 exons (exon 28-32), which code for the first nucleotide binding fold of the ABC transporter. Nevertheless, ABCA12 pathogenic variants do not seem to play a role in the pathogenesis of LI in patients of other populations and ethnicities\(^2\).

**References:**