Keratin 1, 10 and 2 Gene Analysis in Epidermolytic Ichthyosis (EI)

Disorder also known as: Epidermolytic Hyperkeratosis (EHK); Bullous congenital ichthyosiform erythroderma (BCIE); Bullous erythroderma ichthyosiform congenita of Brocq

Clinical Features:
EI presents at birth with erythroderma, blisters or erosions, and larger areas of denuded skin. While skin fragility decreases with age, severe hyperkeratosis with a verrucous, ridged or cobblestone surface develops over time. Palms and soles may be severely involved or completely spared. There is a mosaic form of the disease, likely due to somatic mutation during embryonic development, in which the affected individual has features of the disease limited to certain areas of the skin, and often following the lines of Blaschko (so-called 'linear epidermolytic hyperkeratotic nevus'). A mild variant of EI with superficially peeling or denuded areas described as 'molting' or 'Mauserung' is known as superficial epidermolytic ichthyosis (SEI; previously termed ichthyosis bullosa of Siemens).

Genetics:
EI is an autosomal dominant condition, of which about 50% of pathogenic variants are sporadic. It is caused by heterozygous variants in the genes encoding keratin 1 and keratin 10 (KRT1, KRT10). These keratins are expressed in the differentiated upper layers of the epidermis, which are the sites of disease pathology in this disorder. Pathogenic variants in KRT1 are usually associated with severe palmoplantar keratoderma, whereas pathogenic variants in KRT10 spare palms and soles because the gene is not expressed at these locations. SEI is due to heterozygous variants in the KRT2 gene, which is found exclusively in the granular cell layers of the epidermis.

Test Methods:
KRT1, KRT10, and sometimes KRT2 are screened by bi-directional sequence analysis. Clinical features in an individual help determine the priority of keratins to screen. Pathogenic variants resulting in amino acid substitutions in the ends of the keratin rod domains are sequenced first (hotspot regions); if no variant is found, bi-directional sequence analysis may be performed on the entire coding sequence of the keratin gene. There are patients who exhibit a mosaic form of EI. In these patients, genomic DNA from buccal brushes as well as from skin biopsies obtained from involved skin is usually necessary to identify a keratin variant.

Test Sensitivity:
Sequence analysis of KRT1 and KRT10 or KRT2 identifies pathogenic variants in approximately 80% of patients with the clinical and histological features of epidermolytic

ichthyosis/superficial epidermolytic ichthyosis. Identification of pathogenic variants is far less sensitive in patients with a mosaic form of the disease.

Variant spectrum:

Most pathogenic variants in keratin genes (about 86%) are missense changes that affect the ends of the rod domains of the keratin proteins and affect stability of keratin intermediate filaments. These regions are considered hotspots for pathogenic variants. In SEI, pathogenic variants preferentially involve the glutamic acid codon E493 at the end of the rod domain.

References:

1. Irvine & McLean (1999) Br J Dermatol 140:815-828.