Keratin and Plectin gene testing in Epidermolysis Bullosa Simplex (EBS)

Disorders Included: Dowling-Meara EBS; Weber-Cockayne EBS; Koebner EBS; Ogna EBS

Clinical Features:
Depending on the clinical sub-type, blistering begins in the neonatal period through early adolescence. Blisters can be generalized (Koebner type), with clustered (Dowling-Meara type), or distributed acrally (Weber-Cockayne type). The separation (blister) occurs above the basal or suprabasal layer of the epidermis, and usually heals without scarring. In cases due to plectin variants the tissue separation (blister) occurs just above the lamina lucida at the level of the hemidesmosome. Plectin staining of a skin biopsy may be reduced or absent consistent with plectin variants.

Inheritance Pattern/Genetics:
EBS is usually an autosomal dominant disorder with high penetrance. Rare autosomal recessive cases have been reported. Sporadic cases (where neither parent is affected) are a frequent occurrence due to new variant in a keratin or plectin gene. The offspring of an affected individual has a 50% risk of also being affected.

Test Methods:
Using genomic DNA obtained from the submitted biological sample, the KRT5 and KRT14 genes are screened for variant by bi-directional sequence analysis. Clinical features in an individual help determine the priority of keratin/region of the gene to screen. Variants resulting in amino acid substitutions in the ends of the keratin rod domains are analyzed first; if no variant is found, the entire coding sequence of the keratin gene is subjected to bi-directional sequence analysis. Sequencing of the coding region and splice sites of the PLEC1 gene is offered in two tiers. Tier 1 comprises the two main exons 31 and 32, while Tier 2 includes bi-directional sequence analysis of the remaining 30 exons. A variant found in the first person of a family to be tested is confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:
Sequence analysis of KRT5 and KRT14 identifies variants in 70% of patients with the clinical and histologic features of epidermolysis bullosa simplex (Rugg 2006, Arin 2009, Jeřábková 2009). The sensitivity of PLEC1 testing in patients with EBS has not been well established since the number of cases described is small (Kossharnes 1997 & 2002).

Most autosomal dominant variants in keratin genes are missense variants that affect the ends of the rod domains of the keratin proteins and affect stability of keratin intermediate filaments. An additional two families with autosomal dominant EBS with PLEC1 variants have also been reported. Autosomal recessive variants in EBS are rare and may be missense, nonsense, insertion or deletion or splice junction variants.

References:

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