Connexin gene testing in Erythrokeratodermia Variabilis (EKV)

Disorder Also Known As: EKV; Mendes de Costa; Giroux-Barbeau; Erythrokeratodermia figurate variabilis; Keratosis rubra figurata

Clinical Features:
This skin disorder presents in infancy with transient, erythematous patches that remain for minutes to hours or longer. In addition, hyperkeratosis develops which can be either generalized or localized and fixed. Both erythema and hyperkeratotic plaques have sharply demarcated edges. Palmoplantar keratoderma is a variable feature. Giroux-Barbeau type is associated with ataxia, usually evident in middle age.

Inheritance Pattern/Genetics:
EKV is caused by pathogenic variants in 2 connexin genes (*GJB3* and *GJB4*) localized on human chromosome 1p34-p35, which encode the gap junction proteins Beta 3 (Connexin-31) and Beta 4 (Connexin-30.3). It is assumed that these variants alter the structure or function of gap junction channels, thereby resulting in disturbed cell-cell communication and signaling, which impairs normal epidermal differentiation. The inheritance pattern is typically autosomal dominant, although autosomal recessive inheritance has been reported rarely.

Test Methods:
Using genomic DNA obtained from the submitted specimen, the entire coding sequence of the GJB3 gene (coding for Connexin-31) and the GJB4 gene (coding for Connexin-30.3) is screened. A variant found in the proband (first person of a family to be tested) will be confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:
Sequence analysis of these two connexin genes identifies variants in approximately two-thirds of patients with the clinical features of erythrokeratodermia variabilis. If a variant exists in GJB3 or GJB4, the method utilized by GeneDx has a greater than 99% sensitivity to identify such a variant.

All variants reported to date in the connexin genes associated with EKV are missense variants, which can be detected by the methods used by GeneDx. According to published data, about 57% of the variants were found in the GJB3 gene and the remaining 43% in the GJB4 gene. While the majority of variants are autosomal dominant, two families with autosomal recessive GJB3 variants have been reported.

References:

1. Richard et al. Nat Genet 1998; 20: 366-369
2. Richard et al. Hum Genet 106:321-329, 2000
3. Macari et al. Am J Hum Genet 2000, 67:1296-1301
4. Gottfried et al. Hum Mol Genet 11:1311-1316, 2002
5. Richard et al. 2003, JID 120:601-609
6. Terrinoni et al. JID 122:837-839, 2004
7. Common et al. JID 125:920-927, 2005