ATP2C1 Gene Analysis in Hailey-Hailey disease

Disorder also known as: HHD; Familial benign chronic pemphigus

Clinical Features:
Hailey-Hailey Disease (HHD) is a rare inherited skin disorder due to disturbed cell adhesion (acantholysis) in the upper layers of the epidermis. Hailey-Hailey disease usually develops in adolescence with a peak of onset between the second and fourth decade of life. Skin lesions begin with transient blistering, rapidly evolving into crusted erosions and scaling, fissured plaques. Primarily affected are the large skin folds (e.g. armpits, neck) and intertriginous areas (e.g. under the breasts, groin). The skin problems are exacerbated by trauma and irritation, for example due to heat, sweating, and friction. The disorder follows a chronic, recurrent course, often leading to discomfort, pain, and limitation of physical activity.

Genetics:
Autosomal Dominant. Hailey-Hailey Disease (HHD) is very rare. This disorder is caused by pathogenic variants of the ATP2C1 gene on chromosome 3q21-q24. The protein encoded by ATP2C1 is a calcium-transporting ATPase (Type 2C, Member 1). Variants in ATP2C1 result in haploinsufficiency for this intracellular, secretory pathway $Ca^{2+/}Mn^{2+}$ pump and lead to disturb calcium homeostasis in the epidermis.

Test Methods:
Using genomic DNA obtained from the submitted biological material, bi-directional sequence of the coding region and splice sites of the ATP2C1 gene (exons 1-27) is 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:
On average, about 60%-80% of patients with Hailey-Hailey disease tested were found to have a pathogenic variant in the ATP2C1 gene. Sequence analysis as performed by GeneDx is expected to identify all types of previously identified variants in the ATP2C1 gene, if any exist.

References:

1. Hu Z. et al. *Nat Genet* 24:61-65, 2000.
2. Sudbrak R. et al. *Hum Mol Genet* 9:1131-1140, 2000.
3. Dobson-Stone C. et al. *J Invest Dermatol* 118:338-343, 2002.
4. Ikeda S. et al. *J Invest Dermatol* 117:1654-1656, 2001.
5. Foggia and Hovnanian *Am J Med Genet* (Part C) 131C: 20-31, 2004.
6. Hamada T et al. J Dermatol Sci. 2008 Jul;51(1):31-6.
7. Zhang F et al. Dermatology. 2007;215(4):277-83.
8. Cheng TS et al., *JAEDV* 24:1202-1206, 2010.