Hailey-Hailey disease (ATP2C1)

**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 Sensitivity:**
On average, about 60%-80% of patients with Hailey-Hailey disease tested were found to have a pathogenic variant in the ATP2C1 gene.

**Test Methods:**
Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.
References: