

## Darier Disease (ATP2A2)

**Disorder also known as:** Darier-White Disease; Keratosis Follicularis

**Also including:** Acral Hemorrhagic type of Darier Disease; Mosaic Darier Disease; Acrokeratosis Verruciformis

### **Clinical Features:**

Darier Disease (DD) is a rare inherited disorder of cornification of the skin, nails and mucous membranes. It has an estimated prevalence of 1/55,000 individuals and has been reported worldwide. Skin lesions begin with discrete, hard, hyperkeratotic papules mostly confined to chest and forehead. The lesions progressively develop into hyperkeratotic, macerated or crusted, malodorous plaques, which may cover most of the body and lead to secondary infection. DD is often associated with nail changes, in particular V-shaped notches and red and white longitudinal streaks. Skin lesions are exacerbated by trauma, including heat, sweat, friction and restrictive clothing. Peak of onset is between 11 and 20 years of age.<sup>3</sup> The disease follows a chronic, progressive course, often leading to discomfort and disfigurement. In a few families, DD has been associated with a broad spectrum of variable neuropsychiatric abnormalities, such as major affective disorder, schizophrenia and epilepsy.<sup>5,7</sup> DD is caused by pathogenic variants in the ATP2A2 gene located on chromosome 12q23-q24.1.<sup>8</sup>

### **Genetics:**

Darier Disease (DD) has an autosomal dominant pattern of inheritance. ATP2A2 spans about 70 kb and has 21 coding exons. The gene encodes 3 known alternative splice variants differing in their C-terminal sequence, of which only SERCA2b is expressed in the smooth muscle and other tissues, such as skin, appendages and mucous membranes. SERCA2b has 1042 amino acids and is an intracellular calcium pump of the sarcoplasmic/endoplasmic reticulum and closely related to plasma membrane calcium-ATPases. Darier Disease is thought to stem from haploinsufficiency for SERCA2b. Pathogenic ATP2A2 variants markedly affect the protein expression, partially due to enhanced proteasome-mediated degradation and lower calcium channel activity due to dimerization and inhibition of the wildtype protein.<sup>1</sup>

### **Test Sensitivity:**

ATP2A2 is the only gene to date known to be mutated in patients with Darier Disease. Using the variant detection method employed by GeneDx, variants in ATP2A2 are expected to be identified in about two-thirds of patients diagnosed with DD.<sup>6,10,11</sup> However, the test that is being performed will not identify copy number variations (gene deletion or duplication) or pathogenic variants if they exist in any other gene. The frequency of detectable ATP2A2 variants in acrokeratosis verruciformis has not yet been established.

To date, more than 130 distinct ATP2A2 variants have been identified in DD. Most DD patients have variants specific to that individual or family. More than one-half of the variants lead to premature termination of protein translation due to small base deletions/insertions, nonsense or splice site variants. The remainders are missense variants that occur throughout the gene.<sup>6,2</sup> Although there are no hot-spot variants in ATP2A2, there are a small number of recurrent variants, such as R131Q and N767S. The latter variant may be associated with the hemorrhagic variant of DD.<sup>7</sup> In one extended family with acrokeratosis verruciformis, the missense variant P602L in ATP2A2 has been found, suggesting that acrokeratosis verruciformis and DD are allelic disorders.<sup>4</sup>

### 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:

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