Genetic Testing of the ATP2A2 Gene in Darier Disease

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.[3] 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.[5,7] DD is caused by pathogenic variants in the ATP2A2 gene located on chromosome 12q23-q24.1.[8]

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.[1]

Test Methods:
GeneDx offers variant analysis of the ATP2A2 gene involved in Darier disease and Acrokeratosis verruciformis. Using genomic DNA obtained from blood in EDTA or buccal (cheek) swabs, the entire coding sequence (exons 1-21) and adjacent splice sites of the ATP2A2 gene are screened for variants by bi-directional sequence analysis. If a variant is identified, it is confirmed by a second analysis, either using sequence analysis, heteroduplex analysis or restriction fragment analysis.

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.[6,10,11] 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.

Variant Spectrum:

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.[6,2] 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.[7] 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.[4]

References:

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