Genetic Testing of the SPINK5 Gene in Netherton Syndrome

Disorder also known as: NTS; Comèl-Netherton Syndrome; Ichthyosis Linearis Circumflexa; Trichorrhexis Invaginata

Clinical Features:
Netherton syndrome (NTS) is a congenital disorder of the skin, hair and the immune system. NTS usually manifests at birth with generalized redness and scaling of the skin resembling non-bullous congenital ichthyosiform erythroderma (NCIE) or, rarely, with a collodion membrane. Generalized erythema and scaling may either persist lifelong, or develop into itchy, scaling plaques called “ichthyosis linearis circumflexa”. Associated are hair shaft abnormalities, in particular “bamboo hair” also known as “trichorrhexis invaginata”, which may lead to diffuse alopecia of the scalp and loss of eyebrows and eyelashes. Most patients have highly elevated serum levels of Immunoglobulin E and various allergies. In severe cases, failure to thrive, growth retardation, and immune defects resulting in serious recurrent infections may complicate NTS.

NTS is caused by pathogenic variants in the SPINK5 gene on chromosome 5q32. The gene encodes the multi-domain serine protease inhibitor LEKTI, which is predominantly expressed in the lamellar granule system of epithelial and lymphoid tissues. Variants in SPINK5 result in a loss of LEKTI activity and, thus, to premature and uncontrolled proteolytic activity of serine proteases. This process disturbs the delicate balance between lipid-processing enzymes that form the lamellar lipid bilayer system in the skin and severely disrupts the skin barrier function. In addition, LEKTI deficiency likely results in a loss of crucial anti-inflammatory and anti-microbial protection normally provided by LEKTI.

Inheritance Pattern/Genetics:
Autosomal recessive

Test Methods:
Using genomic DNA obtained from the submitted specimen, bi-directional DNA sequence of the coding portion of the SPINK5 gene (exons 1-33) is obtained and analyzed. If a variant is identified, it is confirmed by a second analysis, using sequencing, heteroduplex analysis or restriction fragment analysis.

Test Sensitivity:
SPINK5 is the only gene known to be associated with Netherton syndrome / Ichthyosis linearis circumflexa. Variants in SPINK5 are expected to be identified in two-thirds to three-quarters of patients clinically suspected to have NTS (Richard et al. 2004). The test that is being
performed will only identify variants if they exist in the SPINK5 gene, and not if they exist in any other gene.

References: