Genetic Testing of the CGI-58 (ABHD5) Gene in Chanarin-Dorfman syndrome

Clinical Features:
Chanarin-Dorfman syndrome is also known as neutral lipid storage disease with ichthyosis. Clinically, it is an autosomal recessive form of non-bullous congenital ichthyosiform erythroderma (NCIE), demonstrating fine white scaling on an erythematous background. Babies with Chanarin-Dorfman may be born with a collodion membrane, and cases have been reported with bilateral ectropion and eclabion. Hair, nails, teeth, and mucosa are normal. In addition to NCIE, however, affected individuals have other organ involvement, the most frequent of which is hepatomegaly and liver steatosis. Muscle weakness, ataxia, neurosensory hearing loss, eye findings (subcapsular cataracts, nystagmus and strabismus), and mental retardation may also be present. Histologically, intracellular lipid droplets are found in most tissues and confirmation of the diagnosis can be made on a peripheral blood smear to evaluate the presence of these lipid vacuoles in granulocytes.

Genetics:
The inheritance pattern of Chanarin-Dorfman syndrome is autosomal recessive. The majority of cases are from Middle Eastern countries, although European and Asian patients have also been reported. Even in consanguineous matings in Arab patients, the variants that have been reported are diverse and suggest that there is no founder effect for this rare disorder. Chanarin-Dorfman syndrome is an inborn error of lipid metabolism with accumulation of triglycerides in many organs due to pathogenic variants in the ABHD5 gene, formerly also known as CGI-58, on human chromosome 3p21. This gene, which encodes a protein of the esterase/lipase/thioesterase subfamily, is expressed in the upper epidermis, neurons and hepatocytes. The protein is packaged into lamellar granules, small intracellular lipid transport and secretion granules, which are important for keratinocyte differentiation and formation of the skin lipid barrier.²

Test Methods:
Using genomic DNA obtained from the submitted specimen, bi-directional DNA sequence of all exons and corresponding intron boundaries of the ABHD5 gene (exons 1-7) is obtained and analyzed. If a sequence change is identified, the variant is confirmed by a second analysis, using sequencing, heteroduplex or restriction fragment analysis.

Test Sensitivity:
In one study in which nine families met the diagnostic criteria for CDS (i.e. NCIE and lipid vacuoles in leukocytes), homozygous pathogenic variants were identified in the ABHD5 gene in all affected individuals tested.¹ Other studies identified ABHD5 variants in all patients from 6
unrelated Italian families and in 11 of 12 ABHD5 alleles from 6 unrelated Turkish individuals with CDS.\textsuperscript{4,5} In addition, numerous case reports of CDS patients with ABHD5 variants have been published. Hence, the sensitivity of ABHD5 sequencing is expected to be high in individuals with CDS.

References: