HAX1 Gene Analysis in Severe Congenital Neutropenia

Disorder also known as: SCN3, Kostmann disease, autosomal recessive congenital neutropenia, infantile genetic agranulocytosis

Clinical Features:
Severe congenital neutropenia (SCN) is characterized by a selective decrease in circulating neutrophils, bone marrow maturation arrest at the promyelocyte stage, and occurrence of infections. Typical infections include omphalitis, pneumonia, sinusitis and gingivitis caused by resident bacteria of the skin, mouth, and oropharynx. While all types of severe congenital neutropenia are sometimes called Kostmann disease, the extended family actually described in detail by Kostmann had a recessive disorder now known to be caused by pathogenic variants in HAX1.[1,2] A recent observation is that some, but not all, HAX1 variants are associated with neurological disorders.[3,4,5] Variants in HAX1 are not known to cause any type of cyclic or periodic neutropenia.

Genetics:
Autosomal recessive

Test Methods:
Analysis is performed by bi-directional sequencing of the coding regions and splice sites of exons 1-7 of the HAX1 gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:
In one study of 42 patients with SCN associated with documented myeloid maturation arrest, and no ELA2 variants, homozygous HAX1 variants were found in 16 (15 unrelated) patients[2]. Another study of 109 families with SCN found 33 with autosomal dominant ELA2 variants, 2 with X-linked WAS variants, and 4 with autosomal recessive HAX1 variants.[6] The chance of finding a HAX1 variant in a given patient depends in part on the likelihood of recessive inheritance. Sequencing analysis as performed at GeneDx is expected to identify 99 % of HAX1 variants.

References:

1. Kostmann, R. Infantile genetic agranulocytosis (Agranulocytosis infantilis hereditaria): a new recessive lethal disease in man, Acta Paediatr. 45 (suppl) 1-78. 1956.
2. Klein C., et al, HAX1 deficiency causes autosomal recessive severe congenital neutropenia (Kostmann disease), Nature Genetics 39:86-90, 2007.
3. Matsubara K, et. al, Severe developmental delay and epilepsy in a Japanese patient with severe congenital neutropenia due to HAX1 deficiency, Haematologica 92(12):e123-5, 2007.
4. Germeshausen M, et al. Novel HAX1 mutations in patients with severe congenital neutropenia reveal isoform-dependent genotype-phenotype correlations, Blood 111:4954, 2008
5. Carlsson G, et al, Central nervous system involvement in severe congenital neutropenia: neurological and neuropsychological abnormalities associated with specific HAX1mutations, J Int Med 264:388, 2008
6. Smith BN, et al, Homozygous HAX1 mutations in severe congenital neutropenia patients with sporadic disease: a novel mutation in two unrelated British kindreds. Br J Haematol 144:762, 2009.