

## ELANE (ELA2) Gene Analysis in Severe Congenital Neutropenia or Cyclic Neutropenia

**Disorder also known as:** SCN1, congenital autosomal dominant or sporadic neutropenia, infantile genetic agranulocytosis, Kostmann disease (historically); cyclic hematopoiesis

### **Clinical Features:**

Severe congenital neutropenia (SCN) and cyclic neutropenia (CN) are severe disorders of neutrophil production that cause lifelong problems with recurrent infections. Congenital neutropenia is characterized by very low non-oscillating neutrophil counts with normal hemoglobin and platelet levels. Typical infections include omphalitis, pneumonia, sinusitis and gingivitis. The bone marrow shows a selective defect in neutrophil formation with promyelocytic maturation arrest. While all types of severe congenital neutropenia sometimes are called Kostmann disease, the extended family studied by Kostmann had a recessive disorder now known to be caused by mutations in HAX1, not ELANE.

Cyclic neutropenia often, but not always, follows a 3-week cycle of neutropenia, fever and mouth ulcers. Diagnosis is usually made in infancy and infections may lessen in severity with age.

### **Genetics:**

Autosomal dominant, with pathogenic variants that usually occur *de novo* in SCN and may be inherited in CN.

### **Test Sensitivity:**

In various studies, 35-88% of patients with SCN<sup>1,2</sup> and 44-100% of patients with CN<sup>1,2,3</sup> have had ELANE variants. The sequence analysis performed by GeneDx is expected to detect at least 98% of ELANE variants associated with these dominant disorders.

### **Variant spectrum:**

Both disorders are associated with the production of stable neutrophil elastase proteins of near-normal sequence resulting from missense variants, small deletions, use of alternate splice sites, and distal truncations. Promoter variants resulting in excess normal protein production have been postulated.

### **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:

1. Dale et al, Mutations in the gene encoding neutrophil elastase in congenital and cyclic neutropenia, *Blood* 96: 2317-2322, 2000
2. Bellanne-Chantelot, C, Mutations in the ELA2 gene correlate with more severe expression of neutropenia: a study of 81 patients from the French Neutropenia Registry, *Blood* 103: 4119-4125, 2004.
3. Horwitz, M., Mutations in ELA2, encoding neutrophil elastase, define a 210day biological clock in cyclic haematopoiesis, *Nat. Gen.* 23:433-436, 1999.