

ELANE ProGenotyper[®]

Test Name: ELANE ProGenotyper[®] test

Test Code: 30030

CPT Code: 83890, 83898(x5), 83891(x5), 83904(x10), 83912

Clinical Utility: This test is intended to detect mutations in the neutrophil elastase gene (ELANE or EL2) for the diagnosis of severe congenital neutropenia (SCN) or cyclic neutropenia. ELANE-related neutropenia is inherited in an autosomal dominant manner.

Severe congenital neutropenia is defined by a persistent absolute neutrophil count $< 0.2 \times 10^9/L$, and generally presents with more severe infectious complications than in cyclic neutropenia. Omphalitis immediately after birth may be the first sign of congenital neutropenia. In the first year of life, untreated children may have diarrhea, pneumonia, and deep abscesses in the liver, lungs, and subcutaneous tissues.

Cyclic neutropenia usually manifests within the first year of life based on approximately three-week intervals of fever and oral ulcerations and regular oscillation of blood cell counts. Cellulitis, especially perianal cellulitis, is common during neutropenic periods. Between neutropenic periods affected individuals are generally healthy. Symptoms improve in adulthood.

Background: Mutations in the neutrophil elastase gene cause an arrest in the development of neutrophils at the promyelocyte-myelocyte stage, with very low neutrophil counts in the blood, and early onset of severe bacterial infections. Mutations in the ELANE gene have been found in over 50 locations in the gene. Penetrance is complete, but severity varies. A major concern in these patients is the high risk of development of myelodysplastic syndrome and /or acute myeloid leukemia. Our assay covers the five exons and splice junctions of this gene.

Frequency: SCN: 2-3 per million and cyclic neutropenia, 1 per million of the general population

Physical Manifestations: Congenital and cyclic neutropenia are hematologic disorders characterized by recurrent fever, skin and oropharyngeal inflammation, including:

- Mouth Ulcers
- Gingivitis
- Sinusitis
- Pharyngitis
- Cervical Adenopathy
- Chronic & severe infections of lung, liver, and soft tissues

Specimen Requirements:

- 2mL whole blood (EDTA)
- Ship **overnight** at ambient temperature

Units and Normal Reference Range:

- All 5 exons and intron boundaries in ELANE are sequenced and compared to reference sequence NG_009627. Autosomal dominant mutations in this gene are found in 38-80% of cases of severe congenital neutropenia, and in 90-100% of those with cyclic neutropenia. The remaining patients have a mutation in another gene. Results are reported as no detectable mutation, heterozygous (HET) mutation, homozygous (HOMO) mutation, or unknown (UKN) mutation. A mutation that has not previously been reported in the literature is considered unknown.

Method:

1. Patient DNA is extracted from whole blood.
2. Regions covering all five exons and exon/intron borders are amplified by PCR from the genomic DNA and the products of each are purified.
3. Cycle sequencing is performed with one or two sequencing primers per segment.
4. These products are purified and run on the ABI3730 or ABI3130 Genetic Analyzer
5. The resulting sequence is analyzed in comparison with the reference sequence.

References:

1. Boztug K, Klein C. 2009. Novel genetic etiologies of severe congenital neutropenia. *Curr Opin Immunol* 21(5):472-80.
2. Dale DC, Link DC. 2009. The many causes of severe congenital neutropenia. *N Engl J Med* 360(1):3-5.
3. Dale DC 2009. ELANE-related neutropenia. *GeneReviews*. NCBI Bookshelf. University of Washington, Seattle.
4. Lanciotti M, Caridi G, Rosano C, Pigullo S, Lanza T, Dufour C. 2009. Severe congenital neutropenia: a negative synergistic effect of multiple mutations of ELANE (ELA2) gene. *Br J Haematol* 146(5):578-80.
5. Shiohara M, Shigemura T, Saito S, Tanaka M, Yanagisawa R, Sakashita K, Asada H, Ishii E, Koike K, Chin M, Kobayashi M, Koike K. 2009. ELA2 mutations and clinical manifestations in familial congenital neutropenia. *J Pediatr Hematol Oncol* 31(5):319-24.
6. Ward AC, Dale DC. 2009. Genetic and molecular diagnosis of severe congenital neutropenia. *Curr Opin Hematol.* 16:9-13.
7. Xia J, Bolyard AA, Rodger E, Stein S, Aprikyan AA, Dale DC, Link DC. 2009. Prevalence of mutations in ELANE, GF11, HAX1, SBDS, WAS and G6PC3 in patients with severe congenital neutropenia. *Br J Haematol* 147(4):535-42.
8. Zeidler C, Germeshausen M, Klein C, Welte K. 2009. Clinical implications of ELA2-, HAX1-, and G-CSF-receptor (CSF3R) mutations in severe congenital neutropenia. *Br J Haematol* 144(4):459-67.

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