



Division of Human Genetics

SEVERE CONGENITAL NEUTROPENIA (SCN) AND CYCLIC NEUTROPENIA

GENES TESTED: *ELA2*, *HAX1*, *WAS*

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Additional information and test requisitions are available at:
www.cincinnatichildrens.org/molecular-genetics



Helping you fit the pieces together

Shipping Instructions

Please enclose test requisition with sample. All information must be completed before sample can be processed.

Place samples in Styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday

Ship to:
Cytogenetics and Molecular Genetics Laboratories
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474

Severe congenital neutropenia (SCN) is a disorder of neutrophil production. The incidence of SCN is approximately 3-4 per million births. Children with SCN typically present with severe neutropenia, fever and recurrent infections of the upper respiratory tract, lungs and skin within the first year of life. Malignant transformation, i.e. myelodysplasia and acute myelogenous leukemia, is a significant risk in individuals with SCN secondary to mutations in *ELA2*. Treatment with granulocyte colony-stimulating factor (G-CSF) reduces the duration and severity of the neutropenia and improves clinical outcome.

The diagnostic criteria for SCN include:

- Early childhood onset of profound neutropenia ($<0.5 \times 10^9/L$)
- Recurrent life-threatening bacterial infections
- Promyelocytic maturation arrest in the bone marrow

Cyclic neutropenia is a rare disorder of neutrophil production characterized by periodic cycling of neutrophils, typically at 21 day intervals. Monocytes and reticulocytes cycle out of phase with neutrophils in affected patients. Children with cyclic neutropenia typically present within the first year of life with recurring episodes of fever, skin and oropharyngeal infections. Symptoms often improve in adulthood. During the acute phase of the disorder, the neutrophil count may be extremely low, but tends to improve significantly when the child is asymptomatic. Deep tissue cellulitis and bacteremias are the most serious complications of this disorder and may be fatal. Malignant transformation is not a significant risk in individuals with cyclic neutropenia. Treatment with G-CSF reduces the frequency of neutrophil cycling and improves clinical outcome.

SCN is caused by mutations in several genes:

- *ELA2*—*SCN1* and cyclic neutropenia
- *HAX*—*SCN3* (Kostmann syndrome)
- *WAS*—*X-linked SCN*
- *GF11*—*SCN2*
- *CSF3R* (*GCSFR*)—somatic mutations in some patients with SCN.

Clinical testing is currently available in our laboratory for mutations in the following three SCN-related genes:

***ELA2*:** Mutations in the neutrophil elastase gene, *ELA2*, are the most common cause of SCN, as well as of cyclic neutropenia. *ELA2* maps to 19p13.31 and mutations in the *ELA2* gene are identified in approximately 35-84% of individuals with SCN. SCN and cyclic neutropenia secondary to mutations in *ELA2* are inherited as autosomal dominant conditions. *ELA2* consists of five exons and encodes a 218 amino acid protein known as neutrophil elastase. Neutrophil elastase targets bacterial virulence proteins and serves as the cell's first line of defense against overwhelming bacterial infection. Mutations involving all five exons have been described. Nonsense and frameshift mutations affecting the carboxyl terminus are quite common in SCN patients while missense mutations are seen more commonly in cyclic neutropenia patients. However, there is considerable overlap of genotype with phenotype, even within families.

HAX1: Kostmann syndrome, an autosomal recessive disorder characterized by infantile agranulocytosis, is caused by biallelic mutations in the *HAX1* gene. *HAX1* maps to 1q21.3 mutations in *HAX1* have been identified in 10% of individuals with SCN. Mutations in *HAX1* have not been reported in association with myelodysplasia or AML; otherwise, the disorder is clinically indistinguishable from *ELA2*-related SCN. The *HAX1* gene consists of seven exons and encodes a 279 amino acid protein which plays a role in neutrophil-specific apoptosis.

WAS: X-linked congenital neutropenia (XLN) is caused by mutations in *WAS* that result in constitutive activation of WASP. XLN has been described in the presence of various mutations within the CDC42 binding site. WASP expression in individuals with XLM is comparable to that of normal controls. It is not known if SCN-related mutations in *WAS* are associated with an increased risk of myelodysplasia or AML, as are mutations in *ELA2*.

INDICATIONS:

- Confirmation of diagnosis in a symptomatic individual
- Carrier/Heterozygote detection in individuals with a family history of SCN.
- Prenatal diagnosis of an at-risk fetus, after confirmation of mutation(s) in the parent(s) (by prior arrangement only)

SPECIMEN:

At least 3 mLs whole blood in lavender top (EDTA) tube. Label tube with patient's name, birth date, and date of collection. Cytobrushes are required for analysis in patients who have undergone bone marrow transplantation and may facilitate DNA isolation in patients undergoing chemotherapy or in individuals with leukopenia. Please call for a free cytobrush collection kit.

METHODOLOGY:

Testing is performed by PCR-based sequencing of the entire coding regions and intron/exon boundaries of the *ELA2*, *HAX1* or *WAS* genes. Testing may be ordered sequentially or in tandem.

SENSITIVITY & SPECIFICITY:

The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, small deletions, and insertions in the regions analyzed. Multiple exon deletions, large insertions, genetic recombinational events and rare, primer site mutations may not be identified using these methods.

TURN-AROUND TIME:

1 month

COST:

Please call 1-866-450-4198 for current pricing or with any billing questions.

CPT CODES:

ELA2 83890(x1), 83898(x5), 83894(x7), 83891(x5), 83904(x11), 83909(x11), 83912
HAX1 83890(x1), 83898(x7), 83894(x9), 83891(x7), 83904(x14), 83909(x14), 83912
WAS 83890, 83898(x7), 83891(X6), 83904(x19), 83894(X8), 83912

Family specific mutation analysis 83890, 83898, 83894, 83891, 83904, 83912