SEVERE CONGENITAL NEUTROPENIA
AND CYCLIC NEUTROPENIA
SEQUENCE ANALYSIS

BloodCenter of Wisconsin offers DNA sequencing of the ELANE and HAX1 genes for diagnosis of congenital and cyclic neutropenia.

BACKGROUND:
Severe congenital neutropenia (SCN) is a disorder of neutrophil production that is characterized by recurrent fever, infections and inflammation of the mouth, skin and pharynx. Another hallmark of these disorders is a predisposition to myelodysplastic syndrome and AML. Diagnosis of these disorders is based on clinical findings and serial measurement of the absolute neutrophil count (ANC). Cyclic neutropenia is distinguished from congenital neutropenia by regular oscillations of the ANC and generally milder infectious complications.

Mutations in the ELANE gene have been reported in 90-100% of cyclic neutropenia patients and 38-80% of congenital neutropenia patients. ELANE-related neutropenia is inherited in an autosomal dominant manner. An autosomal recessive form of SCN (Kostmann Disease) is caused by mutations in the HAX1 gene. In one study, homozygous HAX1 mutations were found in approximately one third of SCN patients without ELANE mutations. In some cases, HAX1 mutations are associated with neurological symptoms. Identification of a mutation in the ELANE gene or homozygous mutations in the HAX1 gene confirm a diagnosis of SCN. Mutations in ELANE confirm a diagnosis of cyclic neutropenia. Other genes responsible for rare cases of SCN are GFI1, WAS, CSF3R and G6PC3.

REASONS FOR REFERRAL:
• Confirmation of diagnosis
• Evaluation of family members
• Prenatal diagnosis

METHOD:
PCR amplification and bi-directional DNA sequence analysis are performed. The complete coding region and splice junction of each exon is compared to the reference sequence, and the functional implications of sequence variations are characterized using data in the Human Gene Mutation Database (HGMD).

LIMITATIONS:
Analytical sensitivity is >99%. Rare polymorphisms within primer or probe regions may interfere with detection of gene variants. Large deletions or duplications and mutations that are outside the regions sequenced will not be detected. Clinical sensitivity of ELANE sequence analysis is 90-100% for cyclic neutropenia patients and 38-80% for severe congenital neutropenia. Clinical sensitivity of HAX1 sequence analysis may be as high as 30% in patients without ELANE mutations. Sensitivity will be highest in patients with the classic clinical symptoms defining these disorders with the expected inheritance pattern.
REPORTABLE RANGE:
Sequence variations are reported as heterozygous or homozygous and are classified according to the following system:

I. Sequence variation is previously reported and is a recognized cause of the disorder
II. Sequence variation is previously unreported and is of the type which is expected to cause the disorder.
III. Sequence variation is previously unreported and is of the type which may or may not be causative of the disorder
IV. Sequence variation is previously unreported and is probably not causative of disease.
V. Sequence variation is previously reported and is a recognized neutral variant.
VI. Sequence variations that are not known or expected to be causative of disease, but have been found to be associated with a clinical presentation.

Known polymorphisms are not reported but are available upon request.

SPECIMEN REQUIREMENTS:
7-15 ml amniotic fluid, 5x10^6 cultured amniocytes, or 3-5 ml EDTA (lavender top) whole blood. Contact the laboratory to discuss prenatal sample requirements.

TURNAROUND TIME: 14 days

SHIPPING REQUIREMENTS:
Ship on an ice pack or at room temperature. Place the specimen and the requisition into plastic bags and seal. Insert into a Styrofoam container, seal and place into a sturdy cardboard box, and tape securely. Ship the package in compliance with your overnight carrier guidelines. Label with the following address:

Client Services/Platelet Neutrophil Immunology Laboratory
BloodCenter of Wisconsin
638 N. 18th St.
Milwaukee, WI 53233
Phone: 800-245-3117, ext. 6250

CPT CODES:
ELANE Sequence Analysis
CPT Codes: 81479

HAX1 Sequence Analysis
CPT Codes: 81479

REFERENCES: