

## Severe Congenital Neutropenia via *GFII* gene sequencing (Test #447)

**Brief Description of Clinical Features:** Severe Congenital Neutropenia (SCN; OMIM 202700) comprises a heterogeneous group of disorders of myelopoiesis with varying symptoms and patterns of inheritance. SCN is characterized by absolute neutrophil counts (ANC) consistently below 500/ $\mu$ l and severe systemic bacterial infections beginning in early infancy (see Boxer and Newburger *Pediatr Blood Cancer* 49:609-614, 2007). Patients typically have recurrent fevers and develop sinusitis, gingivitis and other soft tissue infections. A hallmark of SCN is bone marrow ‘maturation arrest’; neutrophils differentiate only to the promyelocyte/myelocyte stage (see Kostman *Acta Paediatr Scand* 64:362-368, 1975). ~ 95% of patients respond to treatment with recombinant granulocyte-colony stimulating factor (G-CSF) with an increase in ANC (Bellanne-Chantelot et al. *Blood* 103:4119-4125, 2004; Freedman et al. *Blood* 96:429-436, 2000), however treated patients are still at risk of sepsis (Donini et al. *Blood* 109:4716-4723, 2007). SCN is a premalignant condition; patients are at an elevated risk of developing myelodysplastic syndrome and acute myeloblastic leukemia (MDS/AML). The risk of malignancy increases upon G-CSF treatment (Gilman et al. *Blood* 36:576-585, 1970; Freedman et al. *Blood* 96:429-436, 2000; Rosenberg et al. *Blood* 107:4628-4635, 2006). In contrast to SCN, MDS/AML have not been diagnosed in patients with cyclic or idiopathic neutropenia.

**Genetics:** Mutations in the *GFII* gene (OMIM 600871) cause a rare form of autosomal dominant SCN. *GFII* encodes Growth Factor Independent-1, a zinc finger protein with transcriptional repressor function that helps regulate cell type differentiation. Mutant *GFII* acts in a dominant negative manner and blocks granulopoiesis (Zarebski et al. *Immunity* 28:370-380, 2008). Causative missense mutations in the zinc finger domain of *GFII* have been reported in only a few families and individuals (Person et al. *Nat Genet* 34:308-312, 2003; Hochberg et al. *Pediatr Blood Cancer* 50:630-632, 2008; Xia et al. *Br J Haematol* 147:535-542, 2009). The *GFII* phenotype includes a circulating population of immature myeloid cells and immunodeficient lymphocytes (Person et al. *Nat Genet* 34:308-312, 2003).

**Description of This Particular Test:** This test involves bidirectional DNA sequencing of all 6 coding exons of the *GFII* gene plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence any single exon (Test #100, \$190) in family members of patients with known mutations, or to confirm research results.

**Reference Sequences:** Genomic: NC\_000001.10 mRNA: NM\_005263.3 Protein: NP\_005254.2 (CCDS 30773.1)

**Indications for Test:** Patients with recurring bacterial infections, a family history of SCN, or neutropenia unrelated to other syndromes (e.g. Chediak-Higashi Syndrome, Hermansky Pudlak Syndrome, or Griscelli Syndrome).

**Sensitivity of Test:** Mutations in the *GFII* gene are a rare cause of SCN.

**Turnaround Time:** Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

**Specimen Requirements:** See bottom of page 4 of Requisition Form

**Price:** Sequencing of *GFII* \$ 560

| CPT Codes    |            |            |            |            |            |            |       |
|--------------|------------|------------|------------|------------|------------|------------|-------|
| Test         | 83890 (x1) | 83891 (x1) | 83898 (x7) | 83904 (x7) | 83894 (x1) | 83912 (x1) | Total |
| <i>GGFII</i> | \$30       | \$40       | \$150      | \$220      | \$30       | \$90       | \$560 |

**Accreditation:** CLIA ID:52D1027685 (expires 1/18/13) CAP ID:7185561, AU ID:1407125 (expires 12/20/12)

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