

Autosomal Recessive Severe Congenital Neutropenia / Dursun Syndrome via *G6PC3* Gene Sequencing (Test #443)

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 (ANCs) consistently below 500/ μ 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 prominent feature of SCN is bone marrow ‘maturation arrest’; neutrophils differentiate only to the promyelocyte/myelocyte stage (see Kostman *Acta Paediatr Scand* 64:362-368, 1975). Mature neutrophils are few in number and are deficient in their antibacterial abilities. About 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). G-CSF reverses neutropenia and decreases infections, but 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: Autosomal recessive forms of SCN have been linked to mutations in the *G6PC3* and *HAX1* genes. Mutations in the *G6PC3* (OMIM 611045) gene result in a very severe form of SCN in which neutropenia is accompanied by developmental defects including structural heart defects, urogenital abnormalities, and venous angiectasia of the trunk and extremities (Boztug et al. *N Engl J Med* 360:32-43, 2009). Recently, the *G6PC3* phenotype has been extended to include monocytosis, lymphopenia, and erythroid hypoplasia resulting in anemia (Dursun et al. *Clin Dysmorph* 18:19-23, 2009). Causative mutations are primarily missense and nonsense, but splice site mutations and small insertions and deletions have been reported (Aróstegui et al. *Blood* 114:1718-1719, 2009; Xia et al. *Br J Haematol* 147:535-542, 2009). *G6PC3* encodes glucose-6-phosphatase (G6P), catalytic subunit 3. G6P is an ER protein that catalyzes hydrolysis of glucose-6-phosphate to glucose and phosphate. Defective G6P is hypothesized to cause ER stress in neutrophil precursors resulting in apoptosis and reduced ANCs (Boztug et al. *N Engl J Med* 360:32-43, 2009).

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 6 coding exons of the *G6PC3* 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) or two exons (Test #200, \$340) in family members of patients with known mutations, or to confirm research results.

Reference Sequences: Genomic: NC_000017.10 mRNA: NM_138387.3 Protein: NP_612396.1 (CCDS 11476.1)

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 *G6PC3* cause a rare form of neutropenia that represents a small fraction of all SCN cases.

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

Specimen Requirements: See page 4 of the Requisition Form

Price: Sequencing of *G6PC3* \$ 530

CPT Codes							
Test	83890 x1	83891 x1	83898 x7	83904 x7	83894 x1	83912 x1	Total
<i>G6PC3</i>	\$30	\$40	\$140	\$200	\$30	\$90	\$530

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

Contact: Dr. Michael Chicka, michael.chicka@preventiongenetics.com, www.preventiongenetics.com