

Piebaldism and Familial Gastrointestinal Stromal Tumors (GISTs) via *KIT* Gene Sequencing – Test #718

Brief Description of Clinical Features: Mutations in the *c-kit* proto-oncogene (*KIT*) cause a variety of disorders, including piebaldism, gastrointestinal stromal tumors (GISTs), germ cell tumors (GCTs) and hematopoietic neoplasms such as acute myeloid leukemia (AML), chronic myeloid leukemia (CML) and malignant lymphoma (reviewed in Akin and Metcalfe, *J Allergy Clin Immunol* 114:13-19, 2004). Piebaldism (OMIM 172800) is an autosomal dominant disorder characterized by patches of skin and hair that entirely lack pigment (Murakami et al. *J Derm Sci* 35:29.33, 2004). These white patches are mainly found on the scalp and forehead, resulting in a distinctive white forelock trait. Gastrointestinal stromal tumors, or GISTs (OMIM 606764), are rare mesenchymal tumors that specifically express the Kit protein and originate in the gastrointestinal (GI) tract or abdomen (Miettinen et al. *Eur J Cancer* 38 Suppl. 5:S39-S51, 2002). In most cases, GISTs spontaneously arise due to somatic mutations of the *KIT* gene. However, families with germline mutations in the *KIT* gene have also been described (Isozaki et al. *Am J Path* 157:1581-1585, 2000; Maeyama et al. *Gastroenterology* 120:210-215, 2001). In these families, inheritance of heterozygous *KIT* mutations leads to cutaneous hyperpigmentation and development of multiple GISTs.

Genetics: Piebaldism is caused by inactivating mutations in *KIT*, while neoplasms (GISTs, GCTs, AML, CML and lymphomas) are caused by activating, or gain-of-function, mutations (Akin and Metcalf, 2004). *KIT* encodes a transmembrane receptor tyrosine kinase that responds to the Stem Cell Factor (SCF) ligand. Kit is expressed on the surface of several different cell types, including melanocytes, gastrointestinal pacemaker cells, hematopoietic progenitor cells, mast cells and germ cells. In melanocytes, Kit signaling is required for migration from the embryonic neural crest; loss of Kit function results in the absence of melanocytes in midline patches of hair and skin. In other cells, signaling through the SCF/c-kit pathway promotes proliferation and survival; constitutive activation of Kit in these cells causes excessive proliferation, malignancy and metastasis. Loss-of-function mutations are found throughout all 21 exons of the *KIT* gene, whereas activating mutations appear to be clustered in exons 2, 8, 9, 11, 13 and 17 (Heinrich et al. *J Clin Oncol* 20:1692-1703, 2002). Importantly, the selective *KIT* inhibitor Gleevec (Novartis Pharmaceuticals, East Hanover, NJ) is a very effective treatment for *KIT*-dependent neoplasms (Tuveson et al. *Oncogene* 20:5054-5058, 2001). However, a few activating mutations, such as D816V, have been shown to be insensitive to Gleevec (Miettinen et al., 2002). As a result, identifying the causative mutation in these neoplasms is critical for determining the most effective mode of treatment.

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 21 coding exons of the *KIT* gene, plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence a single exon (Test #100; \$190) in family members of patients with known mutations, or to confirm research results.

Reference Sequences: Genomic: **NC_000004.11** mRNA: **NM_000222.2** Protein: **NP_000213.1** **CCDS 3496.1**

Indications for Test: Candidates for this test are patients with piebaldism or suspicion of familial GISTs. This test is specifically designed for heritable germline mutations and is not appropriate for the detection of somatic mutations in tumor tissue. This test is also not recommended for patients with mastocytosis (Valent et al. *Eur J Clin Invest* 37:435-453, 2007).

Sensitivity of Test: This test is predicted to detect a loss-of-function mutation in nearly all patients with piebaldism (Syrris et al. *Hum Mut* 20:234-237, 2002) and a gain-of-function mutation in ~60-90% of patients with GISTs (Heinrich et al. 2002).

Turnaround Time: Maximum of 40 calendar days, although most tests are completed in 3-4 weeks.

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

Price:	Sequencing of the <i>KIT</i> Gene:	\$ 1060
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x20	83898 \$ 320	Sequencing x20 83904 \$ 470
Separation x1	83894 \$ 70	Interpretation/Report x1 83912 \$ 130

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

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