

## Hirschsprung Disease (HSCR) via *RET* Gene Sequencing (Test #791)

**Brief Description of Clinical Features:** Hirschsprung disease (HSCR) (OMIM# 142623), aka congenital intestinal aganglionosis, is a birth defect characterized by complete absence of neuronal ganglion cells from a portion of the intestinal tract (Eng & Mulligan *Hum Mutat* 9:97-109, 1997). In 80% of individuals aganglionosis is restricted to the rectosigmoid colon (S-HSCR); in 15%-20% aganglionosis extends beyond the sigmoid colon (L-HSCR); in about 5% aganglionosis affects the entire large intestine (total colonic aganglionosis). HSCR is the main genetic cause of functional intestinal obstruction in infants and children. Affected infants frequently present in the first two months of life with symptoms of impaired intestinal motility such as failure to pass meconium within the first 48 hours of life, constipation, emesis, abdominal pain or distention, and occasionally diarrhea. However, because the initial diagnosis of HSCR may be delayed, HSCR should be considered in anyone with lifelong severe constipation.

**Genetics:** HSCR has an estimated incidence of 1 in 5,000 births, varying among different ethnic groups. About 70% of affected individuals have nonsyndromic form (isolated HSCR), and the rest 30% have syndromic form with multiple congenital anomalies. At least six different genes are associated with isolated HSCR, with different inheritance patterns (Parisi *GeneReview* 2006). *RET* is the primary gene underlying HSCR, and *RET*-related HSCR is inherited in an autosomal dominant manner with reduced and sex-dependent penetrance (Passarge *Nat Genet* 31:11-12, 2002). Loss-of-function mutations in *RET* have been identified in 50% familial and 10-35% of sporadic HSCR cases. The *RET* proto-oncogene is one of the receptor tyrosine kinases, cell-surface molecules that transduce signals for cell growth and differentiation. This gene plays a crucial role in neural crest development. *RET* interacts with the glial-derived neurotrophic factor (GDNF) family of ligands: GDNF, neurturin, persephin, and artemin. Formation of a complex containing two *RET* protein molecules leads to *RET* autophosphorylation and intracellular signaling (Santoro et al. *Endocrinology* 145:5448-5451, 2004).

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

**Reference Sequences:** **Genomic: NC\_000010.10**                      **mRNA: NM\_020975.4**  
**Protein: NP\_066124.1**    **mRNA and Protein: CCDS 7200.1**

**Indications for Test:** Candidates for this test are patients with clinical features consistent with nonsyndromic HSCR and family members of patients who have known *RET* mutations.

**Sensitivity of Test:** This test is predicted to detect disease mutations in 50% of familial HSCR cases and up to 35% of sporadic HSCR cases (Attie et al. *Hum Mol Genet* 4:1381-1386, 1995; Eng & Mulligan. *Hum Mutat* 9:97-109, 1997, Hofstra et al. *Hum Mutat* 15:418-429, 2000; Bolck Gabriel et al. *Nature Genet* 31:89-93, 2002). Among individuals with L-HSCR, *RET* mutation can be detected in as high as 80% of cases (Angrist et al. *Hum Mol Genet* 4:821-830, 1995, Seri et al. *Hum Mutat* 9:243-249, 1997).

**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.

**Prices:**                      **Sequencing of *RET* gene**                      **\$ 1130**

**CPT Codes:**

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x22	83898 \$340	Sequencing x22	83904 \$510
Separation x1	83894 \$ 80	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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