



### Disease Information

Hirschsprung disease (HSCR) is multigenic congenital disease of the large intestine characterized by absence of neuronal ganglia, colon enlargement, and constipation; it is typically suspected in newborns who have not passed meconium 48 hours after birth.<sup>1</sup> Hirschsprung disease has an estimated incidence of one out of 5,000 births, varying almost two-fold depending upon ethnicity, with males being four times more likely affected than females.<sup>2,3</sup> HSCR has been associated with two phenotypes: short segment (S-HSCR or Type I HSCR) and long segment (L-HSCR or Type II HSCR). S-HSCR accounts for 60%-85% of patients and affects the rectum along with a small portion of the colon (the sigmoid). The remaining 15%-25% of patients have L-HSCR which also affects the rectum and extends beyond the upper sigmoid.<sup>1,4</sup> HSCR is associated with multiple congenital abnormalities in approximately 30% of patients.<sup>4</sup> X-ray, barium enema studies, and rectal manometry can be helpful in establishing diagnosis of HSCR, but confirmation requires a rectal biopsy.<sup>1,5</sup>

HSCR is associated with mutations in eight partially-interdependent genes, with mutations occurring primarily in the *RET* gene. Dominant loss-of-function mutations in *RET* have been identified in 50% of familial and 35% of sporadic HSCR cases.<sup>6</sup> *RET* has also been shown to act as a modifier gene in other syndromic forms of HSCR.<sup>7</sup>

### Testing Benefits & Indications

Diagnostic testing is helpful for individuals known or suspected to have Hirschsprung disease especially those with L-HSCR. Testing is available for relatives of HSCR patients in whom the mutation is known and for pregnancies at risk.

### Test Description

*RET* exons 2, 3, 5, 6, 9, 10, 12, 13, and 17 plus at least 20 bases into the 5' and 3' ends of all the introns are analyzed. If a disease causing mutation is not identified, the remainder of the 20 exons of *RET* plus at least 20 bases into the 5' and 3' ends of all the introns will be analyzed. Specific mutation analysis for individual *RET* mutations known to be in the family is also available.

### Mutation Detection Rate

Mutations in the *RET* gene account for 50% of familial cases of HSCR and up to 35% of sporadic cases.<sup>8</sup> The Ambry Test: *RET*-Related Hirschsprung Disease is capable of detecting >99% of described mutations in *RET*.

### Turn-Around-Time

Gene sequence analysis .....	14 – 21 days
Specific mutation analysis .....	10 – 14 days

### Specimen Requirements

**Blood:** Collect 3-5 cc from adult or 2 cc minimum from child into EDTA purple-top tube (first choice) or ACD yellow-top tube (second choice). Store at room temperature or refrigerate. Ship at room temperature.

**Blood Spot:** Call for availability.

**Saliva:** Collect 2 ml into Oragene™ DNA Self-Collection container. Store and ship at room temperature.

**DNA:** Send 20 µg in TE at 50-100 ng/µl. Store frozen and ship on ice or dry ice.

**Prenatal:** Prenatal testing is available. Please call an Ambry Genetic Counselor to discuss your case.

### CPT Codes

Gene sequence or specific mutation analysis .....83891, 83894x21, 83898x20, 83904x35, 83909x35, 83912

### References

<sup>1</sup> Amiel J, Lyonnet S. *J Med Genet.* 2001 Nov;38(11):729-39.

<sup>2</sup> Badner JA et al. *Am J Hum Genet.* 1990 Mar;46(3):568-80.

<sup>3</sup> Chin TW et al. *J Chin Med Assoc.* 2008 Aug;71(8):406-10.

<sup>4</sup> Passarge E. *Nat Genet.* 2002 May;31(1):11-2.

<sup>5</sup> Neville H. (2008) Hirschsprung Disease. eMedicine.

<http://emedicine.medscape.com/article/929733-diagnosis>. Accessed October 12, 2009.

<sup>6</sup> Bolk S et al. *Proc Natl Acad Sci U S A.* 2000 Jan 4;97(1):268-73.

<sup>7</sup> Pontual L et al. *J Med Genet.* 2006;43:419-423.

<sup>8</sup> Tam et al. *Pediatr Surg Int.* 2009;25:543-558.