RET Gene Analysis in Hirschsprung Disease

DISORDER ALSO KNOWN AS
HSCR; Congenital aganglionic megacolon.

CLINICAL FEATURES
Hirschsprung disease is the main genetic cause of functional intestinal obstruction in infants and children, with an incidence of 1 in 5000 births. It is associated with congenital absence of parasympathetic ganglia in the bowel. The majority of patients with HSCR (80%) have a short aganglionic segment (S-HSCR) affecting the region beneath the upper sigmoid. Patients with long-segment HSCR (L-HSCR), representing 20% of cases, have aganglionosis extending to or beyond the splenic flexure. HSCR presents as an isolated finding in ~70% of patients, while ~30% of cases are considered syndromic (associated with either a chromosome abnormality or multiple congenital anomalies). RET is the primary gene underlying HSCR, particularly in families with multiple cases of L-HSCR; however, evidence shows that the phenotype can result from pathogenic variants in several other genes with both recessive and dominant inheritance patterns (acting alone or in combination). Notably, RET variants show incomplete, sex-dependent penetrance and do not always result in the Hirschsprung phenotype.[1,2]

GENETICS
Autosomal dominant with reduced penetrance.

TEST METHODS
Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. If present, apparently homozygous sequence variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

TEST SENSITIVITY
The sequencing approach used by GeneDx is expected to identify >99% of existing variants in RET gene. Constitutional variants in the coding region of the RET gene have been found in up to 50% of familial and10-35% of non-familial (isolated) HSCR. Patients with L-HSCR are more likely than patients with S-HSCR to have an identifiable RET variant. 76% of RET variants that have been reported in association with HSCR are located in the nine select exons listed above, and the remaining variants would be expected to be identified by sequencing of the rest of gene.[1,2] Rarely, deletions of the entire RET gene, which would be detected by ExonArrayDx analysis, have also been reported in association with Hirschsprung disease.[3,4] Additionally, partial deletions of the RET gene have been observed at GeneDx

REFERENCES
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