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Hirschsprung Disease Overview

[*Aganglionic Megacolon, HSCR*]

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Summary

Disease characteristics. Hirschsprung disease (HSCR), or congenital intestinal aganglionosis, is a birth defect characterized by complete absence of neuronal ganglion cells from a portion of the intestinal tract. The aganglionic segment includes the distal rectum and a variable length of contiguous proximal intestine. In 80% of individuals, aganglionosis is restricted to the rectosigmoid colon (short-segment disease); in 15%-20%, aganglionosis extends proximal to the sigmoid colon (long-segment disease); in about 5%, aganglionosis affects the entire large intestine (total colonic aganglionosis). Rarely, the aganglionosis extends into the small bowel or even more proximally to encompass the entire bowel (total intestinal aganglionosis). HSCR is considered a neurocristopathy, a disorder of cells and tissues derived from the neural crest, and may occur as an isolated finding or as part of a multisystem disorder. 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 until late childhood or adulthood, HSCR should be considered in anyone with lifelong severe constipation. Individuals with HSCR are at risk for enterocolitis and/or potentially lethal intestinal perforation.

Diagnosis/testing. The diagnosis of HSCR requires histopathologic demonstration of absence of enteric ganglion cells in the distal rectum. Suction biopsies of rectal mucosa and submucosa are the preferred diagnostic test in most centers because they can be performed safely without general anesthesia. Syndromes associated with HSCR are diagnosed by clinical findings, cytogenetic analysis, or in some cases, by specific molecular or biochemical tests. Isolated HSCR is a multigene disorder that has been associated with mutations in at least six different genes.

Management. Resection of the aganglionic segment and anastomosis of proximal bowel to the anus ("pull-through") is the standard treatment for HSCR. Individuals with extensive intestinal aganglionosis who develop irreversible intestinal failure may be candidates for intestinal transplantation.

Genetic counseling. Recurrence risk depends upon the underlying cause.

Definition

Clinical Manifestations

Hirschsprung disease (HSCR), or congenital intestinal aganglionosis, is a birth defect characterized by complete absence of neuronal ganglion cells from a portion of the intestinal

tract. The aganglionic segment includes the distal rectum and a variable length of contiguous proximal intestine.

- In 80% of individuals, aganglionosis is restricted to the rectosigmoid colon ("short-segment disease").
- In approximately 15%-20%, the aganglionosis extends proximal to the sigmoid colon (long-segment disease).
- In approximately 5% of individuals, aganglionosis affects the entire large intestine (total colonic aganglionosis).
- Rarely, the aganglionosis extends into the small bowel or even more proximally to encompass the entire bowel (total intestinal aganglionosis) [Badner et al 1990].

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 (50%-90% of newborns with HSCR), constipation, emesis, abdominal pain or distention, and occasionally diarrhea. However, initial diagnosis of HSCR later in childhood or in adulthood occurs frequently enough that HSCR should be considered if an individual reports lifelong severe constipation.

Individuals with HSCR are at risk for enterocolitis and/or potentially lethal intestinal perforation.

The incidence of short-segment disease (80% of HSCR) is four times greater in males than in females; equal numbers of males and females present with long-segment HSCR [Badner et al 1990].

Establishing the Diagnosis

The diagnosis of HSCR requires histopathologic demonstration of absence of enteric ganglion cells in the distal rectum. Suction biopsies of rectal mucosa and submucosa are the preferred diagnostic test in most centers because they can be performed safely without general anesthesia. Absence of ganglion cells in the submucosa of 50-75 sections examined from a biopsy establishes the diagnosis. Accessory findings include hypertrophic submucosal nerves and/or an abnormal acetylcholinesterase enzyme staining pattern [Kapur 1999].

The diagnosis may be supported by anorectal manometry, abdominal radiographs that show a dilated proximal colon with empty rectum, or barium enema studies that demonstrate delayed emptying time and a funnel-like transition zone between proximal dilated and distal constricted bowel [Amiel & Lyonnet 2001, de Lorijn et al 2005].

Although radiographic studies may be helpful in delineating the proximal extent of aganglionosis, intraoperative intestinal rectal biopsy is used to establish the precise boundary during surgical resection.

Differential Diagnosis

The following disorders should be readily distinguished from HSCR on the basis of other clinical signs, specific tests for those disorders, and a suction biopsy that does not show evidence of aganglionosis.

In newborns with evidence of intestinal obstruction, other possible causes include the following:

- Gastrointestinal malformations such as atresia, malrotation, or duplication

- Meconium ileus secondary to cystic fibrosis (see *CFTR*-related disorders)
- Conditions that cause ganglioneuromatosis, such as MEN 2B [Smith et al 1999]
- Conditions associated with abnormalities of the enteric nervous system or musculature, termed chronic intestinal pseudoobstruction [including intestinal neuronal dysplasia (IND)] [Kapur 2001]

Acquired forms of severe constipation/obstruction may be caused by maternal factors such as infection, alcohol ingestion, or congenital hypothyroidism [Amiel & Lyonnet 2001].

Prevalence

The incidence of HSCR is approximately one in 5000 live births [Badner et al 1990, Parisi & Kapur 2000].

The incidence varies among different ethnic groups, with 1.5, 2.1, and 2.8 per 10,000 live births in Caucasians, African Americans, and Asians, respectively [Torfs 1998]. Within the Mennonite population of Pennsylvania, a founder mutation in *EDNRB* accounts for a significant proportion of children with HSCR [Puffenberger et al 1994].

Causes

Chromosomal Causes

A chromosomal abnormality is present in approximately 12% of individuals with HSCR (Table 1) [Amiel & Lyonnet 2001].

The most common chromosomal abnormality associated with HSCR is Down syndrome (trisomy 21), which occurs in 2%-10% of all individuals with HSCR [Moore & Johnson 1998]. Although individuals with Down syndrome are at a hundred-fold higher risk for HSCR than the general population [Moore & Johnson 1998], none of the established "HSCR genes" reside on chromosome 21; thus the association between trisomy 21 and HSCR remains unexplained.

Other chromosomal aberrations include deletions that encompass HSCR-associated genes:

- del13q22 *(EDNRB*) Shanske et al 2001]
- del10q11.2 *(RET*) [Fewtrell et al 1994],
- del2q22 *(ZFHX1B*) [Lurie et al 1994, Mowat et al 1998, Amiel et al 2001] (see Table 1)

Identification of individuals with HSCR and such deletions aided in discovery of these genes, and reinforces the haploinsufficiency model of HSCR pathogenesis in individuals with a deletion of one of these genes.

Other chromosomal anomalies have been described in individuals with HSCR, but the relevant gene(s) of interest has/have not been identified.

Table 1. Chromosomal Abnormalities Associated with HSCR

Chromosomal Abnormality	Features	Chromosomal Locus (Gene Symbol)	% of Individuals with HSCR
Down Syndrome	MR, short stature, CHD, craniofacial	Trisomy 21	0.6%-3%
Deletion 10q	MR, hypotonia	del 10q11.2 *(RET)*	Unknown
Deletion 13q	MR, growth failure, craniofacial features	del 13q22 *(EDNRB)*	Unknown
Deletion 2q22	MR, microcephaly, craniofacial features, seizures	del 2q22 *(ZFHX1B)*	Unknown

CHD = congenital heart disease; MR = mental retardation

Single-Gene Causes

Monogenic disorders are those caused by mutation of a single gene and inherited in an autosomal dominant, autosomal recessive, or X-linked manner. Both syndromic and nonsyndromic causes of HSCR are recognized.

Syndromic HSCR —Syndromes associated with HSCR are listed in alphabetical order; the prevalence of HSCR in each syndrome varies widely and is estimated in Table 2.

Bardet-Biedl syndrome (BBS). BBS includes the features of progressive pigmentary retinopathy, obesity, postaxial polydactyly, hypogenitalism, and renal abnormalities, with variable but generally mild mental retardation. HSCR has been reported in approximately 2% of individuals with BBS [Beales et al 1999]. In approximately 10% of affected individuals, BBS overlaps with HSCR and McKusick-Kaufman syndrome (MKKS), which includes hydrometrocolpos and heart disease [Davenport et al 1989]. A total of 11 genes have been identified for BBS, including the *MKKS* that causes McKusick-Kaufman syndrome [Stone et al 2000]. Specific genotype-phenotype correlations with HSCR have not been established. Inheritance is autosomal recessive.

Cartilage-hair hypoplasia. This skeletal dysplasia, prevalent among the Old Order Amish and Finnish populations, is characterized by short-limbed dwarfism, sparse hair, hypoplastic anemia, and a variety of immune defects. HSCR occurs in roughly 7%-9%, and is more likely to be associated with severe manifestations of the disorder [Makitie & Kaitila 1993, Makitie et al 2001]. The causative gene is the endoribonuclease RNase MRP *(RMRP)*, important in processing of nuclear ribosomal RNA and in mitochondrial DNA synthesis [Ridanpaa et al 2001]. Inheritance is autosomal recessive.

Congenital central hypoventilation syndrome (CCHS). Classic CCHS is characterized by adequate ventilation while the affected individual is awake and by hypoventilation with normal respiratory rates and shallow breathing during sleep; more severely affected individuals hypoventilate when both awake and asleep. Both of these phenotypes present in the newborn period. Children with CCHS often have physiologic and anatomic manifestations of a generalized autonomic nervous system dysfunction, tumors of neural crest origin including neuroblastoma, ganglioneuroma, and ganglioneuroblastoma-altered development of neural crest-derived structures (i.e., Hirschsprung disease). Approximately 20% of individuals with CCHS have HSCR [Trang et al 2005], a combination known as Haddad syndrome.

De novo heterozygous mutations in *PHOX2B* have been found in 90% of individuals with CCHS [Amiel et al 2003, Matera et al 2004]. A subset of individuals with CCHS have a heterozygous mutation in *RET*, *EDN3*, *GDNF*, or *BDNF* (Table 3) [Bolk et al 1996, Amiel et

al 1998, Sakai et al 1998, Weese-Mayer et al 2002]. In one study, *RET* was shown to act as a modifier gene for the development of HSCR in persons with CCHS [de Pontual et al 2006].

Familial dysautonomia (FD, Riley-Day syndrome). FD affects the development and survival of sensory, sympathetic, and parasympathetic neurons. It is a debilitating disease present from birth. Progressive neuronal degeneration continues throughout life. Affected individuals have gastrointestinal dysfunction, vomiting episodes, recurrent pneumonia, altered sensitivity to pain and temperature, and cardiovascular instability. About 40% of affected individuals have autonomic crises. FD occurs with relatively high frequency within the Ashkenazi Jewish population (1:3700 live births). FD has been associated with HSCR in some individuals [Azizi et al 1984].

Inheritance is autosomal recessive. The causative gene *IKBKAP*, a molecule with an immune modulatory role [Anderson et al 2001, Slaugenhaupt et al 2001], maps to 9q31, the location for a presumed genetic modifier locus identified in several families with HSCR [Bolk et al 2000].

Fryns syndrome. Fryns syndrome is characterized by hypoplasia of the distal digits, coarse facial features, variable diaphragmatic hernia, and a variety of other anomalies of the cardiac, gastrointestinal, genitourinary, and central nervous systems [Slavotinek 2004]. At least six persons have had HSCR in addition to features of Fryns syndrome, suggesting that Fryns syndrome may represent a neurocristopathy, like HSCR [Alkuraya et al 2005]. Although a specific genetic etiology has not been identified for Fryns syndrome, inheritance is generally presumed to be autosomal recessive.

Goldberg-Shprintzen syndrome. This disorder shares many of the clinical features of Mowat-Wilson syndrome including microcepthaly, mental retardation, facial dysmorphism, and HSCR, but affected individuals may also have cleft palate and colocoma, and the condition is presumed to be inherited in an autosomal recessive manner on the basis of several affected sibling pairs [Goldberg & Shprintzen 1981, Hurst et al 1988, Brooks et al 1999]. Two families with features of microcephaly, mental retardation, generalized polymicrogyria, and variable HSCR were identified as having homozygous mutations in the *KIAA1279* gene, thereby suggesting that this is the Goldberg-Shprintzen gene [Brooks et al 2005].

Note: Goldberg-Shprintzen syndrome is distinct from the Shprintzen-Goldberg syndrome.

Intestinal neuronal dysplasia, type B (IND). IND is associated with severe symptoms of bowel obstruction and may be clinically indistinguishable from HSCR, although age of onset tends to be later (six months to six years) [Kapur 1999, Kapur 2001]. In contrast to HSCR, the pathologic findings include hyperplasia of enteric ganglia (vs absent ganglion cells in HSCR) and other features such as "giant ganglia" that many pathologists find controversial [Kapur 2003]. IND can be found in isolation or proximal to aganglionic bowel in approximately 20% of individuals with HSCR. Attempts to identify mutations in known HSCR-associated genes have been unsuccessful in at least one series of individuals with IND or mixed IND/HSCR [Gath et al 2001].

L1 syndrome Seven individuals with HSCR and X-linked aqueductal stenosis with documented mutations in *L1CAM* have been reported [Okamoto et al 1997, Vits et al 1998, Parisi et al 2002, Okamoto et al 2004, Basel-Vanagaite et al 2006]. No mutation was identified in *RET* in the one individual examined [Parisi et al 2002], although it is unknown whether mutations in other HSCR-associated genes may be implicated in the development of this condition. The association of hydrocephalus and HSCR suggests that the neuronal cell adhesion molecule, L1CAM, may be important for ganglion cell population of the gut. In addition, reduced *L1CAM* expression has been described in the extrinsic innervation of aganglionic gut

from individuals with HSCR [Ikawa et al 1997]. Although HSCR is documented as having a male predominance, *L1CAM* is the only X-linked gene identified in association with HSCR; however, in one series of males with HSCR, no pathogenic *L1CAM* mutations were identified [Hofstra et al 2002].

Mowat-Wilson syndrome (Hirschsprung disease - mental retardation syndrome). Clinical features include microcephaly, mental retardation, seizures, and distinctive facial features (ocular hypertelorism, broad eyebrows, saddle nose, small rotated ears with upturned lobes, and pointed chin) [Lurie et al 1994, Mowat et al 1998]. HSCR has been reported in 41%-71% of affected individuals depending on the series [Mowat et al 2003, Zweier et al 2003, Cerruti Mainardi et al 2004, Zweier et al 2005]. Many individuals also demonstrate short stature, ocular anomalies, agenesis of the corpus callosum, congenital heart defects, and/or genitourinary abnormalities. Mowat-Wilson syndrome is associated with deletions or heterozygous mutations in the *ZFHX1B* (zinc finger homeobox 1B) gene localized to 2q22 (see Table 1) [Amiel et al 2001, Cacheux et al 2001, Wakamatsu et al 2001].

Multiple endocrine neoplasia type 2 (MEN 2)

- **MEN 2A** is an autosomal dominant disorder characterized by neoplastic transformation of C cells in the thyroid (medullary thyroid carcinoma, MTC), parathyroid hyperplasia, and adrenal medullary tumors (pheochromocytoma). In familial MTC (FMTC), development of medullary thyroid cancer in at least four family members is observed, without the other manifestations of MEN 2A. In the majority of individuals and families with MEN 2A or FMTC, the disease is caused by a single base-pair substitution in one of five codons of the *RET* gene, which results in an amino acid substitution for a cysteine residue that confers constitutive activity by dimerization of the receptor [Eng et al 1996, Eng & Mulligan 1997, Sijmons et al 1998]. In some families with *RET* mutations in the cysteine codons 609, 611, 618, or 620, MEN 2A or FMTC is associated with HSCR [Sijmons et al 1998, Eng 1999, Hansford & Mulligan et al 2000], although in one series, this association was found in only 1% of individuals [Yip et al 2003].

  While most individuals with MEN 2A do not have aganglionosis, and vice versa, in some series an estimated 2.5%-5% of individuals with HSCR have a MEN 2A-associated *RET* mutation. As HSCR may be the initial finding in such individuals, molecular genetic testing could lead to recognition of *RET* mutations associated with MEN 2A and a cancer predisposition, with significant impact on care of the affected individual and family members [Amiel & Lyonnet 2001, Pakarinen et al 2005].

- **MEN 2B** manifests as diffuse ganglioneuromas of the alimentary canal, marfanoid skeletal abnormalities, MTC, and pheochromocytoma. A heterozygous mutation in *RET* (p.M918T) that alters its substrate specificity has been identified in more than 90% of individuals with MEN 2B. Individuals with MEN 2B may present in the newborn period with intestinal obstruction that clinically resembles HSCR but is caused by diffuse ganglioneuromatosis [Smith et al 1999]. Aside from one report of coincident HSCR in an individual with MEN 2B and the p.M918T mutation [Romeo et al 1998], the majority of these individuals do not have HSCR.

Neurofibromatosis 1 (NF1). NF1 is an autosomal dominant condition characterized by café-au-lait spots, skin-fold freckling, and neurofibromas, among other neuroectodermal features. Gastrointestinal involvement includes findings described as intestinal neuronal dysplasia with myenteric plexus hypertrophy [Saul et al 1982] as well as HSCR [Clausen et al 1989]. In one family, cosegregation of the NF1 and megacolon phenotypes was associated with inheritance of both an abnormal *NF1* allele from one parent and an abnormal *GDNF* allele from the other

parent [Bahuau et al 2001], thus reinforcing the role of multiple gene interactions in the development of HSCR.

Smith-Lemli-Opitz syndrome (SLOS). SLOS is characterized by microcephaly, congenital heart disease, growth and developmental delays, distinctive facial features, undermasculinization with hypospadias in males, and characteristically, syndactyly of toes two or three. HSCR has been described in several individuals with this disorder, generally with more severe manifestations [Curry et al 1987, Cass 1990], although mild phenotypes of SLOS may be associated with HSCR [Mueller et al 2003]. SLOS is caused by mutations in the gene encoding the enzyme that catalyzes the final step in cholesterol biosynthesis. Inheritance is autosomal recessive.

Waardenburg syndrome type 4 (WS4, Waardenburg-Shah syndrome). Clinical features include HSCR, sensorineural deafness, and pigmentary anomalies (e.g., heterochromic irides, piebaldism). Since melanocytes and the inner hair cells critical for cochlear function are both derived from neural crest cells, WS4 is considered a generalized neurocristopathy.

No evidence exists for *RET* mutations as a cause of WS4, although mutations in *EDN3*, *EDNRB*, and *SOX10* [SRY (sex-determining region Y)-box 10] have been reported in affected individuals. In general, WS4 results from homozygosity for *EDN3* or *EDNRB* mutant alleles, whereas heterozygotes exhibit isolated HSCR without the other features, although this correlation is not always straightforward [Edery et al 1996, Hofstra et al 1996, Syrris et al 1999]. In contrast, all the mutant *SOX10* alleles reported in individuals with WS4 to date have been *de novo* or inherited in an autosomal dominant manner [Pingault et al 1998, Southard-Smith et al 1999]. *SOX10* encodes a transcription factor that is expressed by hindbrain neural crest cells from the stage at which they leave the neural tube and throughout the colonization process [Bondurand et al 1998]. Defects in the *SOX10* gene have been reported in only a small number of individuals with HSCR, and in none with isolated HSCR [Sham et al 2001]. Some individuals with WS4 and *SOX10* mutations in the terminal exon exhibit the additional neurologic symptoms of peripheral neuropathy with central nervous system myelination abnormalities and developmental delays, termed PCWH (peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome, and HSCR) [Inoue et al 2000, Pingault et al 2000, Inoue et al 2004].

Table 2. Monogenic Syndromic Forms of HSCR

Syndrome	Features	Mode of Inheritance	Chromosomal Locus/ Gene Symbol	% with HSCR
Bardet-Biedl syndrome	Retinal dystrophy, obesity, MR, polydactyly, hypogenitalism, renal abnormalities	AR	At least 11 loci/genes	2%-10% [1]
Cartilage-hair hypoplasia	Short-limbed dwarfism, sparse hair, immune defects	AR	9p21-p12/ *RMRP*	7%-9%
CCHS	Hypoxia, reduced ventilatory drive, neuroblastoma	Variable	4p12/ *PHOX2B* 10q11.2/ *RET* 5p13.1-p12/ *GDNF* 20q13.2-q13.3/ *EDN3* 11p13/ *BDNF*	20%
Familial dysautonomia (Riley-Day syndrome)	Sensory and autonomic dysfunction (including abnormal sweat, tear, and saliva production)	AR	9q31/ *IKBKAP*	Unknown
Fryns syndrome	Distal digital hypoplasia, diaphragmatic hernia, CHD, craniofacial, MR	AR	Unknown	Unknown
Goldberg-Shprintzen syndrome	Craniofacial, microcephaly, MR, PMG	AR	10q22.1/ *KIAA1279* Others?	Common
Intestinal neuronal dysplasia	Abnormal intestinal innervation with giant ganglia	Unknown	Unknown	≤20% [1]
L1 syndrome	MR, hydrocephalus, ACC, adducted thumbs	XLR	Xq28/ *L1CAM*	Rare
MEN 2A/FMTC	MTC, pheo, hyperpara-thyroidism [2]	AD	10q11.2/ *RET*	≤1%
MEN 2B	MTC, pheo, mucosal and intestinal neuromas, skeletal abnormalities, corneal changes	AD	10q11.2/ *RET*	Rare
Mowat-Wilson syndrome	MTC, pheo, mucosal and intestinal neuromas, skeletal abnormalities, corneal changes	AD	10q11.2/ *RET*	Rare
Neurofibromatosis 1	Café-au-lait macules, neurofibromas, Lisch nodules	AD	17q11.2/ *NF1*, 5p13.1-p12/ *GDNF?*	Unknown
Smith-Lemli-Opitz syndrome	MR, hypospadias, 2/3 syndactyly, CHD, craniofacial	AR	11q12-q13/ *DHCR7*	Unknown
Waardenburg syndrome type 4 (Waardenburg-Shah syndrome)	Pigmentary abnormalities, deafness	AR (usually)	13q22/ *EDNRB* 20q13.2-q13.3/ *EDN3*	Common
		AD	22q13/ *SOX10*	Almost 100%

MR = mental retardation; CHD = congenital heart disease; PMG = polymicrogyria; AD = autosomal dominant; AR = autosomal recessive; XLR = X-linked recessive; pheo = pheochromocytoma; MTC = medullary thyroid carcinoma; *DHCR7* = 7-dehydrocholesterol reductase; ACC = agenesis of the corpus callosum; *ZFHX1B* = zinc finger homeobox protein 1b; *RMRP* = RNAse mitochondrial RNA processing; *BDNF* = brain-derived neurotrophic factor; *L1CAM* = neural cell adhesion molecule L1; *NF1* = neurofibromin; CCHS = congenital central hypoventilation syndrome; MEN = multiple endocrine neoplasia

1. Limited data are available.
2. In FMTC, affected individuals do not have pheochromocytoma or hyperparathyroidism.

Nonsyndromic HSCR—Nonsyndromic HSCR (in which HSCR occurs without other anomalies) has been associated with mutations in at least six genes [Wartiovaara et al 1998, Kapur 1999, Parisi & Kapur 2000] (Table 3).

Table 3. Genes Associated with Nonsyndromic HSCR

Gene Symbol	Protein Name	Chromosomal Locus	Inheritance	Frequency	Type of HSCR	Syndromic? [1]
RET OMIM	Proto-oncogene tyrosine-protein kinase receptor; ret	10q11.2	AD	17%-38%	Short segment	Yes
				70%-80%	Long segment [2]	
				50%	Familial	
				3%-10% [3]	Simplex	
GDNF [4] OMIM	Glial cell line-derived neutrotrophic factor	5p13.1-p12	AD	<1% [5]	Variable	Yes
NRTN [4] OMIM	Neurturin	19p13.3	AD	<1% [5]	Variable	Unknown
EDNRB OMIM	Endothelin B receptor	13q22	AD/AR	3%-7%	Variable	Yes [6]
EDN3 OMIM	Endothelin-3	20q13.2-q13.3	AD/AR	5%	Variable	Yes [6]
ECE1 OMIM	Endothelin -converting enzyme [1]	1p36.1	AD [5]	<1% [5]	Variable	Unknown

1. Mutations in the gene have also been reported with syndromic forms of HSCR (see Table 2).
2. Homozygous mutations have been associated with total colonic aganglionosis in some cases.
3. *RET* mutations are reported to be higher (10%-35%) in simplex HSCR (HSCR in a single family member) in some referral series (see text).
4. A mutation in this gene is insufficient by itself to cause disease in most cases (see text).
5. Limited data are available.
6. The syndromic form is usually associated with homozygous mutations in this gene.

The genes associated with isolated HSCR fall into two major groups:

Genes for RET and its ligands. The tyrosine kinase receptor, RET (proto-oncogene tyrosine-protein kinase receptor; **re**arranged during **t**ransfection), is expressed by enteric neural precursors shortly after they leave the neural plate and throughout their colonization of the entire gut. GDNF (glial cell line-derived neurotrophic factor) and NRTN (or NTN; neurturin) are two of the ligands for RET expressed by adjacent mesenchymal cells. Although coreceptors for RET and its ligands exist, testing for mutations in the specific coreceptor associated with GDNF (GFR alpha-1) has not revealed any causative mutations in humans [Myers et al 1999].

Mutations in *RET* appear to be dominant loss-of-function mutations with incomplete penetrance and variable expressivity.

RET mutations alone are estimated to account for 7%-41% of all individuals with HSCR and 70%-80% of those with long-segment disease [Angrist et al 1995, Seri et al 1997, Sancandi et al 2000]. Homozygous *RET* mutations have been associated with total colonic aganglionosis in some individuals [Inoue et al 2000, Shimotake et al 2001].

RET is implicated in up to 50% of all familial HSCR [Attie et al 1995, Hofstra et al 2000]. The involvement of *RET* has been estimated to occur in 10%-35% of simplex cases of HSCR (i.e., HSCR in a single family member) in several referral series, which may be biased toward more severe or familial cases [Angrist et al 1995, Attie et al 1995, Eng & Mulligan 1997]; in the few population-based series reported, the incidence is 3%-10% [Svensson et al 1999, Borrego et al 2000, Sancandi et al 2000].

The penetrance of *RET* mutations is approximately 50%-70% [Bolk et al 2000]. Several candidate loci that may be responsible for the incomplete penetrance and variable expressivity observed in individuals with *RET* mutations have already been identified [Bolk et al 2000, Gabriel et al 2002].

Common polymorphisms in *RET* that do not cause amino acid changes appear to be over-represented within a population of individuals with HSCR [Borrego et al 1999, Fitze et al 1999, Borrego et al 2000], adding further complexity to the task of determining if a sequence variant is a disease-causing mutation. In addition, specific *RET* haplotypes, including polymorphisms in promoter elements and 5' introns, may also modify the risk of developing HSCR based on differences in RET protein expression, even in the absence of a pathogenic *RET* gene mutation [Fitze, Appelt et al 2003; Fitze, Schierz et al 2003; Sancandi et al 2003; Burzynski et al 2005; Lantieri et al 2006]. Specific RET promoter single nucleotide polymorphisms that decrease transcription may predispose to the development of HSCR in some populations [Garcia-Barcelo et al 2005], and one enhancer variant with differential effects in males and females may explain the increased occurrence in males, at least in part [Emison et al 2005].

Mutations in *GDNF* and *NRTN* have been identified in only a small minority of individuals with HSCR, and in almost all of those individuals, a mutation was also identified in *RET* or another HSCR gene, suggesting that mutation in one of the ligands is not sufficient by itself to cause disease [Angrist et al 1996, Hofstra et al 1996, Ivanchuk et al 1996, Salomon et al 1996, Doray et al 1998, Eketjall & Ibanez 2002].

***EDNRB* and related genes.** Components of another cell signaling pathway that probably interacts with the RET pathway during enteric neural crest-colonization have been implicated in HSCR [Carrasquillo et al 2002]; these include the endothelin receptor type B *(EDNRB*) and its ligand, endothelin-3 *(EDN3*). Synthesis of the mature active form of endothelin-3 requires post-translational modification by endothelin-converting enzyme 1 (encoded by *ECE1*). *EDNRB* and *EDN3* mutations probably account for approximately 10% of individuals with HSCR [Amiel et al 1996, Kusafuka et al 1996, Svensson et al 1999]. Within the Mennonite community, however, a significant proportion of affected individuals have a missense mutation in the *EDNRB* gene, representing a founder mutation, and some of these individuals have manifestations of Waardenburg syndrome type 4 (WS4) [Puffenberger et al 1994]. In general, individuals with a heterozygous mutation in *EDNRB* or *EDN3* present with HSCR or occasionally features of WS4, while those with homozygous mutations in either gene are more likely to have more severe manifestations of WS4 [Verheij et al 2002]. A mutation in *ECE1* has been reported in only one individual, who also had craniofacial anomalies and a heart defect [Hofstra et al 1999].

Unknown Cause

Approximately 18% of individuals with HSCR have at least one other congenital anomaly [Amiel & Lyonnet 2001]. The association of HSCR with other birth defects is often part of a recognized syndrome resulting from abnormalities in other neural crest derivatives (see Table 2). Often, a specific syndrome cannot be identified (Table 4).

Some of the most frequent anomalies include congenital heart defects (up to 5% of individuals with HSCR, excluding those with Down syndrome), gastrointestinal malformations (including Meckel diverticulum, malrotation, and imperforate anus, with an incidence of up to 4% of individuals with HSCR), central nervous system abnormalities (a broad spectrum of disorders, in up to 4%), and genitourinary abnormalities (including cryptorchidism, hypospadias, and renal malformations, in up to 7%). Craniofacial abnormalities and spina bifida have also been

seen in association with HSCR [Badner et al 1990, Ryan et al 1992, Sarioglu et al 1997, Parisi & Kapur 2000, Amiel & Lyonnet 2001].

Table 4. HSCR with Congenital Anomalies of Unknown Cause

Anomaly	Features	Mode of Inheritance	Genetic Locus/Gene	% in HSCR [1]
Central nervous system	MR, Dandy-Walker malformation, microcephaly	Unknown	Unknown	3.6%-3.9%
Congenital heart disease	ASD, VSD, PDA, tetralogy of Fallot	Unknown	Unknown	2.3%-4.8%
Gastrointestinal	Malrotation, imperforate anus, Meckel diverticulum, sacral-rectal fistula	Unknown	Unknown	3.3%-3.9%
Genitourinary	Cryptorchidism, inguinal hernia, hypospadias, kidney malformations, urethral fistula	Unknown	Unknown	5.6%-7.3%

MR = mental retardation; ASD = atrial septal defect; VSD= ventricular septal defect; PDA = patent ductus arteriosus

1. Incidence figures are derived from Badner et al 1990, Ryan et al 1992, and Sarioglu et al 1997 and exclude cases of Down syndrome. For these associations, the final column represents the % of individuals with HSCR who also have at least one congenital anomaly within this category.

Evaluation Strategy

Identification of the cause of HSCR aids in establishing prognosis and mode of inheritance for genetic counseling.

To help establish the cause of HSCR, the work-up for an individual with HSCR includes the following:

- Physical examination to identify findings that could establish the diagnosis of monogenic syndromic HSCR
- A detailed family history with emphasis on infants with signs of intestinal obstruction and its complications and adults with chronic constipation
- If monogenic causes seem unlikely and if multiple anomalies, growth failure, and/or developmental delay are present, a chromosome analysis of blood that examines at least 20 metaphases at the 550 band level or greater should be performed.

  Note: Chromosome analysis of the parents is recommended only if the proband has an abnormal karyotype (other than trisomy 21).
- If monogenic nonsyndromic HSCR is confirmed or likely, molecular genetic testing of the *RET* gene should be considered. HSCR-associated mutations have been described in each of the 20 *RET* exons and no single specific defect is particularly common. In addition, because of incomplete penetrance of mutant alleles, it is difficult to predict the phenotypic effect of a given sequence change. In some circumstances (e.g., a family with highly penetrant, long-segment HSCR) *RET* molecular genetic testing may be helpful in providing genetic counseling. Some groups recommend testing for the MEN2-associated mutations in *RET* in all individuals with HSCR (see MEN2).

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

If a proband is found to have an inherited or *de novo* chromosome abnormality, a specific syndrome associated with HSCR (see Table 2), or a disease-causing mutation in the *RET* gene (see Evaluation Strategy), counseling for that condition is indicated. In probands with nonsyndromic HSCR without a clear etiology, HSCR is considered to be a polygenic disorder with incomplete penetrance, variable expressivity, and a 4:1 predominance in males.

Risk to Family Members — Nonsyndromic HSCR

Parents of a proband

- Nonsyndromic autosomal dominant HSCR
  - In a significant proportion of affected individuals for whom family studies are available, a mutation identified in a proband has also been identified in a completely unaffected parent.
  - In a few documented cases, the presence of two mutations in different HSCR-related genes in a proband were proposed to be causative of disease, and each parent contributed a single mutant allele (presumably representing digenic inheritance) [Angrist et al 1996, Hofstra et al 1996, Salomon et al 1996, Hofstra et al 2000].
  - A proband with nonsyndromic autosomal dominant HSCR may have the disorder as the result of a *de novo* gene mutation. The proportion of cases caused by *de novo* disease-causing mutations is unknown.
  - Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include physical examination, a detailed medical history with emphasis on signs of intestinal obstruction as an infant and/or chronic constipation, and molecular genetic testing.

    Note: Many individuals diagnosed with nonsyndromic autosomal dominant HSCR have an unaffected parent with the disease-causing mutation; the family history often appears to be negative because of incomplete penetrance and variable expressivity.
- Nonsyndromic HSCR of unknown etiology: empiric risks
  - The parents of probands with nonsyndromic HSCR of unknown etiology are likely to be unaffected.

Sibs of a proband

- Nonsyndromic autosomal dominant HSCR
  - The risk to the sibs of the proband with nonsyndromic autosomal dominant HSCR depends upon the genetic status of the proband's parents.
  - If a parent of the proband is affected and/or has the disease-causing mutation, the risk to the sibs of inheriting the mutation is 50%. Because of incomplete penetrance and variable expressivity, it is not possible to predict if the child will have clinical HSCR.
- Nonsyndromic HSCR of unknown etiology: empiric risks
  - The overall risk to sibs of a proband is 4% (vs 0.02%, the incidence of HSCR in the general population) [Badner et al 1990].

- The risk is higher to sibs of probands with long-segment disease and depends on the sex of the proband and sib (Table 5).
- The risk to sibs of probands with short-segment disease is lower and more consistent with the risks associated with a recessive or multifactorial pattern of inheritance (Table 5).

Table 5. Recurrence Risk for HSCR in Sibs Based on Length of Involved Segment

		Risk to sib for HSCR when the proband has:	
Proband	**Sib**	**Long-segment HSCR**	**Short-segment HSCR**
Male	Male	17%	5%
	Female	13%	1%
Female	Male	33%	5%
	Female	9%	3%

Based on Badner et al 1990

Offspring of a proband

- Nonsyndromic autosomal dominant HSCR
  - Each child of an individual with nonsyndromic autosomal dominant HSCR has a 50% chance of inheriting the mutation.
  - Because of incomplete penetrance, the offspring who inherits a mutant allele may not develop symptoms of HSCR, and for those who do develop HSCR, the degree of severity cannot be predicted.
- Nonsyndromic HSCR of unknown etiology: empiric risks
  - Offspring of a proband with nonsyndromic HSCR of unknown etiology are at increased risk of having HSCR; however, precise estimates are not available.

Other family members of a proband. The risk to other family members depends upon the genetic status of the proband's parents. If a parent is found to be affected, his or her family members may be at risk.

Related Genetic Counseling Issues

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which molecular genetic testing is available on a research basis only or the sensitivity of currently available testing is less than 100%. See DNA banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk for HSCR caused by a *RET* mutation is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed. Because of incomplete penetrance and variable expressivity, it is not possible to predict if the fetus will develop clinical HSCR.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

No laboratories offering molecular genetic testing for prenatal diagnosis for nonsyndromic autosomal dominant HSCR caused by mutations in other genes are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutation has been identified in an affected family member. For laboratories offering custom prenatal testing, see Testing.

Requests for prenatal testing for conditions such as nonsyndromic HSCR are not common since a fetus identified as having a potential disease-causing mutation may never develop symptoms of HSCR. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member. For laboratories offering PGD, see Testing.

Management

Treatment of Manifestations

Resection of the aganglionic segment and anastomosis of proximal bowel to the anus ("pull-through") is the standard treatment for HSCR and can be performed as a single procedure or in stages. A variety of surgical anastomoses have been developed with the general goal of eliminating obstruction while preserving continence.

An effort is generally made to resect a variable length of gut just proximal to the aganglionic zone since this transitional area may have altered pathologic properties (e.g., hypoganglionosis) and physiologic properties that are not conducive to normal intestinal motility [Coran & Teitelbaum 2000]. However, persistent intestinal dysmotility (usually constipation but sometimes diarrhea) after a pull-through procedure occurs frequently and may reflect an underlying abnormality of ganglionic gut that is not understood [Engum & Grosfeld 2004]. Hirschsprung-associated enterocolitis can be a post-surgical complication with significant morbidity [Engum & Grosfeld 2004].

Individuals with extensive intestinal aganglionosis who develop irreversible intestinal failure may be candidates for intestinal transplantation [Bond & Reyes 2004].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

International Foundation for Functional Gastrointestinal Disorders (IFFGD) - Pediatric
Phone: 888-964-2001

Email: aanastas@iffgd.org
www.aboutkidsgi.org

International Foundation for Functional Gastrointestinal Disorders (IFFGD)
PO Box 170864
Milwaukee WI 53217-8076
Phone: 888-964-2001; 414-964-1799
Fax: 414-964-7176
Email: iffgd@iffgd.org
www.iffgd.org

Pull-thru Network
2312 Savoy Street
Hoover AL 35226
Phone: 205-978-2930
Email: info@pullthrought.org
www.pullthrough.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Alkuraya FS, Lin AE, Irons MB, Kimonis VE. Fryns syndrome with Hirschsprung disease: support for possible neural crest involvement. Am J Med Genet A. 2005;132:226–30. [PubMed: 15580636]

Amiel J, Attie T, Jan D, Pelet A, Edery P, Bidaud C, Lacombe D, Tam P, Simeoni J, Flori E, Nihoul-Fekete C, Munnich A, Lyonnet S. Heterozygous endothelin receptor B (EDNRB) mutations in isolated Hirschsprung disease. Hum Mol Genet. 1996;5:355–7. [PubMed: 8852660]

Amiel J, Espinosa-Parrilla Y, Steffann J, Gosset P, Pelet A, Prieur M, Boute O, Choiset A, Lacombe D, Philip N, Le Merrer M, Tanaka H, Till M, Touraine R, Toutain A, Vekemans M, Munnich A, Lyonnet S. Large-scale deletions and SMADIP1 truncating mutations in syndromic Hirschsprung disease with involvement of midline structures. Am J Hum Genet. 2001;69:1370–7. [PubMed: 11595972]

Amiel J, Laudier B, Attie-Bitach T, Trang H, de Pontual L, Gener B, Trochet D, Etchevers H, Ray P, Simonneau M, Vekemans M, Munnich A, Gaultier C, Lyonnet S. Polyalanine expansion and frameshift mutations of the paired-like homeobox gene PHOX2B in congenital central hypoventilation syndrome. Nat Genet. 2003;33:459–61. [PubMed: 12640453]

Amiel J, Lyonnet S. Hirschsprung disease, associated syndromes, and genetics: a review. J Med Genet. 2001;38:729–39. [PubMed: 11694544]

Amiel J, Salomon R, Attie T, Pelet A, Trang H, Mokhtari M, Gaultier C, Munnich A, Lyonnet S. Mutations of the RET-GDNF signaling pathway in Ondine's curse. Am J Hum Genet. 1998;62:715–7. [PubMed: 9497256]

Anderson SL, Coli R, Daly IW, Kichula EA, Rork MJ, Volpi SA, Ekstein J, Rubin BY. Familial dysautonomia is caused by mutations of the IKAP gene. Am J Hum Genet. 2001;68:753–8. [PubMed: 11179021]

Angrist M, Bolk S, Halushka M, Lapchak PA, Chakravarti A. Germline mutations in glial cell line-derived neurotrophic factor (GDNF) and RET in a Hirschsprung disease patient. Nat Genet. 1996;14:341–4. [PubMed: 8896568]

Angrist M, Bolk S, Thiel B, Puffenberger EG, Hofstra RM, Buys CH, Cass DT, Chakravarti A. Mutation analysis of the RET receptor tyrosine kinase in Hirschsprung disease. Hum Mol Genet. 1995;4:821–30. [PubMed: 7633441]

Attie T, Pelet A, Edery P, Eng C, Mulligan LM, Amiel J, Boutrand L, Beldjord C, Nihoul-Fekete C, Munnich A, et al. Diversity of RET proto-oncogene mutations in familial and sporadic Hirschsprung disease. Hum Mol Genet. 1995;4:1381–6. [PubMed: 7581377]

Azizi E, Berlowitz I, Vinograd I, Reif R, Mundel G. Congenital megacolon associated with familial dysautonomia. Eur J Pediatr. 1984;142:68–9. [PubMed: 6714264]

Badner JA, Sieber WK, Garver KL, Chakravarti A. A genetic study of Hirschsprung disease. Am J Hum Genet. 1990;46:568–80. [PubMed: 2309705]

Bahuau M, Pelet A, Vidaud D, Lamireau T, LeBail B, Munnich A, Vidaud M, Lyonnet S, Lacombe D. GDNF as a candidate modifier in a type 1 neurofibromatosis (NF1) enteric phenotype. J Med Genet. 2001;38:638–43. [PubMed: 11565554]

Basel-Vanagaite L, Straussberg R, Friez MJ, Inbar D, Korenreich L, Shohat M, Schwartz CE. Expanding the phenotypic spectrum of L1CAM-associated disease. Clin Genet. 2006;69:414–9. [PubMed: 16650080]

Beales PL, Elcioglu N, Woolf AS, Parker D, Flinter FA. New criteria for improved diagnosis of Bardet-Biedl syndrome: results of a population survey. J Med Genet. 1999;36:437–46. [PubMed: 10874630]

Bolk S, Angrist M, Xie J, Yanagisawa M, Silvestri JM, Weese-Mayer DE, Chakravarti A. Endothelin-3 frameshift mutation in congenital central hypoventilation syndrome. Nat Genet. 1996;13:395–6. [PubMed: 8696331]

Bolk S, Pelet A, Hofstra RM, Angrist M, Salomon R, Croaker D, Buys CH, Lyonnet S, Chakravarti A. A human model for multigenic inheritance: phenotypic expression in Hirschsprung disease requires both the RET gene and a new 9q31 locus. Proc Natl Acad Sci U S A. 2000;97:268–73. [PubMed: 10618407]

Bond GJ, Reyes JD. Intestinal transplantation for total/near-total aganglionosis and intestinal pseudo-obstruction. Semin Pediatr Surg. 2004;13:286–92. [PubMed: 15660322]

Bondurand N, Kobetz A, Pingault V, Lemort N, Encha-Razavi F, Couly G, Goerich DE, Wegner M, Abitbol M, Goossens M. Expression of the SOX10 gene during human development. FEBS Lett. 1998;432:168–72. [PubMed: 9720918]

Borrego S, Ruiz A, Saez ME, Gimm O, Gao X, Lopez-Alonso M, Hernandez A, Wright FA, Antinolo G, Eng C. RET genotypes comprising specific haplotypes of polymorphic variants predispose to isolated Hirschsprung disease. J Med Genet. 2000;37:572–8. [PubMed: 10922382]

Borrego S, Saez ME, Ruiz A, Gimm O, Lopez-Alonso M, Antinolo G, Eng C. Specific polymorphisms in the RET proto-oncogene are over-represented in patients with Hirschsprung disease and may represent loci modifying phenotypic expression. J Med Genet. 1999;36:771–4. [PubMed: 10528857]

Brooks AS, Bertoli-Avella AM, Burzynski GM, Breedveld GJ, Osinga J, Boven LG, Hurst JA, Mancini GM, Lequin MH, de Coo RF, Matera I, de Graaff E, Meijers C, Willems PJ, Tibboel D, Oostra BA, Hofstra RM. Homozygous nonsense mutations in KIAA1279 are associated with malformations of the central and enteric nervous systems. Am J Hum Genet. 2005;77:120–6. [PubMed: 15883926]

Brooks AS, Breuning MH, Osinga J, vd Smagt JJ, Catsman CE, Buys CH, Meijers C, Hofstra RM. A consanguineous family with Hirschsprung disease, microcephaly, and mental retardation (Goldberg-Shprintzen syndrome). J Med Genet. 1999;36:485–9. [PubMed: 10874640]

Burzynski GM, Nolte IM, Bronda A, Bos KK, Osinga J, Plaza Menacho I, Twigt B, Maas S, Brooks AS, Verheij JB, Buys CH, Hofstra RM. Identifying candidate Hirschsprung disease-associated RET variants. Am J Hum Genet. 2005;76:850–8. [PubMed: 15759212]

Cacheux V, Dastot-Le Moal F, Kaariainen H, Bondurand N, Rintala R, Boissier B, Wilson M, Mowat D, Goossens M. Loss-of-function mutations in SIP1 Smad interacting protein 1 result in a syndromic Hirschsprung disease. Hum Mol Genet. 2001;10:1503–10. [PubMed: 11448942]

Carrasquillo MM, McCallion AS, Puffenberger EG, Kashuk CS, Nouri N, Chakravarti A. Genome-wide association study and mouse model identify interaction between RET and EDNRB pathways in Hirschsprung disease. Nat Genet. 2002;32:237–44. [PubMed: 12355085]

Cass D. Aganglionosis: associated anomalies. J Paediatr Child Health. 1990;26:351–4. [PubMed: 2149988]

Cerruti Mainardi P, Pastore G, Zweier C, Rauch A. Mowat-Wilson syndrome and mutation in the zinc finger homeo box 1B gene: a well defined clinical entity. J Med Genet. 2004;41:e16. [PubMed: 14757866]

Clausen N, Andersson P, Tommerup N. Familial occurrence of neuroblastoma, von Recklinghausen's neurofibromatosis, Hirschsprung's agangliosis and jaw-winking syndrome. Acta Paediatr Scand. 1989;78:736–41. [PubMed: 2512759]

Coran AG, Teitelbaum DH. Recent advances in the management of Hirschsprung's disease. Am J Surg. 2000;180:382–7. [PubMed: 11137692]

Curry CJ, Carey JC, Holland JS, Chopra D, Fineman R, Golabi M, Sherman S, Pagon RA, Allanson J, Shulman S, et al. Smith-Lemli-Opitz syndrome-type II: multiple congenital anomalies with male pseudohermaphroditism and frequent early lethality. Am J Med Genet. 1987;26:45–57. [PubMed: 3812577]

Davenport M, Taitz LS, Dickson JA. The Kaufman-McKusick syndrome: another association. J Pediatr Surg. 1989;24:1192–4. [PubMed: 2681663]

De Lorijn F, Reitsma JB, Voskuijl WP, Aronson DC, Ten Kate FJ, Smets AM, Taminiau JA, Benninga MA. Diagnosis of Hirschsprung's disease: a prospective, comparative accuracy study of common tests. J Pediatr. 2005;146:787–92. [PubMed: 15973319]

de Pontual L, Pelet A, Trochet D, Jaubert F, Espinosa-Parrilla Y, Munnich A, Brunet JF, Goridis C, Feingold J, Lyonnet S, Amiel J. Mutations of the RET gene in isolated and syndromic Hirschsprung's disease in human disclose major and modifier alleles at a single locus. J Med Genet. 2006;43:419–23. [PubMed: 16443855]

Doray B, Salomon R, Amiel J, Pelet A, Touraine R, Billaud M, Attie T, Bachy B, Munnich A, Lyonnet S. Mutation of the RET ligand, neurturin, supports multigenic inheritance in Hirschsprung disease. Hum Mol Genet. 1998;7:1449–52. [PubMed: 9700200]

Edery P, Attie T, Amiel J, Pelet A, Eng C, Hofstra RM, Martelli H, Bidaud C, Munnich A, Lyonnet S. Mutation of the endothelin-3 gene in the Waardenburg-Hirschsprung disease (Shah-Waardenburg syndrome). Nat Genet. 1996;12:442–4. [PubMed: 8630502]

Eketjall S, Ibanez CF. Functional characterization of mutations in the GDNF gene of patients with Hirschsprung disease. Hum Mol Genet. 2002;11:325–9. [PubMed: 11823451]

Emison ES, McCallion AS, Kashuk CS, Bush RT, Grice E, Lin S, Portnoy ME, Cutler DJ, Green ED, Chakravarti A. A common sex-dependent mutation in a RET enhancer underlies Hirschsprung disease risk. Nature. 2005;434:857–63. [PubMed: 15829955]

Eng C. RET proto-oncogene in the development of human cancer. J Clin Oncol. 1999;17:380–93. [PubMed: 10458257]

Eng C, Clayton D, Schuffenecker I, Lenoir G, Cote G, Gagel RF, van Amstel HK, Lips CJ, Nishisho I, Takai SI, Marsh DJ, Robinson BG, Frank-Raue K, Raue F, Xue F, Noll WW, Romei C, Pacini F, Fink M, Niederle B, Zedenius J, Nordenskjold M, Komminoth P, Hendy GN, Mulligan LM, et al. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2. International RET mutation consortium analysis. JAMA. 1996;276:1575–9. [PubMed: 8918855]

Eng C, Mulligan LM. Mutations of the RET proto-oncogene in the multiple endocrine neoplasia type 2 syndromes, related sporadic tumours, and hirschsprung disease. Hum Mutat. 1997;9:97–109. [PubMed: 9067749]

Engum SA, Grosfeld JL. Long-term results of treatment of Hirschsprung's disease. Semin Pediatr Surg. 2004;13:273–85. [PubMed: 15660321]

Fewtrell MS, Tam PK, Thomson AH, Fitchett M, Currie J, Huson SM, Mulligan LM. Hirschsprung's disease associated with a deletion of chromosome 10 (q11.2q21.2): a further link with the neurocristopathies? J Med Genet. 1994;31:325–7. [PubMed: 7915329]

Fitze G, Appelt H, Konig IR, Gorgens H, Stein U, Walther W, Gossen M, Schreiber M, Ziegler A, Roesner D, Schackert HK. Functional haplotypes of the RET proto-oncogene promoter are associated with Hirschsprung disease (HSCR). Hum Mol Genet. 2003;12:3207–14. [PubMed: 14600022]

Fitze G, Schierz M, Kuhlisch E, Schreiber M, Ziegler A, Roesner D, Schackert HK. Novel intronic polymorphisms in the RET proto-oncogene and their association with Hirschsprung disease. Hum Mutat. 2003;22:177. [PubMed: 12872262]

Fitze G, Schreiber M, Kuhlisch E, Schackert HK, Roesner D. Association of RET protooncogene codon 45 polymorphism with Hirschsprung disease. Am J Hum Genet. 1999;65:1469–73. [PubMed: 10521317]

Gabriel SB, Salomon R, Pelet A, Angrist M, Amiel J, Fornage M, Attie-Bitach T, Olson JM, Hofstra R, Buys C, Steffann J, Munnich A, Lyonnet S, Chakravarti A. Segregation at three loci explains familial and population risk in Hirschsprung disease. Nat Genet. 2002;31:89–93. [PubMed: 11953745]

Garcia-Barcelo M, Ganster RW, Lui VC, Leon TY, So MT, Lau AM, Fu M, Sham MH, Knight J, Zannini MS, Sham PC, Tam PK. TTF-1 and RET promoter SNPs: regulation of RET transcription in Hirschsprung's disease. Hum Mol Genet. 2005;14:191–204. [PubMed: 15548547]

Gath R, Goessling A, Keller KM, Koletzko S, Coerdt W, Muntefering H, Wirth S, Hofstra RM, Mulligan L, Eng C, von Deimling A. Analysis of the RET, GDNF, EDN3, and EDNRB genes in patients with intestinal neuronal dysplasia and Hirschsprung disease. Gut. 2001;48:671–5. [PubMed: 11302967]

Goldberg RB, Shprintzen RJ. Hirschsprung megacolon and cleft palate in two sibs. J Craniofac Genet Dev Biol. 1981;1:185–9. [PubMed: 7338549]

Hansford JR, Mulligan LM. Multiple endocrine neoplasia type 2 and RET: from neoplasia to neurogenesis. J Med Genet. 2000;37:817–27. [PubMed: 11073534]

Hofstra RM, Elfferich P, Osinga J, Verlind E, Fransen E, Lopez Pison J, de Die-Smulders CE, Stolte-Dijkstra I, Buys CH. Hirschsprung disease and L1CAM: is the disturbed sex ratio caused by L1CAM mutations? J Med Genet. 2002;39:E11.

Hofstra RM, Osinga J, Tan-Sindhunata G, Wu Y, Kamsteeg EJ, Stulp RP, van Ravenswaaij-Arts C, Majoor-Krakauer D, Angrist M, Chakravarti A, Meijers C, Buys CH. A homozygous mutation in the endothelin-3 gene associated with a combined Waardenburg type 2 and Hirschsprung phenotype (Shah- Waardenburg syndrome). Nat Genet. 1996;12:445–7. [PubMed: 8630503]

Hofstra RM, Valdenaire O, Arch E, Osinga J, Kroes H, Loffler BM, Hamosh A, Meijers C, Buys CH. A loss-of-function mutation in the endothelin-converting enzyme 1 (ECE- 1) associated with Hirschsprung disease, cardiac defects, and autonomic dysfunction. Am J Hum Genet. 1999;64:304–8. [PubMed: 9915973]

Hofstra RM, Wu Y, Stulp RP, Elfferich P, Osinga J, Maas SM, Siderius L, Brooks AS, vd Ende JJ, Heydendael VM, Severijnen RS, Bax KM, Meijers C, Buys CH. RET and GDNF gene scanning in Hirschsprung patients using two dual denaturing gel systems. Hum Mutat. 2000;15:418–29. [PubMed: 10790203]

Hurst JA, Markiewicz M, Kumar D, Brett EM. Unknown syndrome: Hirschsprung's disease, microcephaly, and iris coloboma: a new syndrome of defective neuronal migration. J Med Genet. 1988;25:494–7. [PubMed: 3172144]

Ikawa H, Kawano H, Takeda Y, Masuyama H, Watanabe K, Endo M, Yokoyama J, Kitajima M, Uyemura K, Kawamura K. Impaired expression of neural cell adhesion molecule L1 in the extrinsic nerve fibers in Hirschsprung's disease. J Pediatr Surg. 1997;32:542–5. [PubMed: 9126750]

Inoue K, Khajavi M, Ohyama T, Hirabayashi S, Wilson J, Reggin JD, Mancias P, Butler IJ, Wilkinson MF, Wegner M, Lupski JR. Molecular mechanism for distinct neurological phenotypes conveyed by allelic truncating mutations. Nat Genet. 2004;36:361–9.

Inoue K, Shimotake T, Iwai N. Mutational analysis of RET/GDNF/NTN genes in children with total colonic aganglionosis with small bowel involvement. Am J Med Genet. 2000;93:278–84. [PubMed: 10946353]

Ivanchuk SM, Myers SM, Eng C, Mulligan LM. De novo mutation of GDNF, ligand for the RET/GDNFR-alpha receptor complex, in Hirschsprung disease. Hum Mol Genet. 1996;5:2023–6. [PubMed: 8968758]

Kapur RP. Neuropathology of paediatric chronic intestinal pseudo-obstruction and related animal models. J Pathol. 2001;194:277–88. [PubMed: 11439358]

Kapur RP. Hirschsprung disease and other enteric dysganglionoses. Crit Rev Clin Lab Sci. 1999;36:225–73. [PubMed: 10407683]

Kapur RP. Neuronal dysplasia: a controversial pathological correlate of intestinal pseudo-obstruction. Am J Med Genet. 2003;122A:287–93. [PubMed: 14518065]

Kusafuka T, Wang Y, Puri P. Novel mutations of the endothelin-B receptor gene in isolated patients with Hirschsprung's disease. Hum Mol Genet. 1996;5:347–9. [PubMed: 8852658]

Lantieri F, Griseri P, Ceccherini I. Molecular mechanisms of RET-induced Hirschsprung pathogenesis. Ann Med. 2006;38:11–9.

Lurie IW, Supovitz KR, Rosenblum-Vos LS, Wulfsberg EA. Phenotypic variability of del(2) (q22-q23): report of a case with a review of the literature. Genet Couns. 1994;5:11–4. [PubMed: 8031530]

Makitie O, Kaitila I. Cartilage-hair hypoplasia--clinical manifestations in 108 Finnish patients. Eur J Pediatr. 1993;152:211–7. [PubMed: 8444246]

Makitie O, Kaitila I, Rintala R. Hirschsprung disease associated with severe cartilage-hair hypoplasia. J Pediatr. 2001;138:929–31. [PubMed: 11391344]

Matera I, Bachetti T, Puppo F, Di Duca M, Morandi F, Casiraghi GM, Cilio MR, Hennekam R, Hofstra R, Schober JG, Ravazzolo R, Ottonello G, Ceccherini I. PHOX2B mutations and polyalanine expansions correlate with the severity of the respiratory phenotype and associated symptoms in both congenital and late onset Central Hypoventilation syndrome. J Med Genet. 2004;41:373–80.

Moore SW, Johnson AG. Hirschsprung's disease: genetic and functional associations of Down's and Waardenburg syndromes. Semin Pediatr Surg. 1998;7:156–61. [PubMed: 9718653]

Mowat DR, Croaker GD, Cass DT, Kerr BA, Chaitow J, Ades LC, Chia NL, Wilson MJ. Hirschsprung disease, microcephaly, mental retardation, and characteristic facial features: delineation of a new syndrome and identification of a locus at chromosome 2q22-q23. J Med Genet. 1998;35:617–23. [PubMed: 9719364]

Mowat DR, Wilson MJ, Goossens M. Mowat-Wilson syndrome. J Med Genet. 2003;40:305–10. [PubMed: 12746390]

Mueller C, Patel S, Irons M, Antshel K, Salen G, Tint GS, Bay C. Normal cognition and behavior in a Smith-Lemli-Opitz syndrome patient who presented with Hirschsprung disease. Am J Med Genet. 2003;123A:100–6. [PubMed: 14556255]

Myers SM, Salomon R, Goessling A, Pelet A, Eng C, von Deimling A, Lyonnet S, Mulligan LM. Investigation of germline GFR alpha-1 mutations in Hirschsprung disease. J Med Genet. 1999;36:217–20. [PubMed: 10204848]

Okamoto N, Del Maestro R, Valero R, Monros E, Poo P, Kanemura Y, Yamasaki M. Hydrocephalus and Hirschsprung's disease with a mutation of L1CAM. J Hum Genet. 2004;49:334–7.

Okamoto N, Wada Y, Goto M. Hydrocephalus and Hirschsprung's disease in a patient with a mutation of L1CAM. J Med Genet. 1997;34:670–1. [PubMed: 9279760]

Pakarinen MP, Rintala RJ, Koivusalo A, Heikkinen M, Lindahl H, Pukkala E. Increased incidence of medullary thyroid carcinoma in patients treated for Hirschsprung's disease. J Pediatr Surg. 2005;40:1532–4. [PubMed: 16226978]

Parisi MA, Kapur RP. Genetics of Hirschsprung disease. Curr Opin Pediatr. 2000;12:610–7. [PubMed: 11106284]

Parisi MA, Kapur RP, Neilson I, Hofstra RM, Holloway LW, Michaelis RC, Leppig KA. Hydrocephalus and intestinal aganglionosis: is L1CAM a modifier gene in Hirschsprung disease? Am J Med Genet. 2002;108:51–6. [PubMed: 11857550]

Pingault V, Bondurand N, Kuhlbrodt K, Goerich DE, Prehu MO, Puliti A, Herbarth B, Hermans-Borgmeyer I, Legius E, Matthijs G, Amiel J, Lyonnet S, Ceccherini I, Romeo G, Smith JC, Read AP, Wegner M, Goossens M. SOX10 mutations in patients with Waardenburg-Hirschsprung disease. Nat Genet. 1998;18:171–3. [PubMed: 9462749]

Pingault V, Guiochon-Mantel A, Bondurand N, Faure C, Lacroix C, Lyonnet S, Goossens M, Landrieu P. Peripheral neuropathy with hypomyelination, chronic intestinal pseudo- obstruction and deafness: a developmental "neural crest syndrome" related to a SOX10 mutation. Ann Neurol. 2000;48:671–6. [PubMed: 11026454]

Puffenberger EG, Hosoda K, Washington SS, Nakao K, deWit D, Yanagisawa M, Chakravart A. A missense mutation of the endothelin-B receptor gene in multigenic Hirschsprung's disease. Cell. 1994;79:1257–66. [PubMed: 8001158]

Ridanpaa M, van Eenennaam H, Pelin K, Chadwick R, Johnson C, Yuan B, vanVenrooij W, Pruijn G, Salmela R, Rockas S, Makitie O, Kaitila I, de la Chapelle A. Mutations in the RNA component of RNase MRP cause a pleiotropic human disease, cartilage-hair hypoplasia. Cell. 2001;104:195–203. [PubMed: 11207361]

Romeo G, Ceccherini I, Celli J, Priolo M, Betsos N, Bonardi G, Seri M, Yin L, Lerone M, Jasonni V, Martucciello G. Association of multiple endocrine neoplasia type 2 and Hirschsprung disease. J Intern Med. 1998;243:515–20. [PubMed: 9681852]

Ryan ET, Ecker JL, Christakis NA, Folkman J. Hirschsprung's disease: associated abnormalities and demography. J Pediatr Surg. 1992;27:76–81. [PubMed: 1552451]

Sakai T, Wakizaka A, Matsuda H, Nirasawa Y, Itoh Y. Point mutation in exon 12 of the receptor tyrosine kinase proto- oncogene RET in Ondine-Hirschsprung syndrome. Pediatrics. 1998;101:924–6. [PubMed: 9565426]

Salomon R, Attie T, Pelet A, Bidaud C, Eng C, Amiel J, Sarnacki S, Goulet O, Ricour C, Nihoul-Fekete C, Munnich A, Lyonnet S. Germline mutations of the RET ligand GDNF are not sufficient to cause Hirschsprung disease. Nat Genet. 1996;14:345–7. [PubMed: 8896569]

Sancandi M, Ceccherini I, Costa M, Fava M, Chen B, Wu Y, Hofstra R, Laurie T, Griffths M, Burge D, Tam PKH. Incidence of RET mutations in patients with Hirschsprung's disease. J Pediatr Surg. 2000;35:139–43. [PubMed: 10646792]

Sancandi M, Griseri P, Pesce B, Patrone G, Puppo F, Lerone M, Martucciello G, Romeo G, Ravazzolo R, Devoto M, Ceccherini I. Single nucleotide polymorphic alleles in the 5' region of the RET proto-oncogene define a risk haplotype in Hirschsprung's disease. J Med Genet. 2003;40:714–8. [PubMed: 12960220]

Sarioglu A, Tanyel FC, Buyukpamukcu N, Hicsonmez A. Hirschsprung-associated congenital anomalies. Eur J Pediatr Surg. 1997;7:331–7. [PubMed: 9493983]

Saul RA, Sturner RA, Burger PC. Hyperplasia of the myenteric plexus. Its association with early infantile megacolon and neurofibromatosis. Am J Dis Child. 1982;136:852–4. [PubMed: 6810692]

Seri M, Yin L, Barone V, Bolino A, Celli I, Bocciardi R, Pasini B, Ceccherini I, Lerone M, Kristoffersson U, Larsson LT, Casasa JM, Cass DT, Abramowicz MJ, Vanderwinden JM, Kravcenkiene I, Baric I, Silengo M, Martucciello G, Romeo G. Frequency of RET mutations in Hum Mutat. 1997;9:243–9. [PubMed: 9090527]

Sham MH, Lui VC, Fu M, Chen B, Tam PK. SOX10 is abnormally expressed in aganglionic bowel of Hirschsprung's disease infants. Gut. 2001;49:220–6. [PubMed: 11454798]

Shanske A, Ferreira JC, Leonard JC, Fuller P, Marion RW. Hirschsprung disease in an infant with a contiguous gene syndrome of chromosome 13. Am J Med Genet. 2001;102:231–6. [PubMed: 11484199]

Shimotake T, Go S, Inoue K, Tomiyama H, Iwai N. A homozygous missense mutation in the tyrosine E kinase domain of the RET proto-oncogene in an infant with total intestinal aganglionosis. Am J Gastroenterol. 2001;96:1286–91. [PubMed: 11316186]

Sijmons RH, Hofstra RM, Wijburg FA, Links TP, Zwierstra RP, Vermey A, Aronson DC, Tan-Sindhunata G, Brouwers-Smalbraak GJ, Maas SM, Buys CH. Oncological implications of RET gene mutations in Hirschsprung's disease. Gut. 1998;43:542–7. [PubMed: 9824583]

Slaugenhaupt SA, Blumenfeld A, Gill SP, Leyne M, Mull J, Cuajungco MP, Liebert CB, Chadwick B, Idelson M, Reznik L, Robbins C, Makalowska I, Brownstein M, Krappmann D, Scheidereit C, Maayan C, Axelrod FB, Gusella JF. Tissue-specific expression of a splicing mutation in the IKBKAP gene causes familial dysautonomia. Am J Hum Genet. 2001;68:598–605. [PubMed: 11179008]

Slavotinek AM. Fryns syndrome: a review of the phenotype and diagnostic guidelines. Am J Med Genet A. 2004;124:427–33. [PubMed: 14735597]

Smith VV, Eng C, Milla PJ. Intestinal ganglioneuromatosis and multiple endocrine neoplasia type 2B: implications for treatment. Gut. 1999;45:143–6. [PubMed: 10369718]

Southard-Smith EM, Angrist M, Ellison JS, Agarwala R, Baxevanis AD, Chakravarti A, Pavan WJ. The Sox10(Dom) mouse: modeling the genetic variation of Waardenburg- Shah (WS4) syndrome. Genome Res. 1999;9:215–25. [PubMed: 10077527]

Stone DL, Slavotinek A, Bouffard GG, Banerjee-Basu S, Baxevanis AD, Barr M, Biesecker LG. Mutation of a gene encoding a putative chaperonin causes McKusick- Kaufman syndrome. Nat Genet. 2000;25:79–82. [PubMed: 10802661]

Svensson PJ, Von Tell D, Molander ML, Anvret M, Nordenskjold A. A heterozygous frameshift mutation in the endothelin-3 (EDN-3) gene in isolated Hirschsprung's disease. Pediatr Res. 1999;45:714–7. [PubMed: 10231870]

Syrris P, Carter ND, Patton MA. Novel nonsense mutation of the endothelin-B receptor gene in a family with Waardenburg-Hirschsprung disease. Am J Med Genet. 1999;87:69–71. [PubMed: 10528251]

Torfs C. An epidemiological study of Hirschsprung disease in a multiracial California population. The Third International Meeting: Hirschsprung disease and related neurocristopathies. 1998

Trang H, Dehan M, Beaufils F, Zaccaria I, Amiel J, Gaultier C. The French Congenital Central Hypoventilation Syndrome Registry: general data, phenotype, and genotype. Chest. 2005;127:72–9. [PubMed: 15653965]

Verheij JB, Kunze J, Osinga J, van Essen AJ, Hofstra RM. ABCD syndrome is caused by a homozygous mutation in the EDNRB gene. Am J Med Genet. 2002;108:223–5. [PubMed: 11891690]

Vits L, Chitayat D, Van Camp G, Holden JJ, Fransen E, Willems PJ. Evidence for somatic and germline mosaicism in CRASH syndrome. Hum Mutat Suppl. 1998;1:S284–7. [PubMed: 9452110]

Wartiovaara K, Salo M, Sariola H. Hirschsprung's disease genes and the development of the enteric nervous system. Ann Med. 1998;30:66–74. [PubMed: 9556091]

Wakamatsu N, Yamada Y, Yamada K, Ono T, Nomura N, Taniguchi H, Kitoh H, Mutoh N, Yamanaka T, Mushiake K, Kato K, Sonta S, Nagaya M. Mutations in SIP1, encoding Smad interacting protein-1, cause a form of Hirschsprung disease. Nat Genet. 2001;27:369–70. [PubMed: 11279515]

Weese-Mayer DE, Bolk S, Silvestri JM, Chakravarti A. Idiopathic congenital central hypoventilation syndrome: evaluation of brain-derived neurotrophic factor genomic DNA sequence variation. Am J Med Genet. 2002;107:306–10. [PubMed: 11840487]

Yip L, Cote GJ, Shapiro SE, Ayers GD, Herzog CE, Sellin RV, Sherman SI, Gagel RF, Lee JE, Evans DB. Multiple endocrine neoplasia type 2: evaluation of the genotype-phenotype relationship. Arch Surg. 2003;138:409–16. [PubMed: 12686527]

Zweier C, Temple IK, Beemer F, Zackai E, Lerman-Sagie T, Weschke B, Anderson CE, Rauch A. Characterisation of deletions of the ZFHX1B region and genotype-phenotype analysis in Mowat-Wilson syndrome. J Med Genet. 2003;40:601–5. [PubMed: 12920073]

Zweier C, Thiel CT, Dufke A, Crow YJ, Meinecke P, Suri M, Ala-Mello S, Beemer F, Bernasconi S, Bianchi P, Bier A, Devriendt K, Dimitrov B, Firth H, Gallagher RC, Garavelli L, Gillessen-Kaesbach G, Hudgins L, Kaariainen H, Karstens S, Krantz I, Mannhardt A, Medne L, Mucke J, Kibaek M, Krogh LN, Peippo M, Rittinger O, Schulz S, Schelley SL, Temple IK, Dennis NR, Van der Knaap MS, Wheeler P, Yerushalmi B, Zenker M, Seidel H, Lachmeijer A, Prescott T, Kraus C, Lowry RB, Rauch A. Clinical and mutational spectrum of Mowat-Wilson syndrome. Eur J Med Genet. 2005;48:97–111. [PubMed: 16053902]

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