U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Parisi MA. Hirschsprung Disease Overview – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY. 2002 Jul 12 [Updated 2015 Oct 1]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Hirschsprung Disease Overview – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonyms: Aganglionic Megacolon, HSCR

Melissa A Parisi, MD, PhD[1]

Created: July 12, 2002; Updated: October 1, 2015.

Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical 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.

Author Affiliation: 1 Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland; Email: parisima@mail.nih.gov.

Isolated HSCR (i.e., HSCR in the absence of related systemic findings) is a disorder associated with pathogenic variants in a number of genes.

Genetic counseling

Recurrence risk depends on the underlying cause.

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. Individuals with extensive intestinal aganglionosis who develop irreversible intestinal failure may be candidates for intestinal transplantation.

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]. For an example, see *ACTG2*-Related Disorders.

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 5,000 live births [Badner et al 1990, Parisi & Kapur 2000]. The incidence varies among different ethnic groups [Torfs 1998]:

- Persons of northern European origin: 1.5 in 10,000 live births
- African Americans: 2.1 in 10,000
- Asians: 2.8 in 10,000

Within the Mennonite population of Pennsylvania, a founder variant in *EDNRB* accounts for a significant proportion of children with HSCR [Puffenberger et al 1994].

Causes

Chromosomal Causes

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

The most common chromosome abnormality associated with HSCR is Down syndrome (trisomy 21), which occurs in 2%-10% of all individuals with HSCR [Moore & Johnson 1998]. Conversely, approximately 0.6%-3% of individuals with Down syndrome have HSCR [Burkardt et al 2014].

Some chromosome aberrations include deletions that encompass HSCR-associated genes:

- del13q22 (*EDNRB*) [Shanske et al 2001]
- del10q11.2 (*RET*) [Fewtrell et al 1994]
- del10q23.1 (*NRG3*) [Tang et al 2012b]
- del2q22 (*ZEB2*) [Lurie et al 1994, Mowat et al 1998, Amiel et al 2001]
- del 4p12 (*PHOX2B*) [Benailly et al 2003] (see Table 1)

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

Other chromosome anomalies (del 17q21/dup 17q21-q23 [Amiel et al 2008]; see Table 1) have been described in individuals with HSCR; the associated gene(s) have not been identified.

Table 1. Chromosome Abnormalities Associated with HSCR

Chromosome Abnormality	Features	Chromosome Locus (Gene)	% of Individuals w/ HSCR
Down syndrome	ID, short stature, CHD, craniofacial features	Trisomy 21	0.6%-3%
Deletion 10q11	ID, hypotonia	del10q11.2 *(RET)*	Unknown
Deletion 10q23	Mostly isolated HSCR; one w/ rectocutaneous fistula	del10q23.1 *(NRG3)*	Unknown
Deletion 13q	ID, growth failure, craniofacial features	del13q22 *(EDNRB)*	Unknown
Deletion 2q22	ID, microcephaly, craniofacial features, seizures	del2q22 *(ZEB2)*	Unknown
Deletion 4p12-p13	ID, short stature, craniofacial features	del4p12 *(PHOX2B)*	Unknown
Deletions/duplications 17q21	ID, multiple congenital anomalies	del17q21/dup17q21-q23 (unknown)	Unknown

CHD = congenital heart disease; ID = intellectual disability

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 alphabetic order; the prevalence of HSCR in each syndrome varies widely and is estimated in Table 2.

Bardet-Biedl syndrome (BBS) includes the features of progressive pigmentary retinopathy, obesity, postaxial polydactyly, hypogenitalism, and renal abnormalities, with variable but generally mild intellectual disability. 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 19 genes have been identified for BBS, including *MKKS*, pathogenic variants in which cause 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 [Mäkitie & Kaitila 1993, Mäkitie et al 2001]. The gene in which mutation is causative is the endoribonuclease RNase MRP (*RMRP*), important in processing of nuclear ribosomal RNA and in mitochondrial DNA synthesis [Ridanpää 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 pathogenic variants 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 variant 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) 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 (1:3,700 live births). FD has been associated with HSCR in some individuals [Azizi et al 1984].

Inheritance is autosomal recessive. The involved gene, *ELP1* (*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 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 (like HSCR) represent a neurocristopathy [Alkuraya et al 2005]. One report noted that three of 11 individuals with Fryns syndrome who had survived the neonatal period had HSCR [Dentici et al 2009]. Although a specific genetic etiology has not been identified for Fryns syndrome, inheritance is generally presumed to be autosomal recessive.

Goldberg-Shprintzen syndrome shares many of the clinical features of Mowat-Wilson syndrome including microcephaly, intellectual disability, facial dysmorphism, and HSCR, but affected individuals may also have cleft palate and coloboma, and the condition is presumed to be inherited in an autosomal recessive manner on the basis of several affected sib pairs [Goldberg & Shprintzen 1981, Hurst et al 1988, Brooks et al 1999]. Two families with features of microcephaly, intellectual disability, generalized polymicrogyria, and variable HSCR were identified as having homozygous variants in *KIFBP* (*KIAA1279*), thereby suggesting that mutation of *KIFBP* encoding KIF-binding protein (KBP) may cause Goldberg-Shprintzen syndrome [Brooks et al 2005]. This finding was confirmed in several additional families with Goldberg-Shprintzen syndrome [Drévillon et al 2013].

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

Intestinal neuronal dysplasia, type B (IND) is associated with severe symptoms of bowel obstruction and may be clinically indistinguishable from HSCR, although age of onset tends to be later (6 months to 6 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 pathogenic variants in known HSCR-associated genes have been unsuccessful in several series of individuals with IND or mixed IND/HSCR [Gath et al 2001, Tou et al 2006].

L1 syndrome. Several individuals with HSCR and X-linked aqueductal stenosis with documented pathogenic variants 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, Nakakimura et al 2008]. No pathogenic variant was identified in *RET* in the one individual examined [Parisi et al 2002]; it is unknown whether mutation of other HSCR-associated genes is

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 *L1CAM* pathogenic variants were identified [Hofstra et al 2002].

Mowat-Wilson syndrome (Hirschsprung disease - intellectual disability syndrome). Clinical features include microcephaly, intellectual disability, seizures, and distinctive facial features including 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 pathogenic variants in *ZEB2* (zinc finger homeobox 1B) 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 *RET*, 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* pathogenic variants 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 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* pathogenic variant. As HSCR may be the initial finding in such individuals, molecular genetic testing could lead to recognition of *RET* pathogenic variants 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 pathogenic variant in *RET* (p.Met918Thr) 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.Met918Thr pathogenic variant [Romeo et al 1998], these individuals do not generally have HSCR.

Neurofibromatosis 1 (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.

Pitt-Hopkins syndrome (PTHS) is characterized by intellectual disability, distinctive facial features, seizures, and respiratory abnormalities (hyperventilation/breath-holding). Although only one affected individual has been reported with HSCR [Peippo et al 2006], severe constipation is a common finding. Haploinsufficiency for *TCF4* has been implicated in this condition, and the known role of this protein in the PHOX-RET pathway provides a clinical explanation for the features of hyperventilation and constipation/HSCR, similar to CCHS [Zweier et al 2007].

Smith-Lemli-Opitz syndrome (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 pathogenic variants in *DHCR7*, 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 for *RET* pathogenic variants as a cause of WS4 exists, although pathogenic variants 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* pathogenic variants, whereas heterozygotes exhibit isolated HSCR without the other features. However, this correlation is not always straightforward [Edery et al 1996, Hofstra et al 1996, Syrris et al 1999].

In contrast, all the pathogenic *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]. Defects in *SOX10* 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* pathogenic variants 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]. Of note, *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].

Table 2. Monogenic Syndromic Forms of HSCR

Syndrome	Features	MOI	Chromosome Locus [1] / Gene	% w/HSCR
Bardet-Biedl syndrome	Retinal dystrophy, obesity, ID, polydactyly, hypogenitalism, renal abnormalities	AR	≥14 loci / genes	2%-10% [2]
Cartilage-hair hypoplasia-anauxetic dysplasia spectrum disorders	Short-limbed dwarfism, sparse hair, immune defects	AR	9p13.3 / *RMRP*	7%-9%
Congenital central hypoventilation syndrome (CCHS)	Hypoxia, reduced ventilatory drive, neuroblastoma	Variable	4p13 / *PHOX2B* 10q11.21 / *RET* 5p13.2 / *GDNF* 20q13.32 / *EDN3* 11p14.1 / *BDNF*	20%

Table 2. continued from previous page.

Syndrome	Features	MOI	Chromosome Locus [1] / Gene	% w/HSCR
Familial dysautonomia (Riley-Day syndrome)	Sensory & autonomic dysfunction (incl abnormal sweat, tear, & saliva production)	AR	9q31.3 / *ELP1* (*IKBKAP*)	Unknown
Fryns syndrome	Distal digital hypoplasia, diaphragmatic hernia, CHD, craniofacial, ID	AR	Unknown	Unknown
Goldberg-Shprintzen syndrome	Craniofacial, microcephaly, ID, PMG	AR	10q22.1 / *KIFBP* (*KIAA1279*) Others?	Common
Intestinal neuronal dysplasia	Abnormal intestinal innervation with giant ganglia	Unknown	Unknown	≤20% [2]
L1 syndrome	ID, hydrocephalus, ACC, adducted thumbs	XLR	Xq28 / *L1CAM*	Rare
MEN 2A/FMTC	MTC, pheo, hyperparathyroidism [3]	AD	10q11.21 / *RET*	≤1%
MEN 2B	MTC, pheo, mucosal & intestinal neuromas, skeletal abnormalities, corneal changes	AD	10q11.21 / *RET*	Rare
Mowat-Wilson syndrome	ID, microcephaly, craniofacial, CHD, ACC, epilepsy, short stature	AD	2q22.3 / *ZEB2*	41%-71%
Neurofibromatosis 1	Café au lait macules, neurofibromas, Lisch nodules	AD	17q11.2 / *NF1* 5p13.2 / *GDNF?*	Unknown
Pitt-Hopkins syndrome	Craniofacial, ID, seizures hyperventilation, hypoventilation, constipation	AD	18q21.2 / *TCF4*	Unknown
Smith-Lemli-Opitz syndrome	ID, hypospadias, 2/3 syndactyly, CHD, craniofacial	AR	11q13.4 / *DHCR7*	Unknown
Waardenburg syndrome type 4 (Waardenburg-Shah syndrome)	Pigmentary abnormalities, deafness	AR (usually)	13q22.3 / *EDNRB* 20q13.32 / *EDN3*	Common
		AD	22q13.1 / *SOX10*	Almost 100%

ACC = agenesis of the corpus callosum; AD = autosomal dominant; AR = autosomal recessive; *BDNF* = brain-derived neurotrophic factor; CCHS = congenital central hypoventilation syndrome; CHD = congenital heart disease; *DHCR7* = 7-dehydrocholesterol reductase; ID = intellectual disability; *L1CAM* = neural cell adhesion molecule L1; MEN = multiple endocrine neoplasia; MOI = mode of inheritance; MTC = medullary thyroid carcinoma; *NF1* = neurofibromin; pheo = pheochromocytoma; PMG = polymicrogyria; *RMRP* = RNAse mitochondrial RNA processing; XLR = X-linked recessive; *ZEB2* = zinc finger E-box binding homeobox 2

1. Chromosome locus from OMIM

2. Limited data are available.

3. 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 pathogenic variants in a number of genes [Wartiovaara et al 1998, Kapur 1999, Parisi & Kapur 2000, Amiel et al 2008] (Table 3). The genes associated with isolated HSCR fall into four major groups: *RET* and its ligands *GDNF* and *NRTN; EDNRB* and the related genes *EDN3* and *ECE1*; the NRG signaling pathway (*NRG1* and *NRG3*); and the *SEMA* signaling pathway (*SEMA3C and SEMA3D*). Click here (pdf) for more information on genes associated with isolated HSCR.

Table 3. Genes Associated with Nonsyndromic HSCR

Gene / OMIM	Protein	Chromosome Locus [1]	MOI	Frequency	Type of HSCR	Syndromic? [2]
RET [3] / 164761	Proto-oncogene tyrosine-protein kinase receptor ret	10q11.21	AD	17%-38%	Short segment	Yes
				70%-80%	Long segment [4]	
				50%	Familial	
				3%-10% [5]	Simplex	
GDNF [6] / 600837	Glial cell line-derived neutrotrophic factor	5p13.2	AD	<1% [7]	Variable	Yes
NRTN [6] / 602018	Neurturin	19p13.3	AD	<1% [7]	Variable	Unknown
EDNRB / 131244	Endothelin B receptor	13q22.3	AD/AR	3%-7%	Variable	Yes [8]
EDN3 / 131242	Endothelin-3	20q13.32	AD/AR	5%	Variable	Yes [8]
ECE1 [6] / 600423	Endothelin-converting enzyme	1p36.12	AD	<1% [7]	Variable	Unknown
NRG1 [9] / 142445	Neuregulin 1	8p12	AD	<1% [7]	Variable	No [10]
NRG3 [11] / 605533	Neuregulin 3	10q23.1	AD	<1% [7]	Short segment	No [12]
SEMA3C / 602645	Semaphorin 3C	7q21.11	AD	<5% [13]	Short segment	No
SEMA3D / 609907	Semaphorin 3D	7q21.11	AD	<5% [13]	Short segment	No

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

1. Chromosome locus from OMIM

2. Pathogenic variants in the gene have also been reported with syndromic forms of HSCR (see Table 2).

3. In addition to clearly pathogenic *RET* variants that cause HSCR, additional benign variants in *RET* (which may not be causative in themselves) confer increased susceptibility to HSCR. One such variant, found in almost 80% of individuals with HSCR, is associated with simplex cases (i.e., a single occurrence in a family), male gender, and short- or long-segment HSCR (but not total colonic aganglionosis). Click here (pdf) for further details.

4. Homozygous pathogenic variants have been associated with total colonic aganglionosis in some cases.

5. RET pathogenic variants are reported to be higher (10%-35%) in simplex cases with HSCR (i.e., a single occurrence in a family) in some referral series Click here (pdf) for further details.

6. A variant in this gene is insufficient by itself to cause disease in most cases Click here (pdf) for further details.

7. Limited data are available.

8. The syndromic form is usually associated with homozygous pathogenic variants in this gene.

9. Although rare coding pathogenic variants in *NRG1* have been identified in this gene [Tang et al 2012a], benign *NRG1* variants in conjunction with *RET* variants also infer increased susceptibility to HSCR, especially in the Chinese population [Garcia-Barcelo et al 2009].

10. Most pathogenic variants are associated with nonsyndromic forms of HSCR; however, because a few individuals are reported to have other anomalies this form of HSCR may also be syndromic.

11. Copy number variants (mostly deletions) in this gene have also been implicated in HSCR. Most reported deletions have been intragenic rather than large copy number variants [Tang et al 2012b].

12. One individual had a rectocutaneous fistula.

13. Variants in *SEMA3C* and *SEMA3D* predicted to be deleterious had a combined frequency of 4.7% in one survey of individuals with short-segment HSCR [Jiang et al 2015].

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 (≤5% of individuals with HSCR, excluding those with Down syndrome), gastrointestinal malformations (including Meckel diverticulum, malrotation, and imperforate anus, with an incidence of ≤4% of individuals with HSCR), central nervous system abnormalities (a broad spectrum of disorders, in ≤4%), and genitourinary abnormalities (including cryptorchidism, hypospadias, and renal malformations, in ≤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	ID, 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%

ASD = atrial septal defect; ID = intellectual disability; PDA = patent ductus arteriosus; VSD= ventricular septal defect
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 Hirschsprung disease (HSCR) aids in establishing prognosis and mode of inheritance for genetic counseling.

To help establish the cause of HSCR, the workup for an individual with HSCR includes the following:

- **A detailed family history** with emphasis on infants with signs of intestinal obstruction and its complications and adults with chronic constipation
- **Physical examination** to identify findings that could:
  - Establish the diagnosis of monogenic syndromic HSCR (Table 2)
  - Suggest monogenic nonsyndromic HSCR (Table 3)
- **Molecular genetic testing.** Approaches can include single-gene testing, chromosome microarray analysis (CMA), use of a multigene panel, and more comprehensive genomic testing. Note: If the proband has an abnormal finding testing of parents is recommended to help establish recurrence risks. An algorithm for genetic testing has been proposed [Panza et al 2012], but universally accepted guidelines have not been established; moreover, the reduced penetrance of HSCR-associated pathogenic variants complicates the interpretation of genetic test results.

- **Single-gene testing** can be used to confirm a diagnosis of suspected monogenic disorder that is syndromic (Table 2) or nonsyndromic (Table 3).

  For monogenic nonsyndromic HSCR, molecular genetic testing of *RET* should be considered.

  Some groups recommend testing for *RET* pathogenic variants associated with MEN2 link in all individuals with HSCR.

  If a *RET* pathogenic variant is not identified, molecular genetic testing of *EDN3* and/or *EDNRB* may be considered.

- **Chromosome microarray analysis (CMA).** If monogenic causes seem unlikely and if multiple anomalies, growth failure, and/or developmental delay is present, chromosome microarray analysis (CMA) should be considered to identify cryptic rearrangements (Table 1).

- **A multigene panel** that includes some of the genes known to cause HSCR and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **More comprehensive genomic testing** (when available) including exome sequencing, mitochondrial sequencing, and genome sequencing may be considered if serial single-gene testing (and/or use of a multigene panel) fails to confirm a diagnosis in an individual with features of HSCR.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

If a proband has an inherited or *de novo* chromosome abnormality, a specific syndrome associated with HSCR (see Table 2), or a pathogenic variant in *RET*, *EDN3*, or *EDNRB* (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 reduced penetrance, variable expressivity, and a 4:1 predominance in males.

Risk to Family Members – Nonsyndromic HSCR

Parents of a proband

- Nonsyndromic autosomal dominant HSCR
  - A significant proportion of affected individuals have inherited a pathogenic variant from an unaffected parent, a finding that presumably can be attributed to reduced penetrance and variable expressivity.
  - In a few documented cases, affected individuals inherited two (likely pathogenic) variants in different HSCR-related genes, one variant from each parent (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* pathogenic variant. The proportion of cases caused by a *de novo* pathogenic variant is unknown.
  - Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant 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.
- Nonsyndromic HSCR of unknown etiology: empiric risks
  - The parents of a proband 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 on the genetic status of the proband's parents.
  - If a parent of the proband is affected and/or has the pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%. Because of reduced penetrance, sibs who inherit a pathogenic variant may not develop manifestations of HSCR, and for those who do develop HSCR, the degree of severity cannot be predicted.
- 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

Proband	Sib	Risk to Sib for HSCR When the Proband Has:	
		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 pathogenic variant.
    - Because of reduced penetrance, the offspring who inherits a pathogenic variant 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 on the genetic status of the proband's parents.
- If a parent is affected, his or her family members may be at risk.

Related Genetic Counseling Issues

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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing – Nonsyndromic Autosomal Dominant HSCR

Once the pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for nonsyndromic autosomal dominant HSCR are possible.

Requests for prenatal testing for conditions such as nonsyndromic HSCR are not common since a fetus identified as having a potential pathogenic variant may never develop manifestations 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. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Hirschsprung's & Motility Disorders Support Network (HMDSN)**
  United Kingdom
  Phone: 44 7935787776
  Email: info@hirschsprungs.info
  www.hirschsprungs.info

- **My46 Trait Profile**
  Hirschsprung disease

- **International Foundation for Functional Gastrointestinal Disorders (IFFGD)**
  PO Box 170864
  Milwaukee WI 53217-8076
  Phone: 888-964-2001 (toll-free); 414-964-1799

Fax: 414-964-7176
Email: iffgd@iffgd.org
www.iffgd.org

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

- **Pull-thru Network (PTN)**
  2312 Savoy Street
  Hoover AL 35226-1528
  Phone: 205-978-2930
  Email: PTNmail@charter.net
  www.pullthrunetwork.org

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].

References

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;132A:226–30. PubMed PMID: 15580636.

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 PMID: 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 PMID: 12640453.

Amiel J, Lyonnet S. Hirschsprung disease, associated syndromes, and genetics: a review. J Med Genet. 2001;38:729–39. PubMed PMID: 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 PMID: 9497256.

Amiel J, Sproat-Emison E, Garcia-Barcelo M, Lantieri F, Burzynski G, Borrego S, Pelet A, Arnold S, Miao X, Griseri P, Brooks AS, Antinolo G, de Pontual L, Clement-Ziza M, Munnich A, Kashuk C, West K, Wong KK, Lyonnet S, Chakravarti A, Tam PK, Ceccherini I, Hofstra RM, Fernandez R, et al. Hirschsprung disease, associated syndromes and genetics: a review. J Med Genet. 2008;45:1–14. PubMed PMID: 17965226.

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 PMID: 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 PMID: 8896568.

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

Badner JA, Sieber WK, Garver KL, Chakravarti A. A genetic study of Hirschsprung disease. Am J Hum Genet. 1990;46:568–80. PubMed PMID: 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 PMID: 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 PMID: 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 PMID: 10874630.

Benailly HK, Lapierre JM, Laudier B, Amiel J, Attié T, De Blois MC, Vekemans M, Romana SP. PMX2B, a new candidate gene for Hirschsprung's disease. Clin Genet. 2003;64:204–9. PubMed PMID: 12919134.

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 PMID: 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 PMID: 10618407.

Bond GJ, Reyes JD. Intestinal transplantation for total/near-total aganglionosis and intestinal pseudo-obstruction. Semin Pediatr Surg. 2004;13:286–92. PubMed PMID: 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 PMID: 9720918.

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 PMID: 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 PMID: 10874640.

Burkardt DD, Graham JM Jr, Short SS, Frykman PK. Advances in Hirschsprung disease genetics and treatment strategies: an update for the primary care pediatrician. Clin Pediatr (Phila). 2014;53:71–81. PubMed PMID: 24002048.

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 PMID: 11448942.

Cass D. Aganglionosis: associated anomalies. J Paediatr Child Health. 1990;26:351–4. PubMed PMID: 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 PMID: 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 PMID: 2512759.

Coran AG, Teitelbaum DH. Recent advances in the management of Hirschsprung's disease. Am J Surg. 2000;180:382–7. PubMed PMID: 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 PMID: 3812577.

Davenport M, Taitz LS, Dickson JA. The Kaufman-McKusick syndrome: another association. J Pediatr Surg. 1989;24:1192–4. PubMed PMID: 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 PMID: 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 PMID: 16443855.

Dentici ML, Brancati F, Mingarelli R, Dallapiccola B. A. 6-year-old child with Fryns syndrome: further delineation of the natural history of the condition in survivors. Eur J Med Genet. 2009;52:421–5. PubMed PMID: 19800039.

Drévillon L, Megarbane A, Demeer B, Matar C, Benit P, Briand-Suleau A, Bodereau V, Ghoumid J, Nasser M, Decrouy X, Doco-Fenzy M, Rustin P, Gaillard D, Goossens M, Giurgea I. KBP-cytoskeleton interactions underlie developmental anomalies in Goldberg-Shprintzen syndrome. Hum Mol Genet. 2013;22:2387–99. PubMed PMID: 23427148.

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 PMID: 8630502.

Eng C. RET proto-oncogene in the development of human cancer. J Clin Oncol. 1999;17:380–93. PubMed PMID: 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. 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 PMID: 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 PMID: 9067749.

Engum SA, Grosfeld JL. Long-term results of treatment of Hirschsprung's disease. Semin Pediatr Surg. 2004;13:273–85. PubMed PMID: 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 PMID: 7915329.

Garcia-Barcelo MM, Tang CS, Ngan ES, Lui VC, Chen Y, So MT, Leon TY, Miao XP, Shum CK, Liu FQ, Yeung MY, Yuan ZW, Guo WH, Liu L, Sun XB, Huang LM, Tou JF, Song YQ, Chan D, Cheung KM, Wong KK, Cherny SS, Sham PC, Tam PK. Genome-wide association study identifies NRG1 as a susceptibility locus for Hirschsprung's disease. Proc Natl Acad Sci U S A. 2009;106:2694–9. PubMed PMID: 19196962.

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 PMID: 11302967.

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

Hansford JR, Mulligan LM. Multiple endocrine neoplasia type 2 and RET: from neoplasia to neurogenesis. J Med Genet. 2000;37:817–27. PubMed PMID: 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. PubMed PMID: 11897831.

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 PMID: 8630503.

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 PMID: 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 PMID: 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 PMID: 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. PubMed PMID: 15004559.

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 PMID: 10946353.

Jiang Q, Arnold S, Heanue T, Kilambi KP, Doan B, Kapoor A, Ling AY, Sosa MX, Guy M, Jiang Q, Burzynski G, West K, Bessling S, Griseri P, Amiel J, Fernandez RM, Verheij JB, Hofstra RM, Borrego S, Lyonnet S, Ceccherini I, Gray JJ, Pachnis V, McCallion AS, Chakravarti A. Functional loss of semaphorin 3C and/or

semaphorin 3D and their epistatic interaction with ret are critical to Hirschsprung disease liability. Am J Hum Genet. 2015;96:581–96. PubMed PMID: 25839327.

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

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

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

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 PMID: 8031530.

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

Mäkitie O, Kaitila I, Rintala R. Hirschsprung disease associated with severe cartilage-hair hypoplasia. J Pediatr. 2001;138:929–31. PubMed PMID: 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. PubMed PMID: 15121777.

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 PMID: 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 PMID: 9719364.

Mowat DR, Wilson MJ, Goossens M. Mowat-Wilson syndrome. J Med Genet. 2003;40:305–10. PubMed PMID: 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 PMID: 14556255.

Nakakimura S, Sasaki F, Okada T, Arisue A, Cho K, Yoshino M, Kanemura Y, Yamasaki M, Todo S. Hirschsprung's disease, acrocallosal syndrome, and congenital hydrocephalus: report of 2 patients and literature review. J Pediatr Surg. 2008;43:E13–7. PubMed PMID: 18485929.

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. PubMed PMID: 15148591.

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 PMID: 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 PMID: 16226978.

Panza E, Knowles CH, Graziano C, Thapar N, Burns AJ, Seri M, Stanghellini V, De Giorgio R. Genetics of human enteric neuropathies. Prog Neurobiol. 2012;96:176–89. PubMed PMID: 22266104.

Parisi MA, Kapur RP. Genetics of Hirschsprung disease. Curr Opin Pediatr. 2000;12:610–7. PubMed PMID: 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 PMID: 11857550.

Peippo MM, Simola KO, Valanne LK, Larsen AT, Kähkönen M, Auranen MP, Ignatius J. Pitt-Hopkins syndrome in two patients and further definition of the phenotype. Clin Dysmorphol. 2006;15:47–54. PubMed PMID: 16531728.

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 PMID: 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 PMID: 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 PMID: 8001158.

Ridanpää 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 PMID: 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 PMID: 9681852.

Ryan ET, Ecker JL, Christakis NA, Folkman J. Hirschsprung's disease: associated abnormalities and demography. J Pediatr Surg. 1992;27:76–81. PubMed PMID: 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 PMID: 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 PMID: 8896569.

Sarioglu A, Tanyel FC, Buyukpamukcu N, Hicsonmez A. Hirschsprung-associated congenital anomalies. Eur J Pediatr Surg. 1997;7:331–7. PubMed PMID: 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 PMID: 6810692.

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 PMID: 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 PMID: 11484199.

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 PMID: 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 PMID: 11179008.

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

Smith VV, Eng C, Milla PJ. Intestinal ganglioneuromatosis and multiple endocrine neoplasia type 2B: implications for treatment. Gut. 1999;45:143–6. PubMed PMID: 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 PMID: 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 PMID: 10802661.

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 PMID: 10528251.

Tang CS, Cheng G, So MT, Yip BH, Miao XP, Wong EH, Ngan ES, Lui VC, Song YQ, Chan D, Cheung K, Yuan ZW, Lei L, Chung PH, Liu XL, Wong KK, Marshall CR, Scherer SW, Cherny SS, Sham PC, Tam PK, Garcia-Barceló MM. Genome-wide copy number analysis uncovers a new HSCR gene: NRG3. PLoS Genet. 2012b;8:e1002687. PubMed PMID: 22589734.

Tang CS, Ngan ES, Tang WK, So MT, Cheng G, Miao XP, Leon TY, Leung BM, Hui KJ, Lui VH, Chen Y, Chan IH, Chung PH, Liu XL, Wong KK, Sham PC, Cherny SS, Tam PK, Garcia-Barcelo MM. Mutations in the NRG1 gene are associated with Hirschsprung disease. Hum Genet. 2012a;131:67–76. PubMed PMID: 21706185.

Torfs C. An epidemiological study of Hirschsprung disease in a multiracial California population. Evian, France: The Third International Meeting: Hirschsprung Disease and Related Neurocristopathies; 1998.

Tou JF, Li MJ, Guan T, Li JC, Zhu XK, Feng ZG. Mutation of RET proto-oncogene in Hirschsprung's disease and intestinal neuronal dysplasia. World J Gastroenterol. 2006;12:1136–9. PubMed PMID: 16534860.

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 PMID: 15653965.

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

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 PMID: 11279515.

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 PMID: 9556091.

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 PMID: 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 PMID: 12686527.

Zweier C, Peippo MM, Hoyer J, Sousa S, Bottani A, Clayton-Smith J, Reardon W, Saraiva J, Cabral A, Gohring I, Devriendt K, de Ravel T, Bijlsma EK, Hennekam RC, Orrico A, Cohen M, Dreweke A, Reis A, Nurnberg P,

Rauch A. Haploinsufficiency of TCF4 causes syndromal mental retardation with intermittent hyperventilation (Pitt-Hopkins syndrome). Am J Hum Genet. 2007;80:994–1001. PubMed PMID: 17436255.

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 PMID: 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 PMID: 16053902.

Chapter Notes

Author History

Raj Paul Kapur, MD, PhD; University of Washington (2002-2004)
Melissa Parisi, MD, PhD (2002-present)

Revision History

- 5 March 2020 (ma) Retired chapter: Phenotype is too broad.
- 1 October 2015 (me) Comprehensive update posted live
- 10 November 2011 (cd) Revision: sequence analysis and prenatal testing available for mutations in *EDN3* and *EDNRB*
- 26 December 2006 (me) Comprehensive update posted live
- 28 July 2004 (me) Comprehensive update posted live
- 12 July 2002 (me) Overview posted live
- 23 February 2002 (mp) Original submission

Note: Pursuant to 17 USC Section 105 of the United States Copyright Act, the *GeneReview* "Hirschsprung Disease Overview" is in the public domain in the United States of America.

License