Pediatr Surg Int
DOI 10.1007/s00383-012-3175-6

REVIEW ARTICLE

Chromosomal and related Mendelian Syndromes associated with Hirschsprung's disease

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Accepted: 28 August 2012

Abstract Hirschsprung's disease (HSCR) is a fairly frequent cause of intestinal obstruction in children. It is characterized as a sex-linked heterogonous disorder with variable severity and incomplete penetrance giving rise to a variable pattern of inheritance. Although Hirschsprung's disease occurs as an isolated phenotype in at least 70 % of cases, it is not infrequently associated with a number of congenital abnormalities and associated syndromes, demonstrating a spectrum of congenital anomalies. Certain of these syndromic phenotypes have been linked to distinct genetic sites, indicating underlying genetic associations of the disease and probable gene–gene interaction, in its pathogenesis. These associations with HSCR include Down's syndrome and other chromosomal anomalies, Waardenburg syndrome and other Dominant sensorineural deafness, the Congenital Central Hypoventilation and Mowat–Wilson and other brain-related syndromes, as well as the MEN2 and other tumour associations. A number of other autosomal recessive syndromes include the Shah-Waardenburg, the Bardet–Biedl and Cartilage–hair hypoplasia, Goldberg–Shprintzen syndromes and other syndromes related to cholesterol and fat metabolism among others. The genetics of Hirschsprung's disease are highly complex with the majority of known genetic sites relating to the main susceptibility pathways (RET an EDNRB). Non-syndromic non-familial, short-segment HSCR appears to represent a non-Mendelian condition with variable expression and sex-dependent penetrance. Syndromic and familial forms, on the other hand, have complex patterns of inheritance and being reported as autosomal dominant, recessive and polygenic patterns of inheritance. The phenotypic variability and incomplete penetrance observed in Hirschsprung's disease could also be explained by the involvement of modifier genes, especially in its syndromic forms. In this review, we look at the chromosomal and Mendelian associations and their underlying signalling pathways, to obtain a better understanding of the pathogenetic mechanisms involved in developing aganglionosis of the distal bowel.

Keywords Hirschsprung's disease · Associated anomalies · Genetics · Children

Introduction

Hirschsprung's disease (HSCR) accounts for approximately 10 % of intestinal obstruction in the neonatal period and not infrequently presents later with chronic obstructive symptoms. It occurs as an isolated phenotype in at least 70 % of cases, but has not infrequently been associated with a number of congenital abnormalities and associated syndromes.

HSCR is characterized as a sex-linked heterogonous disorder (male predominance) with variable severity and incomplete penetrance [1] giving rise to a variable pattern of inheritance. Affected families are known to carry as high as a 200 times higher risk of recurrence [2]. The higher familial incidence has been shown to particularly apply to (but is not confined to) patients with long-segment aganglionosis (L-HSCR) [3–5] where it has been reported to recur in 15–21 % [6] and as high as 50 % in patients with ultra-long segment aganglionosis [7]. An asymmetrical parental origin is observed for RET coding sequence

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Published online: 23 September 2012

mutations with a higher maternal inheritance. Although a parent-of-origin effect is usually assumed to account for this, there is a hypothesis that the more severe mutations have affected the reproductive rate [8].

Inheritance and familial transmission

Familial transmission of HSCR is well known and affected families are known to carry higher risk of recurrence [2]. The higher occurrence of familial transmission has been shown to particularly apply to (but is not exclusive to) patients with long-segment aganglionosis (L-HSCR) [3–5, 9], where it has been reported to recur in 15–21 % [6] and as high as 50 % in patients with ultra-long segment aganglionosis [7]. In addition, it has also been reported in mono and dizygotic twins [10–12], and has a 12 % association with chromosomal anomalies [2].

HSCR inheritance is variable, however. On the one hand, isolated HSCR (without associated anomalies) has been reported as a non-Mendelian condition with a low, sex-dependent penetrance [13]. These appear to have a variable expression in terms of length of the aganglionic segment [14]. Syndromic HSCR on the other hand has been reported to have all forms of Mendelian inheritance, which suggests other genetic influences [15]. In syndromic expression, it is not clear if the identified genetic association is causative or acts as a modifier influence on one of the main susceptibility pathways.

Genetic counselling remains a challenge in Hirschsprung's disease because no clear pattern of inheritance exists [16, 17]. The majority of HSCR cases can thus be classified as complex genetic disorders where familial aggregation is observed without consistent Mendelian inheritance [18]. Autosomal dominant [19, 20] transmission has been reported, but also recessive [21–23] and multigenic patterns appear [15, 24]. In addition, to this, several of the known syndromic associations are inherited in an autosomal dominant manner [19, 21] Autosomal dominant Mendelian transmission appears to be mediated by the RET proto-oncogene. EDNRB mutations, on the other hand, may be recessive and suggest haplotypic gene–gene interaction.

HSCR-associated conditions

There are several well-known associations which are known or suspected to be related to an increased risk of HSCR. These include Down's syndrome [16], dominant sensorineural deafness [25], Waardenburg syndrome [16, 26–28], neurofibromatosis [26], neuroblastoma [16], Phaeochromocytoma [16, 26, 27], the MEN Type IIB syndrome [27, 29] and other abnormalities [16].

The reported associations with HSCR are significant for at least 2 reasons:

First, it gives insights into the abnormal genetic signalling during ENS development. This has given clues as to the genetic mechanisms involved in HSCR and its pathogenesis. This is particularly true for the Mendelian-linked syndromes.

Second, there is the contribution of associated anomalies on long term prognosis and outcome of these patients.

The reporting of HSCR-associated conditions has already been of great value in revealing many of the genetic associations of the disease [30], and have been a major factor in identifying genes such as the RET [31, 32], Endothelin B receptor (EDNRB) [33, 34] and SOX genes [35, 36] in the Waardenburg syndrome and the PHOX2B gene in congenital hypoventilation [37]. It has also helped identify the potential of genes not in the two main susceptibility pathways (e.g. the ZEB2 and ZFHX1B genes in the Mowat–Wilson syndrome [38, 39]), and the SIP1 gene associations [40]. Other known HSCR associations such as Down syndrome[42], the Bardet–Biedl [42] and cholesterol affecting syndromes [43] in addition to a number of other conditions may well modify the two main susceptibility pathways in some way and remain interesting areas of further research. It is therefore important that the extended form of the condition in 2–13 % of patients [5, 44–46] be explored, so as to assist in genetic counselling, particularly in potential familial recurrences [9].

Genes and the pathogenesis of Hirschsprung's disease

Hirschsprung's disease would appear at a molecular level to result from disruption of normal signalling during the development of the Enteric Nervous system (ENS) due mainly to chromosomal and impaired signalling cascades of controlling genes. As a result, the signals controlling the migration of the neural crest cells are deficient which results in aganglionosis of the distal bowel, leading to a functional intestinal obstruction.

The disorder is complex, as is shown by the number of genes implicated in its pathogenesis (at least, 11 genes and 5 gene loci have reportedly been associated with HSCR) [47]. This has caused much confusion in understanding how these different genetic influences link to give rise to the common Hirschsprung's feature of aganglionosis as considerable differences in HSCR phenotypic expression exist. The associated syndromes are hardly surprising as the signals governing cell migration and development in the embryo are extraordinarily complicated and signalling molecules are notorious for crosstalk and redundancy, as well as having co-ordinate and dependent regulation of expression on occasion. How they do this is still largely a matter of conjecture? Studies of these syndromes do, however, suggest possible relevant pathogenic mechanisms and links.

Known genetic variations have been identified in at least 12 % of HSCR cases [3, 48–51], which is higher than the expected in the normal population. In addition, these genetic variations account for more than 50 % of the observed abnormalities associated with HSCR. HSCR has been associated with high penetrance mutations in at least 11 neuro-developmental genes (viz: RET, GDNF, NRTN, SOX10, EDNRB, EDN3, ECE1, ZFHX1B, PHOX2B, KIAA1279, and TCF4). There is a monogenic subgroup for which rare RET coding sequence mutations with high penetrance are found (45 % of HSCR familial cases [8]. A recent population-based case group study tested for associations between HSCR and common genetic variation has confirmed the associations with RET, HOXB5 and PHOX2B variation, but failed to demonstrate significant association with ASCL1, L1CAM and PROK1 [52]. The association with HOXB5 and PHOX2B provide supportive evidence that genes regulating enteric neuroblast proliferation, migration and differentiation may confer HSCR risk. Although RET variants were strongly associated with HSCR (P 10(-3)-10(-31)), interethnic variation was observed in ethnic African–Americans which suggests interethnic variation in certain race/ethnic groups.

The roles of the major susceptibility genes on chromosome 10 (RET) and chromosome 13 (EDNRB) in the pathogenesis of HSCR, are well established [31, 53]. What is not always appreciated is that 9 of the 11 identified genes are related to these major susceptibility gene signalling pathways [viz: the REarranged during Transfection [RET (RET; GDNF; GFRα; NTN) signalling cascade and the Endothelin B receptor-related pathways (EDNRB; EDN-3; ECE-1; PHOX2B and SOX10)]]. In the developing ENS, the RET gene product and the GDNF family neurotrophic factors [mainly GDNF and GDNF receptor alpha1 (GFR-alpha1)] stimulate the proliferation of enteric neural crest cells by activating numerous signalling pathways to determine ENS development [54, 55]. Under this genetic control, the enteric neuroblasts then migrate from the neural crest to the proximal developing gut and then follow the vagal fibres down the GI tract to form the intermyenteric ganglia and ENS.

The genetic influence appears to vary in terms of the length of the affected segment, long segment Hirschsprung's disease and total colonic aganglionosis being considered to have an autosomal dominant inheritance pattern with incomplete penetrance (mostly RET); whereas isolated short-segment Hirschsprung's disease appears to be transmitted in an autosomal recessive manner or due to multiplicative effects of a number of involved genes [51]. In addition, several known associated syndromes are also inherited in a Mendelian autosomal dominant manner.

Potential gene effects in the pathogenesis of HSCR within these pathways, include loss of function, gain of function, apoptosis, aberrant splicing and decreased gene expression [56]. Other identified genes are mostly related to specific syndromes (Mendelian and other), and their pathogenetic connection to HSCR is not as yet fully understood but low-penetrance polymorphisms have also been identified in other genes (e.g. RET NRG1 and possibly TCF4 genes and are thought to possibly act as genetic modifiers). TCF 4 (transcription factor 4) is broadly expressed, and is thought to play an important role in nervous system development [57]. SMADIP1, (encoding a transcriptional co-repressor of SMAD target genes), possibly plays a role in patterning of neural crest-derived cells [58].

The chromosome 10-associated tyrosine kinase receptor RET appears to be the major gene involved in HSCR development and approximately 45 % of HSCR familial cases have high penetrance RET coding sequence mutations [8]. Current knowledge includes both infrequent coding sequence mutations throughout the genes well as a frequent variant located in an enhancer section which appears to predispose to HSCR [59, 60]. RET also maintains and supports the survival and several neuronal populations in the CNS (e.g. midbrain dopamine neurons and motoneurons) and may also contribute to the development and differentiation of specific cortical interneuron subtypes [54].

Genetic associations with HSCR include Down's syndrome (DS-HSCR), congenital central hypoventilation (CCHS), the Shah-Waardenburgh (WS4), the Bardet–Biedl (BBS), cartilage–hair hypoplasia (CHH), Smith–Lemli–Opitz (SLO), Goldberg–Shprintzen (GSS), and hydrocephalus due to congenital stenosis of the aqueduct of Sylvius (HSAS) in addition to the Mowat–Wilson syndrome (MWS) among others [61].

Chromosomal abnormalities and HSCR

One of the basic questions in HSCR is to explain how a complex series of genes may influence the highly variable HSCR phenotype in terms of gender, length of aganglionosis, familial recurrence, and expression of HSCR. Having already noted that the pattern of conditions associated with HSCR been of great value in unravelling many of the genetic associations of the disease, further study of the associated anomalies appears to indicate further less frequent associations with the condition.

Known chromosomal anomalies are associated with at least 12 % of HSCR cases [2, 48, 51], which is higher than the expected prevalence in the normal population. Chromosomal aberrations are also associated with more than

50 % of the HSCR-associated anomalies reported and genetic-HSCR associations have been identified with a number of related Mendelian syndromes [2, 47, 62]. In particular, associations with chromosomes 2, 9, 20, 21 and 22 may be important as they may act as "modifiers" of the final phenotypic expression [14].

A review showed that apart from Down syndrome, the relative incidence of other phenotypic expressions is of the order of 21 % [2]. Interest in chromosome 22 was first raised by Beedgen et al. [63].

Trisomy 21 and HSCR

HSCR (DS-HSCR) remains the most common of the congenital ENS dysganglionosis associated with DS [1, 16, 64], and there is a clear cut association between Hirschsprung's disease (HSCR) and DS (DS-HSCR) in 2–15 % of patients [2, 16, 30, 65–69]. A mean incidence of 5.82 % was calculated in a collective review of 5249 Downs syndrome patients [41], which is higher than the 0.15–0.17 % expected incidence in the normal population. As a result, all DS children with constipation should be considered as potential candidates for HSCR.

Although the clinical association between Hirschsprung's disease (HSCR) and Down's syndrome (DS) is well established, little consensus exists as to the possible aetiologic factors of the two conditions. The initially observed non-random association of the RET and chromosome 21 in the EDNRB-linked Mennonite kindreds suggested a multiplicative form of inheritance [70]. By this or a similar mechanism, the cumulative effects of multiple mutations appear to represent a likely mode of HSCR pathogenesis. The effect of the extra 21 chromosome on the development of the gastro-intestinal tract remains elusive, however. Initially it was thought to be related to the Down's critical region at 21q22, but is not necessarily part of it [70].

Recent research has identified at least 5 levels at which the developing ENS may be affected and thus result in ENS malfunction in DS [71]. These include a decreased pool of available neuroblasts for migration into the ENS [72], abnormal neuronal cells and post-synaptic connections [73–76], early gene-related influences on the migrating neuroblasts [70], germline and somatic mutations of genes [77], and a possible overfriendly local tissue environment [78].

First, decreased neuronal migration has been reported in the cortex of the brain of animal DS models, under known chemotactic factors (viz: glutamate or N-methyl-D-aspartate (NMDA) stimulation [79]. As a result, the DS brain has been shown to have both a decreased number and density of neurons in most brain regions.

Second, in addition to decreased pool of available neuroblasts in the CNS, the brain of DS patients also typically shows reductions in synaptic density and surface area with a decreased number of postsynaptic spines [73, 75, 80]. This probably reflects an altered neuronal morphology in DS, based on shortened basilar dendrites particularly in the cortical pyramidal tracts resulting in defective cortical layering [73–76]. This failure of the normal dendritic development in the brain of foetuses with DS, results in a "tree in winter" histological picture due to the lack of dendritic branching [72]. The existing spines appear abnormally long, thin, or irregular in contour and appearance [73, 75, 80]. As a result, there are reports of reduced numbers of oesophageal plexus ganglia neurons reported in DS patients provide further evidence of a decrease in neural ENS cells in DS (69 and 75 % of the control value in the deep submucous and Auerbach plexuses, respectively) [81]. It would therefore seem reasonable to extrapolate this decrease in ganglion cells reported in the oesophagus as occurring throughout the GIT, including the colon and may go some way to explain the oesophageal dysfunction (and other GI dysfunction), commonly encountered in DS. In addition, Hypoganglionosis is also not uncommon in the chromosome 21 animal model [82] with some having an aganglionic segment in addition to the abnormally developed ENS [82, 83].

There also appear to be early gene-related influences (germline and somatic mutations) on the migrating neuroblasts, in HSCR–Downs. Our own studies have shown both in a RET enhancer, as well as in the EDNRB gene variations in DS [84]. In the latter, EDNRB 561C/T Polymorphism was over represented in the HSCR/DS ($p < 0.002$, χ^2 with Yates correction = 12.14), suggesting a low-penetrance effect [84]. In addition, we recently identified an association between somatic mutation of SNP2 (rs 2435357) to aganglionic tissue [77]. Both the RET Intron 1HSCR-related SNP 1 (rs2506004) [77] and SNP2 (RET +9.7 (rs2435357:C>T) 10q11.2) [60]. In our own study, the SNP1 (rs2506004) showed variation in all 14 of the DS-patients tested, but was also found in all 3 DS controls (without), and also much less frequently in normal population controls [77].

Although homozygous expressions of SNP1, appeared to correlate with aganglionosis in tissue samples, SNP2 (rs2435357) was found to be heterozygous in normally ganglionated and transition zone tissue but homozygous in four aganglionic tissue samples from the same patients. We were thus able to demonstrate potential disease-related *RET* intronic mutations in DS-HSCR patients, which appeared to undergo somatic mutation in affected tissue [77]. In itself this may be a significant explanation as to why only a segment of bowel is affected. It also suggests

that local micro-environmental (e.g. extracellular matrix (ECM)) factors play a role in HSCR pathogenesis.

The entire ENS in DS appears, therefore, to be potentially affected in a number of ways both by developmental and genetic defects. Disturbances of the GIT are not uncommon in DS and are probably related to an abnormal ENS. Functional GI disturbances may continue into adulthood in DS and require special counselling and follow-up.

Other HSCR-associated chromosomal anomalies

Although the main chromosomal anomaly associated with HSCR is Trisomy 21, there are other reported chromosomal variations which are uncommonly HSCR-associated. These include chromosomal lesions such as deletion of 20p [85], 18p monosomy and 18q Trisomy [86], and XO/XX/XXX mosaicism [87].

There are at least two other chromosomal regions where genomic studies have re-emphasised an already suspected HSCR link. One of these is the association between HSCR and 2q37, which arose because of a possible homology with the splotch mouse model [88]. Since the initial connections with this site, the SMAD interacting protein 1 gene (SIP-1) at 2q22-23 [89], partial duplication of chromosome 2 [90, 91] and the Mowat–Wilson syndrome with its ZEB2 (ZFHX1B) mutations and deletions at 2q22-q24 [91] have been associated with HSCR.

In addition, the 9q31 region has been identified in sib pairs without significant RET variations [92]. This site has been previously associated with reports of tetrasomy of 9p [93] and the association with Riley–Day familial dysautomnia [94], whose IKBKAP gene has been linked to 9q31 [95]. In addition, the RMRP gene mutation in the cartilage–hair hypoplasia syndrome relates to a similar area [96].

Dandy–Walker abnormalities have been reported associated with both HSCR [93] and the Shah-Waardenburgh syndrome [97]. It is frequently associated with genetic anomalies, brain or systemic malformations (e.g. heart, orthopaedic, intestinal, urogenital and facial anomalies) and also part of many syndromes and appears also to be linked to chromosome 9 variations possibly explaining the HSCR connections [92, 93].

Abnormalities of chromosome 22 karyotype have been reported to be associated with both malrotation and aganglionosis both in animal models [98] and in humans [99]. Associations related to this site, include the cat-eye syndrome associated with Trisomy 22pter-q11 [100] and the Di-George velocardiofacial syndrome at del22q11 [101], both of which have been associated with HSCR.

L1 gene (LiCAM) mutations have been associated with both hydrocephalus and HSCR [102]. Although there appears to be some association with L1 [103], it has recently been shown to not be causative in HSCR [52]. It may, however, act as a modifier gene for members of the Endothelin signalling pathway during enteric nervous system development [104].

It is interesting to note that the majority of the reported chromosomal sites that lie outside of the major susceptibility genes, have been identified in patients without major RET mutations, suggesting that these chromosomal sites may have a unique interaction resulting in HSCR [92].

Mendelian inheritability in Hirschsprung's disease

The genetics of Hirschsprung's disease are highly complex. On the one hand, non-syndromic non-familial, short-segment HSCR appears to represent a non-Mendelian condition with variable expression and sex-dependent penetrance [47]. On the other hand, syndromic and familial forms of HSCR have complex patterns of inheritance and have been described as dominant and recessive Mendelian forms of inheritance. In the strict sense, they are not truly Mendelian although many of the associated syndromes appear to be transmitted in a Mendelian manner. As a result, autosomal dominant [19, 20], recessive [21] and polygenic patterns [24], have all been observed in patients with HSCR.

The phenotypic variability and incomplete penetrance observed in Hirschsprung's disease could be explained by the involvement of modifier genes, especially in its syndromic forms.

The pattern of HSCR inheritance also appears to vary in terms of the length of the aganglionic segment, long-segment Hirschsprung's disease being considered to have an autosomal dominant inheritance pattern with incomplete penetrance (mostly RET): whereas short-segment Hirschsprung's disease appears to be transmitted in an autosomal recessive manner or due to multiplicative effects of a number of involved genes [51].

Of the several known associated syndromes inherited in a Mendelian manner those being transmitted autosomal dominantly include the Waardenburg syndrome (mainly when the SOX 10 gene is involved [105]), the Congenital Central Hypoventilation Syndrome [37] the Mowat–Wilson [106], as well as the MEN2A tumour syndrome [107]. Those being transmitted as autosomal recessive include the Shah-Waardenburg [108] the Bardet–Biedl and Cartilage–hair hypoplasia (CHH) [109] and Goldberg–Shprintzen syndromes [110]. The suggestion that Mendelian transmission is related to the non-RET related syndromic types, although interesting, does not fully explain the autosomal dominant transmission in MEN2 among others.

It would appear to be important to look carefully at these syndromes to gain insight into the molecular mechanisms responsible for the HSCR connection.

Mendelian syndromes associated with Hirschsprung's disease

Waardenburg (WS) and Shah-Waardenburgh (WS4) syndromes

Waardenburg syndrome (WS) represents a congenital disorder, resulting from defective neural crest cell development of melanocytes (pigmentary disorders, white forelock), is one of a number of rare conditions where sensorineural deafness may be associated with pigmentary disturbances and Hirschsprung's disease (HSCR). It has a variable phenotype and has been reported to be an autosomally dominant mode of inheritance (especially when a Sox10 gene mutation is involved [105]). In addition to deafness, it may also be associated with maldevelopment of CNS neural cells manifesting as mental retardation plus additional ENS ganglion cell (Aganglionosis; Hirschsprung disease; WS4), autonomic and peripheral nervous system deficits (peripheral neuropathy).

The Shah-Waardenburg syndrome (WS4) is an uncommon autosomal recessive condition referring to the Waardenburg–HSCR association.

Although inheritance of Waardenburg syndrome is autosomal dominant, penetrance is often incomplete, the fact that multiple genes have been implicated in WS, allows certain combinations able to cause more than one WS subtype or combination of phenotypic expression, resulting in a considerable variation in clinical expression.

The identification of a deletion at 13q22-32.1, led to identification of the second major susceptibility gene in the aetiology of Hirschsprung's disease [70, 111–113] and its association with the Waardenburg and other Neurocristopathies. This deletion included the recessive EDNRB gene, located at 13q22 [70, 114, 115]. Other related genes of the EDNRB pathway include and much less frequently associated ligand Endothelin 3 (EDN3) [116], the Endothelin-converting enzyme 1 (ECE1) [117], the sex-dependent Y factor-like homeobox 10 (SOX10) gene [118] as well as Neurturin (NT)N [119]. SOX 8 also appears to be required along with SOX10 to maintain vagal neural crest stem cells [120]. Identification of a deletion at 13q22-32.1 led to identification of the second major susceptibility gene [70, 105, 111–113] and its association with the Waardenburgh and other neurocristopathies. This includes the recessive EDNRB gene, located at 13q22 [70, 114, 115] and much less frequently its ligand Endothelin 3 (EDN3) [116] Other related genes involved in HSCR pathogenesis include the Endothelin-converting enzyme 1 (ECE1) [117], the sex-dependent Y factor-like homeobox 10 (SOX10) gene [118] and Neurturin (NT)N [119]. SOX 8 also appears to be required along with SOX10 to maintain vagal neural crest stem cells [120]. Although mutations in the PAX3 gene are responsible for the majority of these anomalies in WS type 1, genetic variation in the homeobox gene HOXA2 has been reported to cause microtia in at least one previous Iranian family.

Clinical syndromes which are mostly related to the EDNRB gene and Sox10 and include the following:

- Long-segment Hirschsprung's disease in the Waardenburg-Shah syndrome.
- Congenital hypomyelinating neuropathy, central dysmyelination, and Waardenburg-Hirschsprung disease: phenotypes linked by SOX10 mutation.
- Shah-Waardenburgh (Type 1V WS).
- Certain other forms of sensorineural deafness.

Sensory organ and related anomalies appear mostly to be related to genetic disturbances other than RET (e.g. the EDNRB and Sox10 genes).The transcription factors SOX10 as well as ZFHX1B also appear crucial for ENS development. Double mutants of these two genes present with severe ENS maldevelopment, caused by a decrease in the proliferation of enteric neuroblasts as well as increased neuronal differentiation from day E11.5 onwards in experimental mutant mouse models [121]. This is not surprising as Sox10 is known to maintain crest-derived neuroblasts in their uncommitted state, regulating both Ret [122, 123] and EDNRB [124] genes. Sensorineural deafness associated may occur either as part of a Waardenburgh Type 4syndrome(WS4) [16, 17, 26–28, 125, 126] or as a dominant sensorineural deafness [25]. These may be associated with long-segment Hirschsprung's disease in the Waardenburgh-Shah phenotypes (Type 1V WS) as well as certain other forms of sensorineural deafness including congenital hypomyelinating neuropathy, central dysmyelination, and the Yemenite deaf-blind hypopigmentation syndrome. Other associations with ophthalmic anomalies may also be included in those with auriculovertebral syndromes (e.g. Goldenhar syndrome) [127].

Other pigmentary disturbances and HSCR

Pigmentary disturbances are a well-known association with HSCR in the Waardenburg syndrome (WS4) [128] as well as other sensorineural deafness syndromes such as the ABCD [23, 129], Black locks albinism [130], and familial piebaldism [25]. The Yemenite deaf-blind hypopigmentation syndromes have now been shown to be associated with a SOX10 mutation [23].

Cartilage–hair hypoplasia (CHH)

Approximately 10 % of patients with Cartilage–hair hypoplasia syndrome are associated with HSCR [131]. This syndrome represents an autosomal recessive skeletal

dysplasia with metaphyseal to spondylo-meta-epiphyseal dysplasia and anaemia, immunodeficiency, and gastrointestinal Malabsorbtion as well as HSCR [109]. There is also a predisposition to cancer and the syndrome has been attributed to an RMRP gene mutation [96, 132] (which maps to chromosome 9p13—a well known associated site [133]).

Other skin conditions may be involved in HSCR-associated pathology. These include the KID (keratitis, ichthyosis and deafness) syndrome [134] and familial ichthyosis [5, 134, 135]. Although the exact genetic links with ichthyoids are unknown, two more recent publications indicate Xp22.3 [136] and 2q35 [137] both of which are close to areas with known HSCR connections.

Congenital central hypoventilation syndrome (CCHS)

Congenital central hypoventilation syndrome (CCHS) is an uncommon autonomic nervous system dysfunction as a result of a decrease in the hypercarbic response. CCHS is inherited in an autosomally dominant way and is linked to polyalanine expansion mutations and malfunction of the paired-like homeobox 2B (PHOX2B) gene. [37]. These patients also have impaired autonomic functions such as thermoregulation, cardiac rhythm, and digestive motility, but these appear less severe than other in conditions. Affected neonates die because they fail to breathe despite progressive hypercapnoea and hypoxia, if untreated. CCHS and Haddad syndromes share a link with a Hirschsprung-like phenotype [138]. In addition to being linked to congenital colonic aganglionosis (Hirschsprung's disease), PHOX2B is also associated with neural crest-related tumours and diffuse autonomic dysregulation.

Studies have shown that PHOX2 maintains noradrenergic differentiation during embryogenesis in the main noradrenergic centre as well as requiring ongoing expression in sympathetic ganglia [139]. The majority of PHOX2B mutations are sporadic in nature, but there is some reported association with specific mutated alleles and the severity of the disease. It may also be associated with abnormalities of the eye and autonomic nervous system, especially when associated with HSCR [140]. Early clinical recognition and genetic screening and treatment may be life saving as well as giving hope of a relatively successful long-term outcome.

The identification of these causative genes allows some speculation as to the possible pathophysiology of this condition. The paired-like homeobox 2 (PHOX2B), gene at chromosome 4p12 is expressed in developing neuroblasts and is essential for neurogenesis [52]. Compound effects of PHOX2B and RET gene variants have been shown in HSCR-associated CCHS [141] and in knockout mice, disruption of the PHOX2B gene results in an almost total intestinal aganglionosis. Malfunction of PHOX2B will result in a decrease in RET expression on the cell surface with resultant phenotypic consequences. It works in conjunction with SOX10, and appears to regulate Ret expression [142]. This was demonstrated by Leon et al. [142] using a reporter construct (a luciferase-reporter plasmid) to demonstrate the ability of PHOX2 to upregulate RET promoter function (178–36 position) demonstrating activation of NKX2-1. Luciferase activity rising by a factor of 6.5.

The Haddad syndrome is an uncommon congenital variant of CCHS due to the co-segregation of central congenital hypoventilation syndrome with HSCR (Usually long segment or TCA). This association relates to the critical role played by the Endothelin system in ENS and melanocyte development which has also been demonstrated in animal models (e.g. EDNRB knockout mice) [143] and is probably SOX10 related. Recent studies in transgene-insertion mutant mouse line (Hry), which display incomplete aganglionosis, melanocyte loss, and reduced Sox10 expression but have negative Sox10 coding sequences, has shown that a 15.9-kb deletion underlies the observed WS4 phenotype and probably removes sequences essential for Sox10 expression, suggesting that non-coding regulatory sequences are disrupted [35].

Syndromes related to cholesterol and fat metabolism

Smith–Lemli–Opitz (SLO)

Other less common associations with HSCR include syndromes related to cholesterol and fat metabolism such as the Smith–Lemli–Opitz [43, 144, 145], Bardet–Biedl non-syndromic obesity [BBS] [42, 146, 147] and the related McKusick-Kaufman syndrome [148] has a 10 % HSCR incidence [149].

Bardet–Biedl syndrome (BBS)

The Bardet–Biedl non-syndromic obesity [BBS] is a familial syndrome characterised by progressive retinal dystrophy, postnatal obesity, post-axial polydactyly, renal dysfunction, learning difficulties and hypogonadism with Undescended testes [150]. The rare association between the Bardet–Biedl and Hirschsprung's disease, is mostly being reported from families in the Middle East. They also belong to a group which includes other syndromes related to cholesterol and fat metabolism such as the Smith–Lemli–Opitz and the related McKusick-Kaufman syndrome.

The 11 BBS loci identified to date are examples of 'oligogenic' inheritance (i.e. conditions not inherited as simple single-gene Mendelian disorders and yet are not classic complex traits, but rather fit a model in which

mutations in a small number of genes may interact genetically to manifest the phenotype). In the case of BBS has led to the concept of 'triallelic inheritance', whereby families with at least three mutations from genes at two different BBS loci, are at highest risk of transmitting the condition [151]. The same could apply to many cases of HSCR.

Although BBS is generally accepted to be multigenic in origin and to have an autosomal recessive pattern of inheritance, this association with HSCR suggests a common signalling pathway possibly related to the major susceptibility genes [14].

Chromosome 3 (3p21) has been identified as an important link on genomic scanning of HSCR [42, 146, 147]. The BBS and HSCR susceptibility genes have been shown to interact and concomitant mutations of BBS genes and regulatory RET elements, suggest that BBS mutations can potentiate HSCR predisposing RET alleles, which by themselves are insufficient to be causative [152]. Homozygosity for the common hypomorphic T allele plus an 11 bp deletion in the enhancer of RET in association with missense mutations in the BBS genes may help explain this association. Gut innervation can then be affected, probably through complementary, yet independent, modifying pathways that have a similar biological function.

Mowat–Wilson syndrome

Mowat–Wilson syndrome (MWS) appears to have a genetic aetiology and has been shown to recur in families with an approximate 1–2.3 % recurrence risk [153–155]. Autosomal dominant transmission, with at least three sibling recurrences has been reported [106, 153, 155, 156].

Clinically, MWS represents a spectrum of congenital dysmorphic features of the head and face (microcephaly, corpus callosal agenesis, hypertelorism, prominent columella, pointed chin, and uplifted earlobes) as well as GI motility disturbances which include Hirschsprung's disease (HSCR) and/or severe constipation [157, 158]. In addition, there are numerous other associated anomalies such as genitourinary anomalies (especially hypospadias and renal tract anomalies), congenital heart defects, short stature and eye defects [39]. The ocular abnormalities may include bilateral microphthalmia, cataract, and retinal aplasia [159], as well as coloboma [160]. The clinical diagnosis of MWS may prove difficult due to phenotypic variation, especially when HSCR is absent. In these cases, a molecular diagnosis of the ZEB2 gene is required to confirm the diagnosis.

What makes MWS interesting is that ZEB2 is not part of the two main HSCR susceptibility pathways, but appears to be the result of heterozygous deletions or truncating mutations of the ZFHX1B/ZEB2 (SIP1) gene on chromosome 2q22 [39]. Although mutations of this gene are diagnostic [158, 161] and can be identified in most MWS patients, not all patients with MWS and ZEB2 gene variations have HSCR (the association occurring somewhere between 41 and 71 % [58, 156]). As a result, it suggests a modifying or indirect signalling connection to the main susceptibility pathways. In this context, MWS probably represents an association of multiple gene-based abnormalities and has also been associated with chromosome 21-linked HSCR [160].

In addition to the intellectual disability, the main long-term clinical problem in MWS is the (often severe) association with functional GI motility disturbances, especially Hirschsprung's disease [91]. The persisting dysmotility in these patients may become a major issue in longer term patient management. In those with HSCR, the length of the aganglionic segment varies and not always reported in large reviews [156]. Bonnard et al. [162], however, reported Total colonic aganglionosis (TCA) in 3 out of 5 cases (60 %) and Isihara et al. [163] in seven cases, suggesting an association with TCA. In MWS, the GI motility disturbances (including Hirschsprung's disease and/or severe constipation) may be partly due to variations in the severity of the ENS architecture as well as a possible prolonged transitional zone [163].

Goldberg–Shprintzen syndrome (GSS)

Goldberg–Shprintzen syndrome is an uncommon autosomal recessive genetic condition, characterized by short-segment Hirschsprung disease, cleft palate, microcephaly, mild mental retardation, short stature and distinctive facial appearance [110]. It has been described in siblings [164] and is regarded as having an Mendelian inheritance pattern, because of recurrence in siblings and parental consanguinity in some families.

It is currently thought that GSS is caused by inactivating mutations in the Kinesin Binding Protein (KBP) gene KIAA1279 (10q22.1) [165], which localizes to the mitochondria and interacts with the SCG10[stmn2-b; stathmin-like 2] gene [166], thus linking the Goldberg–Shprintzen syndrome to microtubule dynamics and the differentiation of enteric neurones. SCG10 does not appear to be directly implicated in HSCR pathogenesis [167], although its role as modifying factor cannot be ruled out.

It is an interesting association, as it falls within the ambit of a number of conditions linking HSCR with CNS anomalies such as microcephaly, mental retardation, poor brain growth and various dysmorphic features. The associated CNS anomalies also includes patients with an absent corpus callosum (either isolated or in association with the Goldberg–Shprintzen [168, 169] and Mowat–Wilson syndromes [39]).

HSCR associations with tumours

Associations between HSCR and a number of associated tumours related to neural cell development include neuroblastoma [16], phaeochromocytoma [16, 26, 27] and the MEN Type II A and B syndromes and medullary thyroid carcinoma (MTC) [27, 29, 170], among others [16]. MEN2A is an autosomal dominant genetic condition characterized by the development of a number of tumours including phaeochromocytoma, medullary thyroid carcinoma (MTC), thyroid C-cell hyperplasia and Parathyroid tumours [107].

Reports of the relatively uncommon co-segregation of HSCR and MEN2 in the same patient [50, 170–182] exists, because of the common factor of the RET gene being associated with both conditions [HSCR, MEN type 2 and MTC]. This is an extremely interesting observation, as it involves both gain and loss of function of the same gene in the same patient.

The HSCR–MTC relationship also appears to be bi-directional and RET gene activation or suppression appeared to vary over succeeding generations within the same family [183, 184]. Butter et al. [185] reported a 50 % incidence of HSCR in 20 patients undergoing a prophylactic thyroidectomy for RET-associated MTC risk (a RET C620 mutation). In one further reported case of familial MTC with a C620S point mutation [186], the MTC developed 12 years after surgical correction of HSCR in the child plus a maternal MTC 7 years after the child's birth. In our own reported series [183], MTC was detected in the parent 5 years following the birth of the affected child.

In addition, HSCR is associated with other tumours of neural origin with neurofibromatosis and other autonomic nervous system disturbances [187]. In familial Neuroblastoma it would appear that the most likely genetic candidate is PHOX2B gene as it appears to be the major susceptibility gene in CCHS, as well as being associated with familial NB [188] and HSCR–NB associations [187, 189].

Conclusion

Hirschsprung's disease represents a wide spectrum conditions, characterized by aganglionosis of varying lengths of distal bowel. Whereas Chromosomal and Mendelian associations are largely absent in the non-syndromic non-familial, short-segment HSCR, syndromic and familial forms of HSCR have complex patterns of inheritance and have been described as dominant and recessive Mendelian forms of inheritance. Investigation of the underlying signalling pathways has yielded valuable information as to the pathogenesis of the disease.

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