Gastrointestinal motility disorders in children: etiology and associated behaviors

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Chapter 2

Infantile hypertrophic pyloric stenosis - genetics and syndromes

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Abstract

Infantile hypertrophic pyloric stenosis (IHPS) is a common condition in neonates that is characterized by an acquired narrowing of the pylorus. The aetiology of isolated IHPS is still largely unknown. Classic genetic studies have demonstrated an increased risk in families of affected infants. Several genetic studies in groups of individuals with isolated IHPS have identified chromosomal regions linked to the condition; however, these could usually not be confirmed in subsequent cohorts, suggesting considerable genetic heterogeneity. IHPS is associated with many clinical syndromes that have known causative mutations. Patients with syndromes associated with IHPS can be considered as having an extreme phenotype of IHPS and studying these patients will be instrumental in finding causes of isolated IHPS. Possible pathways in syndromic IHPS include: (neuro)muscular disorders; connective tissue disorders; metabolic disorders; intracellular signaling pathway disturbances; intercellular communication disturbances; ciliopathies; DNA-repair disturbances; transcription regulation disorders; MAPK-pathway disturbances; lymphatic abnormalities; and environmental factors. Future research should focus on linkage analysis and next-generation molecular techniques in well-defined families with multiple affected members. Studies will have an increased chance of success if detailed phenotyping is applied and if knowledge about the various possible causative pathways is used in evaluating results.
Introduction

Infantile hypertrophic pyloric stenosis (IHPS) is a common condition in neonates that is defined by acquired narrowing of the pylorus.\(^1\) Hypertrophy of the pyloric muscle progressively leads to almost complete obstruction of the gastric outlet, which causes symptoms when the neonate is 3–6 weeks old. The typical symptom is projectile postprandial vomiting.\(^2\)

IHPS can occur as an isolated entity or might be linked with chromosomal abnormalities, congenital malformations and clinical syndromes, which indicates that there is a genetic involvement. The exact aetiology of isolated IHPS is unknown. Various potential genetic loci have been identified, but no studies in large cohorts have confirmed these associations with isolated IHPS. By studying nonisolated, syndromic forms of IHPS, valuable clues can be obtained about the pathogenetic pathways involved in IHPS.

The aim of this Review is to gain further insight into the pathogenesis of isolated IHPS by establishing which pathways are involved in syndromes associated with IHPS. We provide an overview of molecular and genetic studies in patients with isolated IHPS and subsequently categorize the various syndromes associated with IHPS. We have also included definitions of the key terms used in these studies (Box 1).

Epidemiology of IHPS

In western countries, the incidence of IHPS is two per 1,000 live births; IHPS is less common in other parts of the world.\(^2,3\) A decline in the incidence of IHPS has been reported over the past two decades in northern European countries.\(^4,5\) A comparable decline in the incidence of sudden infant death syndrome has been observed since parents were first encouraged to put babies in a supine sleeping position.\(^4\) As it has been suggested that IHPS is related to a prone sleeping position,\(^4\) this change in sleeping position could explain the drop in the incidence of IHPS. However, in other countries, this simultaneous decline in the incidence of IHPS and sudden infant death syndrome could not be demonstrated.\(^6\) The incidence of IHPS might vary seasonally, but results are contradictory (B. Peeters et al., unpublished work).

IHPS affects males more often than females (male:female ratio of 4–5:1).\(^7\) A clear explanation for this striking skewed sex distribution is lacking, and the cause for this distribution can only be hypothesized. Genetic factors located at the X or Y chromosome might be considered; however, transmission patterns within families do not point to this solution.\(^8-14\) An influence of preferential X-chromosome inactivation patterns in females could be present that would inactivate a gene with an important influence in
the aetiology of IHPS. Epigenetic changes might also lead to gender-specific alterations in gene expression. Lastly, sex hormones could also be involved, although disorders that have a known change in the levels of sex hormones do not show an increased IHPS incidence, which argues against such an influence. A study published in 2011 investigated testosterone levels in umbilical-cord blood of 46 patients with IHPS and a matched control group and found no statistically significant differences.15

IHPS is considered as a complex disorder that results from genetic and environmental factors.7, 16 Maternal smoking and alcohol consumption during pregnancy might be environmental factors that contribute to IHPS.17-19 Prenatal and postnatal exposure to medication and hyperacidity in neonates have been the subject of research, without producing conclusive data.20, 21 The role of early exposure to erythromycin, a macrolide antibiotic, in the pathogenesis of IHPS deserves consideration. Erythromycin is an agonist of motilin that is known to induce contractions of the gastrointestinal tract. Since a rise in IHPS incidence was reported in infants prophylactically treated with erythromycin during a pertussis epidemic in 1999,22 others have reported comparable results in children exposed to this drug.23, 24 However, up until now, no notable alterations in the gene that encodes motilin have been found in patients with IHPS.

Young maternal age (<20 years) has also been indicated as a risk factor for IHPS, but results are inconsistent.25-27 Firstborn babies are more likely to develop IHPS than subsequent babies.7 Data on risks related to birth weight and feeding practices are still inconclusive.16 In premature infants, the onset of symptoms is delayed compared with infants born at term.26 This observation suggests the need for postnatal maturation before IHPS can develop.26 Local infections, for example, with Helicobacter pylori, have been considered as well; however, H. pylori gastritis is usually not demonstrable in gastric biopsy samples from patients with IHPS.28, 29

We conclude that numerous environmental factors are possibly associated with IHPS, but their true influence remains uncertain.

**Isolated IHPS: family studies**

Genetic studies usually first study affected twins and familial IHPS.30-33 The male:female sex ratio in familial cases (3:1) is less skewed than in isolated cases (4–5:1).11, 13 In 1961, Carter proposed a multifactorial sex-modified threshold model of inheritance for IHPS in which females are protected by their sex.34 In a further study, Carter and Evans described an almost three times higher prevalence of IHPS in offspring of affected mothers compared with offspring of affected fathers.32 They hypothesized that affected mothers have a direct effect on their foetuses that contributes to the babies developing IHPS. Several other studies have also reported a higher prevalence of IHPS in offspring of affected mothers than in offspring of unaffected mothers.35, 36
A reanalysis of IHPS familial aggregation patterns showed that familial recurrence patterns were inconsistent with single major locus inheritance, but were compatible with multifactorial threshold inheritance as proposed by Carter or with effects of multiple interacting loci. No support was found for a maternal factor. Krogh et al. studied familial occurrence in first degree, second degree and third-degree relatives of 3,362 affected children in a national Danish birth cohort. A 200-fold increase in prevalence was found among monozygotic twins and a 20-fold increase was found among siblings of affected children. Heritability was estimated to be as high as 87% by using a best fitting model of variance, taking into account additive genetic factors and nonshared environmental components. No higher prevalence in maternal relatives compared with paternal relatives was found. An overview of aggregation studies in IHPS is provided (Table 1).

The abovementioned studies indicate that genetic factors have an important role in the aetiology of IHPS and that IHPS is probably inherited as a multifactorial trait, aggregating in families under the influence of multiple environmental and genetic factors.

**Isolated IHPS: molecular studies**

**Linkage analysis**

Linkage studies are summarized in Table 2; only the most salient findings are discussed below. Following the occurrence of IHPS in patients with a duplication of chromosome 9q, Chung et al. performed linkage analysis of candidate region 9q11–q33 in 20 families with IHPS but did not find a major predisposing locus in this population. However, chromosome 9q cannot be excluded as a possible factor in the aetiology of IHPS, as the small sample size was small; therefore, further studies in other populations will be needed.

Vanderwinden et al. suggested that reduced expression of neuronal nitric oxide synthase (nNOS) in the pylorus of patients with IHPS contributed to the development of the condition. nNOS catalyzes nitric oxide (NO), which influences muscle relaxation in the gut (Figure 1), and it was hypothesized that a reduced concentration of NO leads to continuous constriction and eventually hypertrophy of the pylorus. Chung et al. demonstrated statistically significant linkage between IHPS and NOS1a on chromosome 12q in 13 of 27 families. These UK families had at least three affected family members. A Swedish study could not replicate the results in three families with multiple affected members. Three generations of a family that included 10 affected members were analyzed by a single nucleotide polymorphism (SNP)-based genome-wide scan and mapped to chromosome 16p12–p13 (LOD score 3.23). 10 additional families with at least six affected members were analyzed without yielding statistically significant LOD scores. Sequencing of major candidate genes in the region encoding proteins involved in smooth muscle relaxation...
(for example, MYH11 and GRIN2A) did not show pathogenic mutations. Linkage to NOS1 was excluded. A genome-wide linkage scan of 81 pedigrees with 302 individuals (206 affected) showed susceptibility loci on chromosome 11q14–q22 (maximum LOD score 3.4) and Xq23 (maximum LOD score 4.8). Both chromosomal regions included candidate genes involved in the functioning of ion channels that are involved in smooth muscle control (that is, TRPC5 and TRPC6). Yet, a study of 168 affected Chinese individuals failed to replicate the association between SNPs in the TRPC6 promoter and IHPS. Linkage to another susceptibility locus on chromosome 16q24 (maximum LOD score 3.7) could not be replicated in 14 other pedigrees, and sequencing of candidate gene SLC7A5, which is involved in the transport of factors that transduce NO activity, did not show pathogenic mutations. In 37 Swedish and 31 British families with IHPS, linkage to four regions (including the NOS1 region) was found. Sanger sequencing of two candidate genes, encoding glucagon-like peptide 2 and neuropeptide Y, did not yield positive results.

We conclude that different loci have been identified by linkage analysis in families with multiple IHPS individuals; however, subsequent attempts to confirm these associations in other families were frequently unsuccessful, which suggests that IHPS is genetically heterogeneous.

Genome-wide association studies

A genome-wide association study (GWAS) was performed in 1,001 Danish individuals with IHPS and 2,401 control individuals. Three SNPs, harbouring candidate genes MBNL1 and NKX2–5, could be replicated in a subsequent cohort of patients with IHPS and control individuals. MBNL1 is a regulator of splicing transitions in the first weeks of life and NKX2–5 encodes a homeobox transcription factor. Increased knowledge of pathogenetic pathways involved in IHPS is needed before further correlations and improved interpretation of GWAS results can be achieved.

Candidate gene and expression studies

Kusafuka et al. studied the expression of NOS1 at the mRNA level in muscle biopsy samples from six patients with IHPS and three control individuals. A considerably lower expression was found in patients with IHPS than in control individuals, but study numbers were small. Saur et al. confirmed the altered NOS1 expression in pyloric tissue of patients with IHPS and showed that 3 of 16 investigated patients with IHPS had genetic alterations in a regulatory region of NOS1 exon 1c that influences the expression of NOS1, whereas 81 control individuals showed no abnormalities. Individuals carrying the affected allele had an appreciably increased risk of developing IHPS. The association could not be replicated in a Swedish population consisting of 54 patients with familial IHPS and 28 patients with sporadic IHPS, or in a Chinese population consisting of 56 patients with
IHPS and 86 control individuals.\textsuperscript{48, 49} Researchers from Germany sequenced the complete coding region of \textit{NOS1} in 43 patients with IHPS and 47 healthy control individuals without finding a statistically significant association with IHPS.\textsuperscript{50} In 2008, Svenningsson and co-workers\textsuperscript{51} sequenced the gene that encodes motilin (\textit{MLN}) in 57 patients with IHPS and 184 control individuals. Motilin is a hormone known to be involved in generating contractions in the gastrointestinal tract. No association between \textit{MLN} and IHPS was demonstrated. Direct sequencing of \textit{RET}, which is associated with motility disturbances in patients with Hirschsprung disease, did not yield statistically significant differences in variations between 32 patients with IHPS and 48 control individuals.\textsuperscript{52}

In pyloric biopsy samples from infants with IHPS, the expression of desmin, which is involved in the organization and functioning of muscle fibres, was higher than in samples from control individuals.\textsuperscript{53} A comparably high expression of desmin was found in the pyloric tissue from two stillborn babies (gestational age 27 and 30 weeks), which suggests that in neonates with IHPS the organization of the pyloric muscle is in a foetal stage. Kobayashi et al.\textsuperscript{54} investigated whether innervation of smooth muscle cells was inappropriate in patients with IHPS. They found a lack of expression of neural cell adhesion molecule (NCAM) and NADPH-diaphorase within the pylorus of 18 affected individuals. Interstitial cells of Cajal, which have an important role in gastrointestinal motility, were found to be lacking in pyloric tissue of patients with IHPS.\textsuperscript{55, 56}

We have summarized above only results of major published molecular investigations. Further studies that focus on, for example, hormonal factors, smooth muscle cell components, growth factors, extracellular matrix proteins, factors involved in muscle innervation and interstitial cells of Cajal have been published, without explaining the pathogenesis of isolated IHPS in more detail and are reviewed by Panteli \textit{et al.}\textsuperscript{57}

\section*{Animal studies}

In 1970, Dodge \textit{et al.}\textsuperscript{58} succeeded in inducing IHPS in puppies after maternal stimulation with pentagastrin, a hormone that stimulates gastric acid secretion via the release of histamine. Subsequent studies investigating preoperative and postoperative levels of gastrin in children with IHPS have yielded contradictory results.\textsuperscript{59, 60} Vanderwinden’s\textsuperscript{41} NO hypothesis was confirmed in various mouse models that induced hypertrophy of the pyloric sphincter by targeted knockout of \textit{NOS1}.\textsuperscript{61, 62} Other studies demonstrated pyloric hypertrophy in animals following perinatal inhibition of NO synthase.\textsuperscript{63-65} An \textit{Hph1} mouse mutant, originally developed as a model for phenylketonuria, was found to have an increased risk of developing IHPS.\textsuperscript{66} In humans, phenylketonuria is known to be associated with IHPS.\textsuperscript{67} \textit{Hph1} mice are deficient in tetrahydrobiopterin, which is a cofactor to the enzyme NOS. As a result, \textit{Hph1} mice show diminished NOS activity, which possibly leads to pyloric hypertrophy. The findings from these animal models indicate that NO synthase
is indeed essential for normal pyloric functioning. In 2008, it was reported that pyloric sphincter manometry in nNOS knockout mice yielded pressure levels and motility indices that were not statistically significantly different from wild-type controls. Still, nNOS deficiency in these mice led to clinical gastric stasis and bezoars. Animal models for many other human syndromes that are associated with IHPS have been reported, but we have been unable to find descriptions of models with increased frequencies of IHPS.

**Syndromic IHPS**

A large number of syndromes are associated with IHPS. The exact prevalence of syndromic forms of IHPS is unknown. However, in a retrospective study, the prevalence of at least one major congenital malformation in 4,000 patients with IHPS from New York State registries was increased compared with the general population (7% versus 3.7%). We performed a literature search to identify clinical syndromes that are associated with IHPS. Some of the thus retrieved syndromes are common, others rare, some are almost always associated with IHPS, in others the association has been reported only infrequently. We decided to tabulate all the syndromes here irrespective of frequencies, as data regarding the frequency of IHPS can be biased and incomplete. We subcategorized all syndromes according to their (presumed) pathogenesis (Tables 3–7). The functioning of the pyloric sphincter is complex and many hypotheses regarding the pathogenesis of IHPS exist (see below). We have categorized the syndromes in the pathogenetic subcategory that we assumed to have the most notable involvement. We discuss a single syndrome from each subcategory to illustrate the presumed pathogenesis of IHPS.

**Neuromuscular**

X-linked myotubular myopathy 1, a recessive disorder, is characterized by abnormalities of skeletal muscles leading to severe hypotonia and respiratory distress (Table 3). In the majority of patients, X-linked myotubular myopathy 1 is caused by mutations in \( \text{MTM1} \). This gene is located at Xq28 and encodes myotubularin, which is required for muscle cell differentiation. Mutations in \( \text{MTM1} \) lead to an accumulation of central nuclei in skeletal muscle. A zebrafish model of X-linked myotubular myopathy 1 showed abnormal neuromuscular junction organization, which suggests that impaired neuromuscular transmission is present. Herman et al. described a history of IHPS in 4 of 35 patients with X-linked myotubular myopathy 1. The pathogenesis of IHPS in these patients remains unknown. The abnormal differentiation of muscle cells might lead to localized morphological muscle changes. Impaired neuromuscular transmission, as observed in zebrafish, could also result in abnormal pyloric innervation, leading to obstruction of the pylorus.
Connective tissue

Patients with Ehlers–Danlos syndrome (EDS) type III present with joint hypermobility and might have aortic or mitral regurgitation (Table 3). EDS type III can be caused by mutations in *TNXB*, which encodes the extracellular matrix protein tenascin XB. In one patient with the clinical characteristics of EDS type III, a mutation in *COL3A1* (which encodes procollagen III) has been reported; this mutation typically causes EDS type IV with severe skin problems and vascular ruptures. De Felice et al. described noteworthy asymptomatic joint hypermobility in children with IHPS and their parents. The patients with joint hypermobility showed an increased frequency of absent mandibular frenulum, suggesting a systemic abnormality of the extracellular matrix. Other studies have found high amounts of newly synthesized procollagen in the pylorus of patients with IHPS, suggesting that the pylorus is actively synthesizing collagen, which results in hypertrophy.

Metabolic

Smith–Lemli–Opitz syndrome (SLOS) is a multiple congenital malformation syndrome caused by mutations in *DHCR7* that result in a deficiency of 7-dehydrocholesterol reductase (Table 4). This enzyme is the last in the cholesterol biosynthesis cascade and a deficiency leads to the accumulation of cholesterol precursors and consequently reduced concentrations of cholesterol. Symptoms include intellectual disability, failure to thrive, behavioural abnormalities, unusual face morphology, gastrointestinal disorders and skeletal.

![Figure 1 | Nitric oxide and its influence in smooth muscle relaxation.](image)
Simplified scheme of the metabolic pathway of nitric oxide and its role in smooth muscle cell relaxation in the gastrointestinal tract. Abbreviations: cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; NO, nitric oxide; NOS, nitric oxide synthase.
genital and organ malformations.\textsuperscript{78} Schechter \textit{et al.}\textsuperscript{26} calculated the incidence of SLOS in infants with IHPS to be 157-fold higher than in control individuals. IHPS was reported in 14\% of 164 patients with histochemically confirmed SLOS.\textsuperscript{78} A study investigating plasma levels of sterol in 10 patients with isolated IHPS and full analysis of the cholesterol pathway in fibroblasts in three of the patients showed no detectable cholesterol abnormalities.\textsuperscript{80} How IHPS develops in patients with SLOS remains unknown.

**Intracellular signalling pathway disturbances**

Familial nodular heterotopia is characterized by periventricular heterotopic nodules and seizures. The condition has been linked to mutations in \textit{FLNA}, which is located on chromosome Xq28. \textit{FLNA} encodes filamin A, a protein that regulates the reorganization of the actin cytoskeleton by interaction with integrins, transmembrane receptor complexes and second messengers. Filamin A is important for modulation of cell migration, therefore mutations in \textit{FLNA} might lead to neuronal and non-neuronal migration defects. Mutations in \textit{FLNA} might also result in chronic idiopathic intestinal pseudo-obstruction (OMIM\# 300048) and FG syndrome 2 (OMIM\# 300321), both of which are associated with IHPS. How disturbed intracellular signalling might lead to IHPS is unknown.

Nezelof\textsuperscript{81} reported X-linked periventricular nodular heterotopia associated with a short gut, intestinal malrotation and IHPS in three patients. The myenteric plexus of these patients was normal, which suggests that a neuronal migration or neuromuscular transmission defect might be responsible for the clinical symptoms of X-linked periventricular nodular heterotopia.

**Intercellular communication disturbances**

Hypoplastic left heart syndrome is characterized by an underdevelopment of the left ventricle and its components, which results in a disturbed circulation with patent ductus arteriosus and foramen ovale and enlargement of the right atrium, right ventricle and pulmonary artery (Table 4).\textsuperscript{82} \textit{GJA1}, localized at 6q21, has been associated with hypoplastic left heart syndrome.\textsuperscript{83} \textit{GJA1} encodes gap junction \(\alpha1\) protein, a major component of gap junctions containing intracellular channels, which are important for diffusion of ions and signalling molecules from cell to cell. Gap junctions are thought to have an important role in the synchronized heart contraction and in embryonic development. IHPS has been described in a case report of a patient with hypoplastic left heart syndrome.\textsuperscript{84} \textit{GJA1} has also been associated with oculodentodigital dysplasia (OMIM\# 164200). Patients with oculodentodigital dysplasia often present with a spastic bladder.\textsuperscript{85} Therefore, one could speculate that a gap junction disorder can lead to overstimulation of the bladder in patients with oculodentodigital dysplasia and of the pylorus in patients with hypoplastic left heart syndrome.
Ciliopathies

Kallmann syndrome is characterized by hypogonadotropic hypogonadism and anosmia (Tables 3 and 5). Other features include delayed skeletal maturation, cleft lip and/or palate, renal agenesis and manual synkinesis. Six genes have been identified that are associated with Kallmann syndrome (Tables 3 and 5) but in nearly 70% of cases the genetic defect remains to be discovered.\textsuperscript{86} Deletions in \textit{KAL1} have been found in about 7% of patients with Kallmann syndrome. \textit{KAL1} encodes a protein—anosmin-1—that has notable similarities with proteins involved in neural cell adhesion and axonal path finding, as well as the movement of cellular components.\textsuperscript{87} This finding suggests that \textit{KAL1} could have a specific role in neuronal migration and has functional characteristics resembling those of cilia. Cilia are omnipresent organelles that function as antennae of the developing cell.\textsuperscript{88} How this property relates to IHPS is uncertain.\textsuperscript{89}

DNA-repair disturbances

Cornelia de Lange syndrome is characterized by growth retardation, intellectual disability, characteristic facial features, limb defects, hirsutism, gastrointestinal dysfunction and cardiac, ophthalmologic and genitourinary abnormalities (Table 5).\textsuperscript{90} Jackson et al.\textsuperscript{91} reported that 12 of 310 patients with Cornelia de Lange syndrome had a history of IHPS. Cornelia de Lange syndrome is associated with mutations in \textit{NIPBL}, located at 5p13–14, in up to 56% of patients. The fly homologue of NIPBL, Nipped-B, facilitates enhancer–promoter communication and regulates Notch signalling and other developmental pathways.\textsuperscript{92} Nipped-B is also homologous to a family of chromosomal adherins with roles in chromatid cohesion, chromosome condensation and DNA repair. In human cells with mutant \textit{NIPBL}, the binding of cohesin to promoter regions of actively expressed genes is reduced, suggesting another role of NIPBL in transcriptional dysregulation.\textsuperscript{93} Cornelia de Lange syndrome is regarded as a cohesinopathy, but it remains uncertain whether the disturbed chromatid cohesion or transcription regulation causes the increased incidence of IHPS in patients with this syndrome.

Transcription regulation disorders

Renal cysts and diabetes syndrome is characterized by renal cysts, maturity-onset diabetes of the young, genital tract malformations and gout (Table 5).\textsuperscript{94} Mutations in \textit{HNF1B}, which encodes transcription factor HNF-1\beta, can cause the phenotype. HNF-1\beta is also expressed in the human gut.\textsuperscript{95} In 1989, the cases of a mother and son with hypoplastic glomerulocystic kidney disease were described. The mother had a history of IHPS and the son did not.\textsuperscript{96} In 2001, Bingham et al.\textsuperscript{95} described that both patients had developed early onset diabetes. IHPS has been found in several other diseases associated with renal cysts (Tables 4 and 5). No clear explanation for this association is available. However, in rats with polycystic
kidney disease, down-regulation of NO was involved in cyst formation\(^9^7\) and NO has been identified as a presumably important factor in the pathogenesis of IHPS.\(^4^1\)

**MAPK-pathway disturbances**

Costello syndrome is a systemic disorder characterized by increased prenatal growth, postnatal growth retardation, coarse face, loose skin, nonprogressive cardiomyopathy, a predisposition for malignancies, developmental delay and an outgoing friendly behaviour (Table 5).\(^9^8\) Over 80% of patients share the same \(HRAS\) mutation that affects the MAPK pathway.\(^9^9\) Gripp et al.\(^1^0^0\) reported IHPS in 5 of 58 patients with Costello syndrome who had an \(HRAS\) mutation and speculated that IHPS might result from a localized muscular hypertrophy similar to the hypertrophic cardiomyopathy that is frequently part of Costello syndrome. IHPS has also been described in some other disorders caused by mutations in the MAPK pathway (Table 5). In neurofibromatosis type 1, an adult case with pyloric obstruction by a neurofibroma has been reported, but obviously this was not a patient with IHPS.\(^1^0^0\) This case might suggest that neonates with neurofibromatosis type 1 can present with symptoms similar to those seen in classical IHPS that are caused by a neurofibroma obstructing the pylorus.

**Lymphatic abnormalities**

Lymphoedema-lymphangiectasia-intellectual disability syndrome (LLIDS) is characterized by congenital lymph vessel dysplasia manifesting as congenital lymphoedema of the limbs and intestinal lymphangiectasia, accompanied by unusual facial morphology, variable intellectual disabilities and infrequently other malformations (Table 6).\(^1^0^1\) Mutations in \(CCBE1\) have been found in 23% of patients, suggesting genetic heterogeneity.\(^1^0^2\) Hogan et al.\(^1^0^3\) suggested that \(CCBE1\) defines an independent regulator of lymphangioblast budding and possibly migration. IHPS has been described in one patient with LLIDS, but also in other syndromic forms of lymphatic abnormalities.\(^1^0^4-1^0^6\) The exact mechanism behind the co-occurrence of lymphatic abnormalities and IHPS is unknown.

**Environmental**

Of all the teratogenic agents, alcohol is probably the most common in the general population. Foetal alcohol syndrome results from ethanol exposure during pregnancy and consists of a broad spectrum of developmental defects (foetal alcohol spectrum disorders). Growth retardation, malformations, certain facial features and impairment of the central nervous system are the most common manifestations (Table 6). Neuronal and glial cells seem to be especially vulnerable to ethanol exposure. IHPS has been described in several patients with foetal alcohol syndrome.\(^1^8^,^1^9,^1^0^7\) No clear explanation for this association exists.
Chromosomal

IHPS is present as a clinical feature in several chromosomal abnormalities (Table 7). This finding suggests that IHPS might be part of contiguous genetic syndromes that involve genes necessary for normal pyloric functioning.\textsuperscript{108} Except for duplication 9q syndrome, no regions of these chromosomal anomalies have been studied in more detail to identify genes associated with IHPS. Nowadays, array-comparative genomic hybridization (array-CGH) has become the first test to perform in patients with congenital malformations or other syndromes.\textsuperscript{109} With array-CGH, imbalances in groups of genes and sometimes even in individual genes can be identified. Therefore, such arrays might yield valuable results in patients with IHPS, especially those with nonisolated forms. As array-CGH has been applied for a limited number of years in a limited number of countries at the present time, interesting results might be expected in the near future.

Unknown

The pathogenesis of many syndromes that are associated with IHPS is unknown (Table 6). As our knowledge of gene defects and gene functioning increases, our understanding of the pathophysiology of IHPS will probably improve rapidly in the near future.

Conclusions

We have demonstrated that extensive research in isolated IHPS has shown that genetic factors have an important role in the pathophysiology of IHPS, but despite this observation no causative gene or genes have been recognized. Linkage studies have provided heterogeneous results and could not be replicated in subsequent studies. In the first GWAS, only a very small proportion of IHPS cases could be explained by the identified loci.\textsuperscript{110} The explanations for this lack of robust results remain uncertain. One explanation might be clinical and genetic heterogeneity of IHPS. Our observation that nonisolated IHPS can be caused by mutations in genes with very different functions provides additional evidence that isolated IHPS will probably be similarly heterogeneous. Indeed, genetic heterogeneity in disorders is much more frequent than anticipated, as has been shown in schizophrenia and intellectual disability.\textsuperscript{111, 112} If a similarly large genetic heterogeneity does exist in IHPS, it would hamper GWAS considerably. A second explanation might be differences between study populations. These differences might be in genetic make-up, that is, the presence of differences in several variants within the genome, but it might also be caused by differences in environmental factors, such as nutrition and cultural habits. Our DNA is subject to continuous changes induced by such environmental factors that result in changes in imprinting status and thereby gene expression, which can be inherited over several generations.\textsuperscript{113} This pattern will not become apparent when performing
GWAS. Therefore, the role of epigenetic factors should also be considered when studying IHPS in different populations.

Nowadays, the strategy to detect causes of heterogeneous disorders is often the use of next-generation technologies in extreme phenotypes and/or GWAS in large cohorts of patients. Causative genes of many of the syndromes in Tables 3–7 have been found by positional cloning techniques, but in recent years next-generation techniques have proved to be increasingly successful. Still, positional cloning studies in families with multiple affected members are valuable and have a considerable chance for success. Interpretation of results of GWAS has been more difficult as a result of the heterogeneity of many disorders. Interpretation will probably become more successful if the various ways a disorder can be caused are known. Knowledge of pathogenetic pathways and networks will enable more targeted evaluation of data and recognition of correlations in evaluating results of GWAS. This Review outlines our present knowledge of causes of both isolated and syndromic IHPS, and is a first attempt to group causes of syndromic IHPS on the basis of presumed pathogenesis. A reliable clue for the pathogenesis of IHPS could be found in only a limited number of syndromes. Categorizing the disorders generates the general hypotheses regarding the pathogenesis of isolated IHPS (Box 2).

Undoubtedly the tabulation will contain mistakes, as with time more and possibly other functions of genes will become clear. Furthermore, in more syndromic conditions a correlation between the syndrome and IHPS will become evident, which might open new avenues of investigation. IHPS is a very heterogenic disorder. Research in the near future should therefore focus on extreme phenotypes that are present in syndromic forms of IHPS, and on well-defined large multigenerational families with multiple affected members or GWAS. Studies will have the best chance for success if detailed phenotyping is applied and if knowledge about the various possible causative pathways is used. We hope this Review will serve as a basis for future studies in IHPS, and will stimulate researchers to use the results of extreme phenotype studies in evaluation of their results in isolated IHPS.

Review Criteria

The PubMed, Embase and Online Mendelian Inheritance in Man (OMIM) databases and London Medical Databases (LMDB) were searched using the term ‘pyloric stenosis’ combined with ‘epidemiology’, ‘family’, ‘aggregation’, ‘clustering’, ‘linkage (genetics)’, ‘genome wide association study’, ‘genetic association studies’, ‘genes’, ‘syndrome’, ‘disease’, ‘disorder’, ‘genetic’. IHPS was defined as an acquired hypertrophy of the pylorus in a baby with a maximum age of 12 months. Patients born with an obstruction of the pylorus or prenatally diagnosed IHPS were excluded. No language restrictions were applied. Reference lists of retrieved papers were hand searched for other relevant papers.
Chapter 2

Box 1 Definitions of genetic terms

**Epigenetics** is the study of heritable changes in DNA expression by changes other than mutations in the DNA sequence itself. The best known examples are alterations in DNA methylation or histone modification, which both lead to a change in reading the DNA sequence and therefore in production of the proteins coded for by that part of the DNA.

**Familial aggregation describes** clustering of a disorder within a family beyond what might be expected by chance. Such clustering is usually caused by genetic factors or shared environmental factors.

**Heritability** is the proportion of differences in a particular sign or symptom within individuals that is attributable to genetic differences.

**Linkage analysis** is the method to determine whether a disorder is inherited within a family together with certain parts (loci) of the DNA, which would point to localization of the cause of the disorder in these cosegregating parts. The analyses use markers spread more or less evenly throughout the genome.

**SNP** are a variation in the sequence of the DNA that can exist between persons. Usually SNPs have two different forms but some have more. SNPs are most often found in noncoding regions of the DNA and are less common within genes.

**Whole-exome sequencing** is the selective sequencing of the total genome of only the coding regions of genes (exons) and not the non-coding DNA within genes (introns) or between genes.

**Next-generation sequencing** is a high throughput method of sequencing making it possible to sequence the complete genome or large regions of the genome in a short period of time for acceptable costs.

**Genome-wide association studies** examine genetic variants (SNPs) in individuals of a population to identify an association between a disorder and such variants. This way one hopes to identify genes that cause the disorder.

**Genome-wide array comparative genomic hybridization** is a high-resolution analysis of copy number variations in the whole genome. This method enables very small structural changes of chromosomes (deletions or duplications) to be detected.

**Extreme phenotype** is the occurrence of a sign or symptom in a person with a disorder in such a way that it clearly sets this person apart from others with this disorder. This sign or symptom can be directly related to the disorder but also completely unrelated. It enables recognition of specific subgroups in individuals with a disorder, which has proven to be extremely helpful in finding causes of disorders.
Box 2 Identified pathogenetic pathways that can be associated with IHPS

**Neuromuscular disorders**
Changes in differentiation or innervation of the pylorus, either innate or acquired, might lead to hypertrophy of the pylorus. This results in an obstruction causing IHPS.

**Connective tissue disorder**
Abnormal or excess of connective tissue in the pylorus gradually developing after birth leads to a mechanic obstruction of the pylorus or to altered muscular functioning resulting in prolonged contractions of the pylorus.

**Metabolic disorder**
We assume disturbed intracellular metabolism in the pylorus or a storage phenomenon might both be possible.

**Intracellular pathway disturbance**
Unknown mechanism.

**Intercellular communication disturbance**
One may postulate that disturbed signalling between cells causes abnormal stimulation of pyloric muscle cells.

**Ciliary malfunctioning**
Unknown mechanism.

**DNA-repair disturbance**
Unknown mechanism.

**Transcription regulation disorder**
Unknown mechanism.

**MAPK-pathway disturbances**
Unknown mechanism; it has been suggested that hypertrophy of the pyloric muscle has the same pathogenesis as the hypertrophic cardiomyopathy that can be a manifestation of a disturbance of this pathway.

**Lymphatic abnormalities**
Unknown mechanism.

**Environmental factors**
Unknown mechanism.
Table 1 | Overview of familial aggregation studies investigating the risk for IHPS*

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>M:F ratio</th>
<th>Incidence population</th>
<th>Heritability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krogh et al. (2010)</td>
<td>1,999,738 children of whom 3362 had IHPS</td>
<td>4.4:1</td>
<td>1.7/1.000 M 2.7 F 0.7</td>
<td>87%</td>
</tr>
<tr>
<td>Czeizel &amp; Tusnady (1984)‡</td>
<td>148 Hungarian cases</td>
<td>4-5:1</td>
<td>1.5/1.000 M 2.2 F 0.7</td>
<td>NR</td>
</tr>
<tr>
<td>Adelstein &amp; Fedrick (1976)†</td>
<td>220 UK cases</td>
<td>5.5:1</td>
<td>2.5/1.000 M 4.1 F 0.8</td>
<td>NR</td>
</tr>
<tr>
<td>Dodge (1970)§</td>
<td>480 Irish cases</td>
<td>4:1</td>
<td>2.5/1.000 M 4.2 F 1.0</td>
<td>1st degree 58%; 2nd degree 24%; 3rd degree 38%</td>
</tr>
<tr>
<td>Carter &amp; Evans (1969a)‡</td>
<td>563 UK cases</td>
<td>5:1</td>
<td>3/1.000 M 5.0 F 1.0</td>
<td>1st degree 76%; 2nd degree 27%; 3rd degree 50%</td>
</tr>
<tr>
<td>Carter &amp; Evans (1969b)‡</td>
<td>426 UK cases</td>
<td>5:1</td>
<td>3/1.000 M 5.0 F 1.0</td>
<td>1st degree 76%; 2nd degree 27%; 3rd degree 50%</td>
</tr>
<tr>
<td>McKeown et al. (1951)‡</td>
<td>489 UK cases</td>
<td>4.2:1</td>
<td>3/1.000 M 4.7 F 1.1</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Risks are displayed as sex specific rate ratios (incidence in relatives/incidence in reference population according to sex).
‡Included in the re-analysis by Mitchell et al.37§Male and female incidence rates were estimated by the authors of this actual paper based on the given overall incidence rate and sex ratio. Risk ratios were calculated based on data provided by Mitchell et al.37 Abbreviations: IHPS, infantile hypertrophic pyloric stenosis; F, female; M, male.

Table 2 | Overview of linkage studies in infantile hypertrophic pyloric stenosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Targeted on candidate region</th>
<th>Significant linkage</th>
<th>Chromosomal region (candidate gene(s))</th>
<th>Replication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chung (1993)§</td>
<td>20 families</td>
<td>Yes</td>
<td>No</td>
<td>9q11-q33 (dupl 9q syndrome)</td>
<td>No</td>
</tr>
<tr>
<td>Chung (1996)§</td>
<td>27 families</td>
<td>Yes</td>
<td>Yes</td>
<td>12q (NOS1)</td>
<td>Unsuccessful (Söderhall 1998)</td>
</tr>
<tr>
<td>Söderhall (1998)§</td>
<td>3 families</td>
<td>Yes</td>
<td>No</td>
<td>12q (NOS1)</td>
<td>No</td>
</tr>
<tr>
<td>Capon (2006)†</td>
<td>1 family</td>
<td>No</td>
<td>Yes</td>
<td>16p12–13 (MYH11, GRIN2A)</td>
<td>Unsuccessful in 10 additional families (Capon 2006)</td>
</tr>
<tr>
<td>Everett (2008)§</td>
<td>81 families</td>
<td>No</td>
<td>Yes</td>
<td>11q14–q22, Xq23 (TRPC5, TRPC6)</td>
<td>No</td>
</tr>
<tr>
<td>Everett (2008)†</td>
<td>1 family</td>
<td>No</td>
<td>Yes</td>
<td>16q24 (SLC7A5)</td>
<td>Unsuccessful in 14 additional families (Everett 2008)</td>
</tr>
<tr>
<td>Svenningsson (2012)‡</td>
<td>37 families and 31 additional families</td>
<td>No</td>
<td>Yes</td>
<td>2q24 (GLP-2), 6p21 (MLN), 7p21 (NPY), 12q24 (NOS1)</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 1

<table>
<thead>
<tr>
<th>Study Population</th>
<th>M:F ratio</th>
<th>Incidence population</th>
<th>Heritability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mother</td>
<td>NR</td>
<td>4.4:1</td>
<td>M 2.7</td>
</tr>
<tr>
<td>Father or mother</td>
<td>NR</td>
<td>1.7/1.000</td>
<td>F 0.7</td>
</tr>
<tr>
<td>Brother</td>
<td>16.7, 17.5, 13.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sister</td>
<td>29.8, 28.2, 37.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brother or sister</td>
<td>18.5, 18.8, 17.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monozygotic twin sibling</td>
<td>overall 182</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizygotic twin sibling</td>
<td>overall 29.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2

Table 3 | Neuromuscular and connective tissue syndromes associated with IHPS

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>OMIM</th>
<th>Mayor manifestations</th>
<th>Inheritance</th>
<th>Gene/chromosome region</th>
<th>Incidence syndrome*</th>
<th>Number of IHPS cases (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuromuscular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital generalized lipodystrophy type IV</td>
<td>613327</td>
<td>Congenital generalized lipodystrophy, ECG abnormalities, muscular dystrophy</td>
<td>AR</td>
<td>PTRF/17q21</td>
<td>1:25,000–100,000</td>
<td>5–10</td>
</tr>
<tr>
<td>X-linked myotubular myopathy</td>
<td>310400</td>
<td>Congenital hypotonia, facial diplegia, myopathy</td>
<td>XL</td>
<td>MTM1/Xq28</td>
<td>1:25,000–100,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Marden–Walker syndrome</td>
<td>248700</td>
<td>Microcephaly, blepharophimosis, joint contractures</td>
<td>AR</td>
<td>Unknown</td>
<td>1:100,000–1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Paramyotonia congenita</td>
<td>168300</td>
<td>Prolonged myotonia induced by exposure to cold, inability to relax muscles</td>
<td>AD</td>
<td>SCN4A/17q23</td>
<td>1:25,000–100,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Connective tissue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apert syndrome</td>
<td>101200</td>
<td>Craniosynostosis, complete syndactyly of fingers and toes</td>
<td>AD</td>
<td>FGFR2/10q26</td>
<td>1:65,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Beare–Stevenson syndrome</td>
<td>123790</td>
<td>Craniosynostosis, acanthosis nigricans, cutis gyrata</td>
<td>AD</td>
<td>FGFR2/10q26</td>
<td>1:100,000–1,000,000</td>
<td>1–4</td>
</tr>
</tbody>
</table>
## Table 3 | Cont.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>OMIM</th>
<th>Mayor manifestations</th>
<th>Inheritance</th>
<th>Gene/chromosome region</th>
<th>Incidence syndrome*</th>
<th>Number of IHPS cases (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotic syndrome type 1</td>
<td>256300</td>
<td>Proteinuria, renal failure</td>
<td>AR</td>
<td>NPHS1/19q13</td>
<td>1:25,000–100,000 (1:8,000 in Finland)</td>
<td>5–10</td>
</tr>
<tr>
<td>Denys–Drash syndrome</td>
<td>194080</td>
<td>Proteinuria, ambiguous genitalia, Wilms tumour</td>
<td>AR</td>
<td>WT1/11p13</td>
<td>1:25,000–100,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Ehlers–Danlos type III</td>
<td>130020</td>
<td>Joint hypermobility</td>
<td>AD</td>
<td>TNXB/6p21</td>
<td>1:10,000–25,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Ehlers–Danlos type IV</td>
<td>130050</td>
<td>Vascular fragility, thin skin, prominent eyes, thin nose, decreased subcutaneous fat</td>
<td>AD, AR</td>
<td>COL3A1/2q32</td>
<td>1:100,000–1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Kallmann syndromeb</td>
<td>308700,</td>
<td>Anosmia, hypogonadotropic hypogonadism</td>
<td>AD, AR,</td>
<td>KAL1/Xp22, FGFR1/8p11,</td>
<td>1:10,000–25,000</td>
<td>1–4</td>
</tr>
<tr>
<td></td>
<td>147950,</td>
<td></td>
<td>XL, M</td>
<td>PROKR2/20p12, PROK2/3p13, CHD7/8q12, FGF8/10q24, WDR11/10q26</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>607123,</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>607002,</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>600483,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>608892</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Knobloch syndrome type 2</td>
<td>608454</td>
<td>Myopia, retinal detachment, encephalocele</td>
<td>unknown</td>
<td>Unknown</td>
<td>1:100,000–1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Osteoglophonic dwarfism</td>
<td>166250</td>
<td>Craniosynostosis, short stature, skeletal dysplasia</td>
<td>AD</td>
<td>FGFR1/8p11</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Pfeiffer syndrome</td>
<td>101600</td>
<td>Craniosynostosis, broad thumbs and big toes, syndactylies</td>
<td>AD</td>
<td>FGFR1/8p11, FGFR2/10q26</td>
<td>1:100,000–1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>X-linked intellectual disability, ZDHHC9-related</td>
<td>300799</td>
<td>Intellectual disability, marfanoid habitus</td>
<td>XL</td>
<td>ZDHHC9/Xq26</td>
<td>1:100,000–1,000,000</td>
<td>1–4</td>
</tr>
</tbody>
</table>

For further information about the syndromes in the Table, please use the (freely available) internet sites of OMIM (www.ncbi.nlm.nih.gov/omim), Genereviews (www.ncbi.nlm.nih.gov/sites/GeneTests/review) and Orphanet (www.orpha.net) or the most commonly used textbook ‘Gorlin’s Syndromes of the Head and Neck’. 133 *Estimated incidence of entity according to OMIM and Gorlin’s Syndromes of the Head and Neck. 1 No classical pyloric stenosis; elongation of pyloric channel. 3 Kallmann syndrome is also mentioned in the ciliopathies. Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ECG, electrocardiography; IHPS, infantile hypertrophic pyloric stenosis; M, microdeletion; OMIM, online mendelian inheritance in man; XL, X-linked.
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>OMIM</th>
<th>Mayor manifestations</th>
<th>Inheritance</th>
<th>Gene/ chromosome region</th>
<th>Incidence syndrome*</th>
<th>Number of IHPS cases (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Bary syndrome</td>
<td>614438</td>
<td>Cutis laxa, progeroid features, ophthalmological abnormalities, intrauterine growth retardation</td>
<td>AR</td>
<td>PYCR1/17q25</td>
<td>1:100,000–1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>261600</td>
<td>Intellectual disability, abnormal gait, eczema, epilepsy</td>
<td>AR</td>
<td>PAH/12q23</td>
<td>1:10,000</td>
<td>5–10</td>
</tr>
<tr>
<td>Smith–Lemli–Opitz syndrome</td>
<td>270400</td>
<td>Intellectual disability, failure to thrive, unusual face, skeletal, genital and organ malformations, gastrointestinal motility disorders</td>
<td>AR</td>
<td>DHCR7/11q13</td>
<td>1:25,000</td>
<td>11–50</td>
</tr>
<tr>
<td>X-linked ichthyosis</td>
<td>308100</td>
<td>Ichthyosis, corneal opacities, behavioural problems</td>
<td>XL, M</td>
<td>STS/Xp22</td>
<td>1:6,000 males</td>
<td>5–10</td>
</tr>
<tr>
<td>Zellweger syndrome</td>
<td>214100</td>
<td>Extreme hypotonia, seizures, tall forehead, retinopathy, hepatic dysfunction, renal cysts</td>
<td>AR</td>
<td>PEX1/7q21, PEX2/8q21, PEX3/6q23, PEX5/12p13, PEX6/6p21, PEX10/1p36, PEX12/17q12, PEX13/2p15, PEX14/1p36, PEX16/11p12, PEX19/1q22, PEX26/22q11</td>
<td>1:35,000</td>
<td>1–4</td>
</tr>
<tr>
<td><strong>Intracellular signalling pathway disturbances</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic idiopathic intestinal pseudo-obstruction</td>
<td>300048</td>
<td>Abnormal gastrointestinal mobility, short bowel, hydrenephrosis</td>
<td>XL</td>
<td>FLNA/Xq28</td>
<td>1:100,000–1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Dextro-looped transposition of the great arteries</td>
<td>608808</td>
<td>Complete inversion of the great vessels</td>
<td>S</td>
<td>CFC1/2q21</td>
<td>1:25,000–100,000</td>
<td>1–4</td>
</tr>
<tr>
<td>FG syndrome</td>
<td>305450, 300321, 300406, 300422, 300581</td>
<td>Hypotonia, macrocephaly, anal malformations, constipation</td>
<td>XL</td>
<td>MED12/Xq13, FLNA/Xq28, FG53/Xp22, FG54/Xp11, FG55/Xq22</td>
<td>1:100,000–1,000,000</td>
<td>5–10</td>
</tr>
<tr>
<td>Osteopathia striata with cranial sclerosis</td>
<td>300373</td>
<td>Metaphyseal striations, macrocephaly, cranial sclerosis</td>
<td>XL</td>
<td>FAM123B/Xq11</td>
<td>1:100,000–1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Ulnar-mammary syndrome</td>
<td>181450</td>
<td>Ulnar ray defects, underdeveloped mammea, obesity</td>
<td>AD</td>
<td>TBX3/12q24</td>
<td>1:100,000–1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Visceral neuropathy (familial)</td>
<td>243180</td>
<td>Chronic intestinal pseudo-obstruction</td>
<td>AR, AD</td>
<td>Unknown</td>
<td>&lt;1:1,000,000</td>
<td>5–10</td>
</tr>
</tbody>
</table>
Table 5 | Ciliopathies and disturbances of gene regulation associated with IHPS

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>OMIM</th>
<th>Mayor manifestations</th>
<th>Inheritance</th>
<th>Gene/ chromosome region</th>
<th>Incidence syndrome*</th>
<th>Number of IHPS cases (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ciliopathies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beemer–Langer syndrome†</td>
<td>269860</td>
<td>Dwarfism, oedema, macrocephaly, cleft lip, small external genitalia, dysostosis</td>
<td>AR</td>
<td>Unknown</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Kallmann syndrome†</td>
<td>308700, 147950, 607123, 607002, 600483, 608892</td>
<td>Anosmia, hypogonadotropic hypogonadism</td>
<td>AD, AR, XL, M</td>
<td>KAL1/Xp22, FGFR1/8p11, PROKR2/20p12, PROK2/3p13, CHD7/8q12, FGF8/10q24, WDR11/10q26</td>
<td>1:10,000–25,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Autosomal recessive polycystic kidney disease†</td>
<td>263200</td>
<td>Cystic kidneys, respiratory failure, fibrosis of liver, biliary duct hyperplasia</td>
<td>AR</td>
<td>PKHD1/6p12</td>
<td>1:10,000</td>
<td>1–4</td>
</tr>
<tr>
<td><strong>DNA-repair disturbances</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cornelia de Lange syndrome†</td>
<td>122470</td>
<td>Intellectual disability, prenatal and postnatal growth retardation, unusual face, small hands, limb defects</td>
<td>AD, XL, S</td>
<td>NIPBL/5p13, SMCI/A/Xp11</td>
<td>1:80,000</td>
<td>11–50</td>
</tr>
<tr>
<td>Chromosome 2q37 deletion syndrome†</td>
<td>600430</td>
<td>Intellectual disability, round face, brachydactyly, seizures</td>
<td>AD, M</td>
<td>HDAC4/2q37</td>
<td>1:100,000–1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Glomerulonephritis with sparse hair and telangiectases</td>
<td>137940</td>
<td>Glomerulonephritis, sparse hair, telangiectasias</td>
<td>AD</td>
<td>Unknown</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Lenz microphthalmia†</td>
<td>309800, 300166</td>
<td>Microphthalmia, colobomas of the iris, simple ears, clefting, narrow shoulders, digital anomalies</td>
<td>XL</td>
<td>MAA/Xq27, BCOR/Xp11</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
</tbody>
</table>

For further information about the syndromes in the Table, please use the (freely available) internet sites of OMIM (www.ncbi.nlm.nih.gov/omim), Genereviews (www.ncbi.nlm.nih.gov/sites/GeneTests/review) and Orphanet (www.orpha.net) or the most commonly used textbook ‘Gorlin’s Syndromes of the Head and Neck’.133 *Estimated incidence of entity according to OMIM and Gorlin’s Syndromes of the Head and Neck. Abbreviations: AD, autosomal dominant; AR, autosomal recessive; IHPS, infantile hypertrophic pyloric stenosis; M, microdeletion; OMIM, online mendelian inheritance in man; S, sporadic; XL, X-linked.
Table 5 | Cont.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>OMIM</th>
<th>Mayor manifestations</th>
<th>Inheritance</th>
<th>Gene/ chromosome region</th>
<th>Incidence syndrome*</th>
<th>Number of IHPS cases (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rothmund–Thomson syndrome^{154}</td>
<td>268400</td>
<td>Poikiloderma, photosensitivity, cataract, growth failure, thumb anomalies</td>
<td>AR</td>
<td>RECQL4/8q24</td>
<td>1:25,000–100,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Simpson-Golabi- Behmel syndrome type 1^{155}</td>
<td>312870</td>
<td>Prenatal and postnatal overgrowth, coarse face, congenital heart defects, diaphragmatic hernia, intellectual disability</td>
<td>XL</td>
<td>GPC3/Xq26</td>
<td>1:25,000–100,000</td>
<td>1–4</td>
</tr>
</tbody>
</table>

**Transcription regulation disorder**

| Renal cysts-diabetes syndrome^{96}             | 137920| Renal cysts, renal and genital malformations, diabetes, gout | AD          | HNF1B/17q12             | 1:10,000–25,000     | 1–4                     |

**MAPK-pathway disturbances**

| Costello syndrome^{99, 156}                    | 218040| High birth weight, unusual face, periorificial papillomata, cardiomyopathy, short stature, intellectual disability | AD          | HRAS/11p15              | 1:25,000–100,000    | 5–10                    |
| Noonan syndrome^{157}                          | 163950| Short stature, unusual face, webbed neck, pulmonary stenosis, pectus excavatum, bleeding diathesis | AD          | PTPN11/12q24, KRAS/12p12, SOS1/2p22, RAF1/3p25, NRAS/1p13.2 | 1:1,000             | 1–4                     |

For further information about the syndromes in the Table, please use the (freely available) internet sites of OMIM (www.ncbi.nlm.nih.gov/omim), Genereviews (www.ncbi.nlm.nih.gov/sites/GeneTests/review) and Orphanet (www.orpha.net) or the most commonly used textbook ‘Gorlin’s Syndromes of the Head and Neck’.^{133} *Estimated incidence of entity according to OMIM and Gorlin’s Syndromes of the Head and Neck. ^Kallmann syndrome is also mentioned in the connective tissue syndromes. †Probably allelic to Rothmund-Thomson syndrome. §Not truly a DNA disturbance but involved in cell division control, growth regulation and apoptosis. Abbreviations: AD, autosomal dominant; AR, autosomal recessive; IHPS, infantile hypertrophic pyloric stenosis; M, microdeletion; OMIM, online mendelian inheritance in man; S, sporadic; XL, X-linked.
### Table 6 | Lymphatic abnormalities and syndromes of environmental and unknown origin associated with IHPS

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>OMIM</th>
<th>Mayor manifestations</th>
<th>Inheritance</th>
<th>Gene/ chromosome region</th>
<th>Incidence syndrome*</th>
<th>Number of IHPS cases (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lymphatic abnormalities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cantú syndrome(^\text{104})</td>
<td>239850</td>
<td>Hypertrichosis, osteodysplasia, cardiomegaly, intellectual disability, lymphoedema</td>
<td>AR, AD</td>
<td>Unknown</td>
<td>1:100,000–1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Congenital chylothorax(^\text{106})</td>
<td>603523</td>
<td>Congenital chylothorax</td>
<td>AR</td>
<td>Unknown</td>
<td>1:25,000–100,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Lymphoedema-Lymphangiectasia-Intellectual disability syndrome(^\text{158, 159})</td>
<td>235510</td>
<td>Intestinal lymphangiectasia, lymphoedema, unusual face, intellectual disability</td>
<td>AR</td>
<td>CCBE1/18q21</td>
<td>1:25,000–100,000</td>
<td>1–4</td>
</tr>
<tr>
<td><strong>Environmental</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal alcohol syndrome(^\text{18, 19, 107})</td>
<td>NA</td>
<td>Prenatal and postnatal growth retardation, microcephaly, unusual face, intellectual disability</td>
<td>E</td>
<td>Unknown</td>
<td>1:800</td>
<td>5–10</td>
</tr>
<tr>
<td>Fetal penicillamine embryopathy(^\text{160})</td>
<td>NA</td>
<td>Cutis laxa, contractures, CNS abnormalities, inguinal hernia</td>
<td>E</td>
<td>Unknown</td>
<td>1:100,000–1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthrogryposis, Perthes disease and upward gaze palsy(^\text{161})</td>
<td>NA</td>
<td>Arthrogryposis, upward gaze palsy, avascular necrosis of capital femoral epiphysis, atopy, congenital heart disease</td>
<td>AR</td>
<td>Unknown</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Crow syndrome(^\text{162})</td>
<td>NA</td>
<td>Agammaglobulinaemia, microcephaly, craniosynostosis, cleft palate</td>
<td>AR</td>
<td>Unknown</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Fine–Lubinsky syndrome(^\text{163})</td>
<td>601353</td>
<td>Brachycephaly, cataract, deafness, microstomia, brachydactyly, intellectual disability</td>
<td>AR</td>
<td>Unknown</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Fryns syndrome(^\text{164})</td>
<td>229850</td>
<td>Diaphragmatic hernia, unusual face, distal limb anomalies</td>
<td>AR</td>
<td>Unknown</td>
<td>1:12,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Harrod syndrome(^\text{165, 166})</td>
<td>601095</td>
<td>Thin body build, narrow face, arachnodactyly, megacolon, intellectual disability</td>
<td>AR</td>
<td>Unknown</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Kaufman oculocerebrofacial syndrome(^\text{167})</td>
<td>244450</td>
<td>Microcephaly, hypertelorism, microcornea, myopia, unusual face, intellectual disability</td>
<td>AR</td>
<td>Unknown</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Lowry–Maclean syndrome(^\text{168})</td>
<td>600252</td>
<td>Congenital heart disease, diaphragmatic hernia, clefting, intellectual disability</td>
<td>AD</td>
<td>Unknown</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
</tbody>
</table>
Toriello–Carey syndrome\(^{170}\) 217980 Hypotonia, cleft palate, heart defects, agenesis corpus callosum, unusual face, intellectual disability AR Unknown 1:100,000–1,000,000 1–4

Yunis-Varón syndrome\(^{171}\) 216340 Ossification defects of skull and clavicles, absent thumbs and halluces, alopecia AR Unknown 1:100,000–1,000,000 1–4

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Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system; E: environmental; IHPS, infantile hypertrophic pyloric stenosis; NA, not applicable; OMIM, online mendelian inheritance in man.

### Table 7 | Chromosomal abnormalities associated with IHPS

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>OMIM</th>
<th>Mayor manifestations</th>
<th>Incidence syndrome(^*)</th>
<th>Number of IHPS cases (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deletion 1q25(^{172})</td>
<td>NA</td>
<td>Microdolichocephaly, unusual face, digital anomalies, intellectual disability</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Maternal uniparental disomy 21(^{173})</td>
<td>NA</td>
<td>Prenatal and postnatal growth retardation, unusual face, renal failure</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Deletion 3q29(^{174}) 609425</td>
<td>growth retardation, unusual face, intellectual disability</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
<td></td>
</tr>
<tr>
<td>Translocation (8;17)(q24;q25)(^{175})</td>
<td>NA</td>
<td>Intellectual disability, developmental delay, unusual face, dysmorphic features, epilepsy, behavioural problems</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Duplication 9q (inv insert (12;9) (p13;q23q13) maternal)(^{39})</td>
<td>NA</td>
<td>Unusual face, preauricular pits, abnormalities of hands, hypotonia, intellectual disability</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Translocation (10;13) (p15.1;q34)(^{176})</td>
<td>NA</td>
<td>Growth retardation, unusual face, heart defect, inguinal hernia, intellectual disability</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Deletion 10p13(^{177})</td>
<td>NA</td>
<td>Microcephaly, micrognathia, congenital heart disease, unusual face, intellectual disability</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Deletion 11q23(^{178}) 147791</td>
<td>growth retardation, trigonocephaly, eye abnormalities, thrombocytopenia, intellectual disability</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
<td></td>
</tr>
<tr>
<td>Partial trisomy 13q22, partial monosomy 18q21(^{179})</td>
<td>NA</td>
<td>Unusual face, anomalies of hands and feet, heart defects</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Trisomy 13(^{180})</td>
<td>NA</td>
<td>Growth retardation, clefting, occipital skin defects, brain malformations, cardiac anomalies, anomalies of hand and feet, intellectual disability</td>
<td>1:12,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Duplication 14q/deletion 14q(^{181})</td>
<td>NA</td>
<td>Hypotonia, short stature, unusual face, intellectual disability</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Trisomy 18(^{180})</td>
<td>NA</td>
<td>Unusual face, cardiac and central nervous system abnormalities, omphalocele, intellectual disability</td>
<td>&lt;1:1,000,000</td>
<td>5–10</td>
</tr>
<tr>
<td>Deletion 18qter&lt;sup&gt;182&lt;/sup&gt;</td>
<td>133705</td>
<td>Narrow external auditory canal, vertical talus, hypertelorism, anal atresia, intellectual disability</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>--------------------------</td>
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<td>-------------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Deletion 20q11&lt;sup&gt;183&lt;/sup&gt;</td>
<td>NA</td>
<td>Prenatal growth retardation, postnatal overgrowth, unusual face, intellectual disability</td>
<td>&lt;1:1,000,000</td>
<td>1–4</td>
</tr>
<tr>
<td>Trisomy 21&lt;sup&gt;185&lt;/sup&gt;</td>
<td>190685</td>
<td>Hypotonia,, unusual face, cardiac anomalies, Hirschsprung disease, growth retardation, intellectual disability</td>
<td>1:800</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Mosaicism 45,X/46, XX&lt;sup&gt;186&lt;/sup&gt;</td>
<td>NA</td>
<td>Gonadal dysgenesis, short stature, cardiovascular abnormalities, kidney malformations</td>
<td>1:7,500 females</td>
<td>1–4</td>
</tr>
</tbody>
</table>

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