

## Genetic contribution to motility disorders of the upper gastrointestinal tract

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**Core tip:** Achalasia, functional dyspepsia and hypertrophic pyloric stenosis represent the main motility disorders of upper gastrointestinal tract. All these diseases have a less known pathophysiology and a presumable genetic predisposition in common. This review outlines the current knowledge on genes involved in the onset of these pathologies in order to promote further association studies which can help to explain this complex picture and find new therapeutic targets.

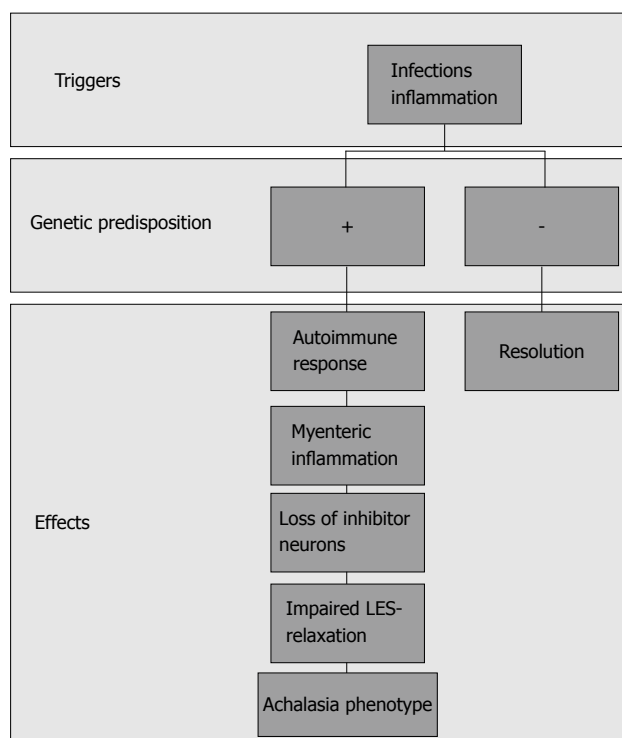
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### Abstract

Motility disorders of the upper gastrointestinal tract encompass a wide range of different diseases. Esophageal achalasia and functional dyspepsia are representative disorders of impaired motility of the esophagus and stomach, respectively. In spite of their variable prevalence, what both diseases have in common is poor knowledge of their etiology and pathophysiology. There is some evidence showing that there is a genetic predisposition towards these diseases, especially for achalasia. Many authors have investigated the possible genes involved, stressing the autoimmune or the neurological hypothesis, but there is very little data available. Similarly, studies supporting a post-infective etiology, based on an altered immune response in susceptible individuals, need to be validated. Further association studies can help to explain this complex picture and find new therapeutic targets. The aim of this review is to summarize current knowledge of genetics in motility disorders of the upper gastrointestinal tract, addressing how genetics contributes to the development of achalasia and functional dyspepsia respectively.

### INTRODUCTION

Digestive motility is a highly coordinated process which enables mixing, absorption and propulsion of the ingesta through the gastrointestinal tract up to expulsion of residues. This function depends on a finely balanced integration between smooth muscle contractility and the related pacemaker activity evoked by the interstitial cells of Cajal (ICCs) that are finely regulated by intrinsic and extrinsic innervations [*i.e.*, enteric nervous system (ENS) and sympathetic and parasympathetic nerves, respectively]<sup>[1,2]</sup>. A disturbed digestive motility can occur as a result of a variety of abnormalities affecting each of these elements (alone or in combination), with consequent altered physiology of gut peristalsis and symptom generation.



**Figure 1** Supposed pathophysiology of achalasia: triggering external factors are able to induce a loss of inhibitor neurons in individuals genetically predisposed, causing an impaired lower esophageal sphincter relaxation.

The symptom complex is site specific and depends on the gastrointestinal tract involved. Thus, patients with disturbed esophageal motility may complain of dysphagia, regurgitation or chest pain, whereas patients with gastric dysmotility may report symptoms of nausea, vomiting, postprandial fullness, early satiety or epigastric pain. Esophageal achalasia and functional dyspepsia are the most representative motility disorders of the upper gastrointestinal (GI) tract, with the first rare and well characterized and the latter highly prevalent and less defined.

Like the majority of functional gastrointestinal disorders (FGIDs), they are characterized by the persistence of symptoms in the absence of reliable biological markers. As for other complex diseases, the pathophysiology of impaired upper GI tract motility diseases is supposed to be multifactorial, with triggering external factors that are able to generate the gastrointestinal dysfunction in individuals who are more or less genetically predisposed (Figure 1). The idea that an individual genotype may contribute to the development of FGIDs is suggested by clinical observations and prospective studies indicating that there is clustering of FGIDs within families<sup>[3,4]</sup> and an increased concordance in monozygotic twins<sup>[5-7]</sup>. The most commonly used approach in functional dyspepsia (FD) to date has been to search for correlations of a candidate gene polymorphism with the symptom based phenotype. More recently, a few studies have aimed to identify correlations between gene polymorphism and biological intermediate phenotypes, such as impaired motility.

In this review, we summarize the current knowledge

on the genetic contribution to upper GI motor disorders. We evaluate the most recent literature on the genetic epidemiology of representative motility disorders of the upper GI tract (UGT). We describe the putative genetic contributions that have been addressed and the potential association with single mechanisms, such as receptors, transporters and translation, or transduction mechanisms involved in the disturbed motility of the esophagus, stomach and pylorus, respectively impaired in esophageal achalasia, functional dyspepsia and hypertrophic pyloric stenosis. Each of the diseases can be considered paradigmatic because of the following: (1) hypertrophic pyloric stenosis (HPS) is characteristic of infants and there is significant evidence about the role of genetic factors; (2) isolated idiopathic achalasia can be considered the prototype of defective esophageal motility in adults and the role of genetic factors is emerging as a major challenge to explain the disease; and (3) functional dyspepsia cannot be paradigmatically considered a primary gastric motor disorder, but is characterized by a significant association between impaired gastric motility and symptoms to which genetic factors contribute.

## IMPAIRED MOTILITY OF THE ESOPHAGUS

### Achalasia

Idiopathic achalasia is the best recognized primary motor disorder of the esophagus. It is characterized by incomplete relaxation of the lower esophageal sphincter (LOS) and absence of peristalsis that causes bolus impaction and generation of symptoms like dysphagia, regurgitation and chest pain<sup>[8]</sup>. Although the pathogenesis of achalasia is still largely unknown, it is now clear that a major issue is the loss of neurons in the esophageal myenteric plexus. We know that neurons gradually disappear in the lower part of the esophagus of achalasia patients. In most cases, this process is the result of a localized infiltration of immune cells, determining an inflammatory-based neurodegeneration<sup>[9,10]</sup>. Interestingly, this process is prevalent for inhibitory neurons containing nitric oxide (NO) and vasoactive intestinal polypeptides (VIP) and accounts for the loss of inhibitory inputs, with consequent abnormal esophageal function<sup>[11-13]</sup>. Notwithstanding this histological background, we do not know the precise pathogenic mechanism of achalasia; consequently, hereditary, degenerative, autoimmune and infectious factors have all been claimed to be possible causes of the disease.

A certain degree of genetic influence in achalasia is suggested by the familial occurrence and twin concordance. However, a systematic analysis of the literature revealed that twin concordance was significant but still inconclusive<sup>[6]</sup>. On the other hand, the only family study of achalasia conducted to date is biased by the small sample size and because the diagnosis of achalasia was based on a self-reported questionnaire<sup>[14]</sup>. In addition, achalasia may present as part of a genetic syndrome or in association with isolated abnormalities or diseases<sup>[15]</sup>.

**Table 1 Overview of genetic association studies in achalasia**

Protein (gene)	Polymorphism	Finding	Ref.
<i>PTPN22</i>	C1858T	Risk factor	[28]
<i>IL-10</i>	GCC	Protective	[29]
<i>IL-23R</i>	G381A	Protective	[30]
<i>iNOS</i>	<i>iNOS</i> 22*A/A	No association	[35]
<i>eNOS</i>	<i>eNOS</i> *4*4°	No association	[35]
<i>iNOS</i>	(CCTTT) n > 12	Risk factor	[36]
<i>cKit</i>	Rs6554199	Risk factor	[37]
<i>VIPR type 1</i>	Rs437876 and rs896	Risk factor	[38]

*iNOS*: Inducible nitric oxide synthase; *IL*: Interleukin; *PTPN22*: Polymorphism C1858T of phosphatase N22.

An achalasia phenotype is indeed present in well characterized genetic syndromes, like Down<sup>[16]</sup> and Allgrove syndromes<sup>[17]</sup>, the familial visceral neuropathy<sup>[18]</sup> and the achalasia microcephaly syndrome<sup>[19]</sup>. In many of the above mentioned syndromes, achalasia does occur in the majority of the patients, but it generally presents in infancy.

Although these findings indicate that genetic factors are involved in the development of an achalasia phenotype, they do not provide insights into the pathogenesis of the sporadic form of achalasia, which affects the vast majority of patients and presents with adult-onset achalasia. As for other complex diseases, it is likely that the etiology of this form of achalasia is multifactorial, *i.e.*, a combination of the cumulative effect of variants in various risk genes and environmental factors leads to the disorder. The idea of an infectious origin of achalasia was first suggested by the evidence of viruses or signs of viral infection in the esophageal tissues of achalasia patients<sup>[20-22]</sup>, but the possibility that the presence of viruses could be sufficient *per se* to explain the disease was ruled out by other observations<sup>[23]</sup>. More recently, the concept that achalasia could be the result of an immune mediated inflammatory disorder induced by a virus has been strongly repurposed<sup>[24]</sup>. Facco *et al*<sup>[24]</sup> demonstrated that HSV-1 or HSV-like antigens were responsible for a significant activation of CD3<sup>+</sup>T cells infiltrating the LES in achalasia patients, likely resulting in an immune-mediated destruction of the myenteric neurons of the LOS. The reasons whereby this process occurs only in esophageal tissues of achalasia patients are unknown, but it is reasonable to assume that some genetic influence may affect the disease phenotype, making some individuals more susceptible to the disease. In addition and most interestingly, several evidences strongly support the idea that genes encoding for proteins involved in the immune response are likely candidates in achalasia.

A significant association between HLA DR or DQ, especially DQA1 \*0103 and DQB1 \*0603, and achalasia has been indeed described<sup>[25-27]</sup>. The increased risk for the development of achalasia in individuals with specific polymorphisms of genes involved in the immune response was also supported by the finding that the polymorphism C1858T of phosphatase N22 (*PTPN22*

gene, chromosome 1), which is a down-regulator of T-cell activation, is significantly associated with achalasia in Spanish women<sup>[28]</sup>. The same researchers have also demonstrated that the GCC haplotype of *IL-10* gene promoter is a protective factor for achalasia. This specific polymorphism enhances the release of *IL-10*, an anti-inflammatory cytokine, resulting in a downregulation of immune response<sup>[29]</sup>. In a similar manner, a single nucleotide polymorphism (SNP) of the *IL 23* receptor (G381A), which regulates T cell differentiation, appears to be protective against achalasia. De León *et al*<sup>[30]</sup> reported that the coding variant 381Gln of *IL-23R* was significantly more common in patients with achalasia compared with healthy controls.

This evidence sustains the role of both genetic predisposition and immune alteration in the pathogenesis of idiopathic achalasia. All data are summarized in Table 1.

### Contribution of genes with a dual effect on motility and immunity

A disturbed inhibitory neurotransmission is a trademark of achalasia<sup>[11]</sup>. In keeping with this, several studies have addressed the role of NO and VIP that are involved in both defense against infections and inhibitory neurotransmission and may represent ideal candidates to explain the spread of inflammation and inhibitory nerve degeneration<sup>[12,13,19,31-33]</sup>.

Nitric oxide is produced by three different forms of NO synthases: neuronal (nNOS), inducible (iNOS) and endothelial (eNOS). As NO production is genetically regulated, Mearin *et al*<sup>[34]</sup> firstly investigated whether SNP in the different *NOS* genes were respectively involved in the susceptibility to suffer from achalasia. Although a trend toward a higher prevalence of genotypes *iNOS*22?A/A and *eNOS*\*4a4a in patients than in controls was observed, the authors failed to find a significant association between *NOS* gene polymorphisms and susceptibility to achalasia. Although the simplest conclusion was that NO is not involved in the pathogenesis of achalasia, this study is biased by the small sample size and by the fact that the SNPs analyzed do not play a major role in gene expression. The lack of any association between the same SNP in the *iNOS* was also confirmed by a Spanish group in a larger population of achalasia patients, further suggesting that these specific polymorphisms play a minor role in the functional expression of the *iNOS* gene<sup>[35]</sup>. More recently, our group showed a significant association between the pentanucleotide (CCTTT) polymorphism in the *iNOS* gene promoter and achalasia. Since *in vitro* data showed that the *iNOS* promoter activity increases in parallel with the repeat number of (CCTTT)n, we concluded that individuals carrying longer forms have an increased risk of achalasia by higher nitric oxide production.

Moreover, growing evidence suggests that esophageal interstitial cells of Cajal, a group of specialized cells that constitutively expresses c-kit and contribute to nitrergic neurotransmission, may be involved in the pathogenesis

of achalasia. Alahdab *et al.*<sup>[36]</sup> have indeed shown that the rs6554199, but not rs2237025, c-kit polymorphism is significantly prevalent in achalasia patients in a Turkish population. Importantly, alterations in ICC have already been reported in other congenital diseases with abnormal peristalsis, emphasizing the key role of these cells in the regulation of GI motor function.

The implication of VIP in the pathogenesis of achalasia was also recently reported<sup>[37]</sup>. Two different SNPs, rs437876 and rs896, in the VIP-receptor type 1 gene were found to be significantly associated with the late onset achalasia. Interestingly, the authors suggest that this was probably related to a genetically based abnormal VIP-R1 signaling that may protect individuals carrying the specific genotype by delaying the immune-mediated neurodegeneration. Although these data need to be replicated, they are extremely interesting because they may suggest that early and late onset forms of idiopathic achalasia are genetically distinct disorders<sup>[38]</sup> (Table 1).

## IMPAIRED MOTILITY OF THE STOMACH

### FD

FD is defined by the presence of persistent symptoms in the upper part of the abdomen in the absence of organic or metabolic pathology<sup>[39]</sup>. On the basis of the Rome III criteria, patients who suffer from functional dyspepsia in the absence of any organic disease are categorized as having postprandial distress syndrome or epigastric pain syndrome<sup>[40]</sup>.

In spite of this, the pathogenesis of FD is still largely unknown and, although delayed gastric emptying, impaired gastric accommodation and visceral hypersensitivity have been all claimed as major underlying mechanisms, it is supposed to be a multifactorial disease<sup>[39]</sup>.

The classic assumption in studies addressing the association between genetic factors and a single or a cluster of diseases postulates that a specific functional gene polymorphism that results in altered protein function may play a role in disease pathophysiology<sup>[41]</sup>. This paradigm that implies a clear correlation between impaired physiological function and symptom generation, however, cannot be applied to FD whose pathophysiology is complex and not necessarily associated with specific symptoms. Since functional dyspepsia is one of the most prevalent FGIDs, a certain genetic influence is suggested by both symptom familial clustering and twin studies reported for FD and IBS<sup>[3]</sup>. So far, most of the studies conducted were designed to search for correlations of a candidate gene polymorphism with the symptom-based phenotype of FD. The candidate genes that have been studied for possible associations with functional dyspepsia are summarized in Table 1.

In a subset of dyspepsia patients, *Helicobacter pylori* (*H. pylori*) infection, even in the absence of ulceration or erosion in gastroduodenal mucosa, has been proposed to play a role in generation of symptoms. A Japanese

group found an association between TLR-2 -196 to -174 allele with a lower risk for developing FD in *Helicobacter pylori* positive subjects. Since the same group had previously demonstrated that the TLR-2 -196 to -174 increases the severity of *H. pylori*-induced inflammation, it is reasonable to hypothesize that the TLR-2 genotype influences the onset of dyspeptic symptoms modulating the degree of inflammatory response<sup>[42]</sup>.

Serotonin (5-HT) is a key signaling molecule affecting upper GI motor and sensory functions<sup>[43]</sup> and thus genes of the serotonergic system are critical candidates in assessing the role of genetic determinants in FD. The action of 5-HT is terminated by the 5-HT transporter (serotonin transporter, SERT) mediated uptake, thereby determining 5-HT availability at the receptor level. A single nucleotide insertion/deletion in the SERT gene, by creating a long (L) and short (S) allelic variant, results in reduced SERT expression and 5-HT uptake<sup>[44]</sup>. Although the SS genotype of the SERT promoter polymorphism has been reported to be associated with diarrhea-predominant irritable bowel syndrome (IBS), two different studies from the United States<sup>[45]</sup> and Europe<sup>[46]</sup> failed to find any significant association between such polymorphisms and FD. Similarly, association studies between SNPs of the 5-HT<sub>3</sub>, 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors in FD patients failed to yield significant association<sup>[45,46]</sup>. Although both studies were conducted on small populations of patients, the results suggest that the serotonergic pathway plays a minor role in the pathophysiology or, at least in part, in the generation of dyspeptic symptoms.

Another genetic association reported in functional dyspepsia is the link to GNB $\beta$ <sup>[47]</sup>. G-proteins mediate the response to the release of 5-HT and several other neurotransmitters modulating gastroduodenal sensory and motor function.

A common polymorphism of GNB $\beta$  gene has been described and is associated with different genotypes that are predictive of an enhanced G-protein activation. A significant association between different GNB $\beta$  polymorphisms and both uninvestigated and investigated dyspepsia has been reported in different studies from the United States<sup>[45]</sup>, Europe<sup>[46,47]</sup> and Asia<sup>[48,49]</sup>. Although the sample sizes remain relatively small in all of these studies, which may account for some of the variability in the associations detected, it is of note that the different classifications of dyspepsia also contribute to the diverse distribution of polymorphisms. In fact, while homozygous GNB $\beta$  825T allele was found to influence the susceptibility to EPS-like dyspepsia in a Japanese population of dyspeptics<sup>[49]</sup>, in a report from the United States, the same polymorphism was associated with postprandial dyspeptic symptoms and lower fasting gastric volumes<sup>[45]</sup>. Other studies failed to identify single genetic factors as a predominant factor in the pathogenesis of functional dyspepsia and symptom generation. As sympathetic adrenergic dysfunctions may affect both gastric sensitivity, Camilleri *et al.*<sup>[45]</sup> analyzed the role of presynaptic inhibi-

**Table 2 Overview of genetic association studies in functional dyspepsia**

Protein (gene)	Polymorphism	Finding	Ref.
TLR-2	(192-174)del	Protective for <i>Helicobacter pylori</i> -infected patients	[43]
SERT	SS variant	No association	[45]
5-HT1A	-Pro16Leu	No association	[46,47]
5-HT2A	-1438 G/A	No association	[46,47]
HTR3A	C178T	No association	[46,47]
GNB3	C825T	Risk factor	[48-50]
GNB3	CT and TT carriers	Risk factor for PDS	[48-50]
GNB3	CC and TT carriers	Risk factor	[48-50]
GNB3	C825T	Risk factor for EPS	[50]
GNB3	TT carriers	Risk factor for EPS	[50]
Presynaptic inhibitory $\alpha$ 2A and $\alpha$ 2C adrenoceptor	-1291 C>G ( $\alpha$ 2A) and -del 1322-325 ( $\alpha$ 2A)	No association	[46]
Fatty acid amide hydrolase	C385A	No association	[51]
TRPV1	G315C	Risk factor	[52]
Na (V) 1.8	SCN10A 3218CC	Protective	[53]

PDS: Post discharge surveillance; EPS: Encapsulating peritoneal sclerosis; TLR: Toll-like receptor; TRPV: Transient receptor potential vanilloid.

tory  $\alpha$ 2A and  $\alpha$ 2B adrenoceptors polymorphism, but they failed to find any significant association with dyspepsia symptoms. The same group also failed to find any significant association between the genetic variation in the endocannabinoid metabolism (*i.e.*, a SNP in the human fatty acid amide hydrolase gene-C385A-) and both impaired fundus accommodation and delayed gastric emptying in a small subgroup of dyspepsia patients<sup>[50]</sup>. Conversely, in a recent report, the involvement of the transient receptor potential vanilloid 1 (TRPV1) was investigated in a small population of Japanese dyspeptic patients. The authors found that in a population of 109 dyspeptics, individuals carrying the G315C polymorphism, known to affect the *TRPV1* gene and to alter its protein level, were at lower risk for both epigastric pain and postprandial distress syndrome. In addition, the authors showed that dyspeptics with that specific polymorphism had a baseline and cold water induced symptom severity<sup>[47]</sup>. Although this finding needs to be reproduced in different ethnic populations and validated on a large sample, it is of note that TRPV1 pathways may be ideal candidates as they are involved in nociception and in acid sensitivity, with the latter being claimed to have a role in the generation of dyspepsia symptoms. On the same line, the same group have found a significant association between a polymorphism of the tetrodotoxin-resistant (TTX-r) sodium channel Na (V) 1.8, a channel expressed by C-fibers and involved in nociception, and functional dyspepsia. Indeed, the SCN10A 3218 CC variant, which determines a lower activity of this Na (V)-channel, was significantly associated with a decreased risk for the de-

velopment of FD<sup>[52]</sup> (all data are summarized in Table 2).

### Post-infectious dyspepsia

By summarizing what we have described above, we can say that although it is unlikely that a single genetic factor causes FD, it is more likely that a genetic factor (or factors) modulates the risk of developing the abnormalities after exposure to one or more specific environmental factors<sup>[53]</sup>. This paradigm is well supported by the hypothesis of a post-infectious origin of dyspepsia. Indeed, it is now evident that in a subgroup of patients with functional dyspepsia, acute GI infections may precipitate symptoms. Data from the literature indicate that in presumed post-infectious dyspepsia patients there is an increased prevalence of impaired gastric accommodation to the meal that is likely dependent on inflammatory-induced impaired nitergic innervation of the gastric wall<sup>[54]</sup>. However, only one study systematically addressed the genetic contribution to post-infectious dyspepsia and the data presented are quite controversial since a significant association between macrophage migration inhibitory factor-173C and IL17F-7488T polymorphisms was only observed in the subgroup of patients with symptoms suggestive of EPS-like dyspepsia<sup>[55]</sup>. Indirect evidence for a role of inflammatory products gene in the genesis of FD is also suggested by a Japanese study in which a significant association between a COX1 polymorphism and EPS-like symptoms was observed in a subgroup of dyspeptic female patients<sup>[56]</sup>. However, a very recent study investigating the role of a polymorphism in the receptor for neuropeptide S receptor gene (NPSR1) that is involved in inflammation, anxiety and nociception failed to reveal any significant association with FD<sup>[57]</sup> (Table 3).

### Hypertrophic pyloric stenosis

Isolated HPS is a common condition characterized by the hypertrophy of the muscle surrounding the pylorus, with impaired sphincter relaxation and consequent gastric outlet obstruction which causes severe non-bilious vomiting. The etiology of this disease is still largely unknown; however, epidemiological studies indicate that genetic factors play an important role in the pathophysiology of this entity<sup>[58]</sup>. Krogh *et al.*<sup>[59]</sup> have shown a 200-fold increased risk of HPS in monozygotic twins and a 20-fold increased risk among siblings of affected children. In particular, different studies have demonstrated a higher prevalence of HPS in offspring of an affected mother compared with offspring of an affected father, suggesting a major role of maternal factors; however, this evidence was not confirmed in further studies<sup>[60]</sup>. In addition, HPS is associated with several well-defined genetic syndromes, sustaining the hypothesis that genetic factors are largely involved in the pathogenesis of this disease<sup>[58]</sup>.

A reduced expression of NOS1 was demonstrated at the mRNA level in pyloric tissue of patients with HPS, suggesting a pathogenic role of nNOS in this disease.

**Table 3** Overview of genetic association studies in post-infectious dyspepsia

Protein (gene)	Polymorphism	Finding	Ref.
<i>MIF</i>	-173C	Risk factor for EPS	[56]
<i>IL17</i>	-7488T	Risk factor for EPS	[56]
<i>COX-1</i>	T1676C	Risk factor for EPS	[57]
<i>NPS-R</i>	rs2609234, rs6972158, and rs1379928	No association	[58]

IL: Interleukin; COX-1: Cyclooxygenase-1; EPS: Encapsulating peritoneal sclerosis; MIF: Macrophage migration inhibitory factor.

For this reason, several researchers have analyzed the gene of *NOS1*; however, only a Chinese group found a linkage between HPS and NOS1a on chromosome 12q<sup>[61]</sup>, but this result was not confirmed by another study<sup>[62]</sup>. Moreover, the analysis of the complete coding region of *NOS1* in patients and controls revealed no significant difference, confirming that the impaired nNOS function in the pylorus of these patients is not related to a direct mutation of the gene encoding for *NOS1*<sup>[63]</sup>.

Several studies have demonstrated a linkage between HPS and different loci in affected patients of the same family, but larger studies on additional families were usually unsuccessful. A Chinese group described a linkage of a SNPs of chromosome 16 (16p12-p13) in 10 affected members of the same family, but this association was not observed in 10 additional families<sup>[64]</sup>. Moreover, the major candidate genes of this region encoding for *MYH11* and *GRIN2A*, proteins involved in smooth muscle relaxation, have not shown mutations<sup>[64]</sup>. In members of the same family, Everett *et al.*<sup>[65]</sup> found an association with *SLC7A5* (16q24), a gene which influences NO activity; however, they failed to confirm these data on additional 14 families. In a genome-wide linkage study, the same group demonstrated an association between HPS and some loci on chromosome 11q14-q22 and Xq23, both encoding for protein involved in the functioning of ion channels (*TRPC5* and *TRPC6*) in 81 families with 206 affected members<sup>[66,67]</sup>; however, a subsequent Chinese study failed to replicate the association with *TRPC6*<sup>[68]</sup>.

Finally, a Danish group in a recent genome-wide association study (GWAS) on 1001 individuals affected by HPS and 2401 healthy controls demonstrated an association between HPS and three SNPs of *MBNL1* and *NKX 2-5*, genes involved in the splicing and transcription processes<sup>[69]</sup>, but it was the first GWAS and these results could explain only a very small proportion of HPS cases (all reviewed associations are summarized in Table 4).

In conclusion, hypertrophic pyloric stenosis is a multifactorial disease and both genetic and environmental factors could contribute to the pathophysiology of this condition. Especially for the syndromic form of HPS, different mutations in different genes involved in different functions have been associated with the onset of this disease, but we are still far from a single unifying pathogenetic factor. Conversely, in the sporadic form of

**Table 4** Overview of genetic association studies in hypertrophic pyloric stenosis

Protein (gene)	Chromosome	Finding	Ref.
<i>NOS1</i>	12q	Association	[62,63]
<i>MYH11-GRIN2A</i>	16p12-p13	Association	[65]
<i>SLC7A5</i>	16q24	Association	[66]
<i>TRPC5 and TRPC6</i>	11q14-q22 and Xq23	Association	[67-69]

the disease, the contribution of the genetic background is even more scanty and complex and no clear triggering factors have been described yet, further sustaining the great heterogeneity of this disease.

## CONCLUSION

Several association studies have established a genetic component in the genesis of motility disorders of the upper gastrointestinal tract, like esophageal achalasia, functional dyspepsia and hypertrophic pyloric stenosis. Although candidate gene studies have identified a few gene polymorphisms that may be correlated with these syndromes, small sample size, lack of reproducibility in large data sets, and the unreliability of the clinical phenotype represent a major limit to identify a unifying factor in the pathophysiology of these syndromes in any of the reported polymorphisms.

Whether the genetic contribution plays a crucial role in the generation of upper GI tract symptoms therefore deserves further studies. More specifically, the recruitment of large case-control samples appears to be mandatory in order to provide a powerful tool for the identification of risk genes, especially for diseases like achalasia and functional dyspepsia, in which a multifactorial inheritance is assumed. In this direction, genome-wide association studies will allow for the unbiased and systematic identification of risk genes and may represent the greatest challenge for all future studies of upper GI tract motility disorders.

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