Review

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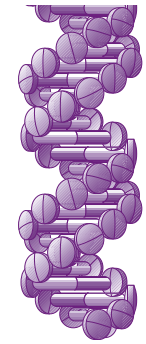
Pharmacogenomics



Pharmacogenetics and the treatment of functional gastrointestinal disorders

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The diagnosis and management of functional gastrointestinal disorders (FGIDs) remain very challenging. In the era of precision medicine, it is important to individualize the treatment of these conditions by providing targeted and effective therapies while minimizing the risk of medication side effects. By using genetic information that predicts and affects the responses to specific medications, it is anticipated that the science of pharmacogenetics in FGIDs will advance the practice of precision medicine. The pathophysiology of FGIDs is complex, involving the interaction between predisposing genetic and environmental factors. Studies have shown that genetic polymorphisms may contribute to the variable responses to specific medications among individuals with FGIDs. Genetic variations in the CYP450 system can affect the metabolism and, hence, the pharmacokinetics of drugs used to treat FGIDs. Polymorphisms in the genes controlling proteins that are involved in the direct action of medications targeting the serotonergic, cannabinoid, adrenergic and bile acid pathways can affect the pharmacologic effects of the medications. In this review, we summarize the published literature on the pharmacogenetics of FGIDs and address the potential clinical utility and future challenges in this field. Since it was the dominant topic in the majority of the articles relevant to FGIDs, our review will focus on irritable bowel syndrome.

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Functional gastrointestinal disorders & individualized medicine

Functional gastrointestinal disorders (FGIDs) are highly prevalent worldwide. Despite their benign nature, they have a significant impact on quality of life and inflict a substantial financial burden on healthcare systems [1]. The pathophysiology of FGIDs, such as irritable bowel syndrome (IBS), involves multiple central and peripheral mechanisms [2] that may constitute targets for therapy. The management of these conditions remains challenging, and pharmacotherapy usually follows a trial-and-error approach with modest or no improvement in symptoms, which leads to a protracted course of illness and to frustration for both patients and healthcare providers [3]. This is due, in part, to a poor understanding of various factors such as genetic variations that affect the responses to specific medications.

Precision medicine promises to overcome this challenge, as it incorporates physiological, pathological and environmental factors that are unique to each individual, with the goal of delivering individualized healthcare [4]. It involves the use of patient-specific information that can affect the response to the treatment, including comorbidities, genetic makeup and drug-to-drug interactions. The science of pharmacogenetics studies the effect of genetic variability of patients on the response to medications [5,6]. Applying the concepts

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of pharmacogenetics to the management algorithm of FGIDs may help improve the outcome of specific therapies by maximizing efficacy and minimizing toxicity. Although, the field is in its infancy and there are many challenges still to be overcome, the application of pharmacogenetics in FGIDs has attracted more interest in the last two decades. In this review, we summarize the published literature on the role of pharmacogenetics in the management of FGIDs, particularly in IBS, and we address the future challenges and potential clinical utility in this promising field.

Genetics of FGIDs

Unlike monogenic conditions where phenotypes depend on variability in a single gene, FGIDs are complex polygenic conditions in which polymorphisms in multiple genes interact with environmental factors to produce a certain phenotype [7]. A possible proof of a genetic predisposition in FGIDs comes from epidemiological studies showing a strong familial aggregation in IBS, which suggests hereditary and/or intrafamilial environmental etiologies [8]. Despite, conflicting reports [9], several twin studies point to a probable small genetic contribution to IBS, with higher concordance of the condition in monozygotic compared with dizygotic twins [10], and in dizygotic twins who have mothers with IBS compared with dizygotic twins with cotwins with IBS [11]. The latter observation suggests that environmental factors play a role even in familial IBS. Mechanisms leading to symptoms in FGIDs seem to involve a complex interaction between environmental and genetic factors [12], and strong evidence for a clear genetic predisposition in functional dyspepsia (FD) is lacking [13]. Whether the inherited genetic makeup leads to FGIDs directly, or to associated conditions or intermediate phenotypes remains unclear [14,15].

Applying the candidate gene approach, researchers have studied the correlation between gene polymorphisms and IBS symptoms or intermediate phenotypes associated with IBS, such as colonic transit, intestinal immune activation and mucosal permeability. This approach led to further understanding of the highly complex genetics of IBS. The candidate mechanisms associated with genetic variations that have been most revealing to date include genes involved in the serotonergic, cannabinoid, bile acid, adrenergic and immune pathways. Here, we summarize a few examples, though the genetics of IBS has been extensively summarized elsewhere [7,15].

Single nucleotide polymorphisms have been suggested as possible biomarkers involved in underlying mechanisms in FGIDs. However, the evidence is often not replicated in the literature and, therefore, these potential associations are to be interpreted with caution. Examples include the following:

- The serotonergic pathway is a major brain-gut mediator and is implicated in gastrointestinal motility, secretory and sensory functions [16]. After serotonin is secreted, the serotonin reuptake transporter SERT (also called solute carrier 6A4 [SLC6A4]) facilitates reuptake to the cell from which it originates (such as the enterochromaffin cells in the gut, platelets in the circulation or neurons in the brain), thus decreasing the biological effect of the amine transmitter [17]. The main polymorphic region in the transporter gene promoter is the 5-HT transporter long polymorphic region (*5-HTTLPR*). A long (L) and a short (S) variation of the gene affect the function of SERT, with the short variant resulting in reduced serotonin reuptake and, hence, more serotonin available to target the postjunctional receptor;

- Polymorphisms in the gene promoter (*5-HTTLPR*) controlling the serotonin transporter SERT have been described in patients with IBS [18]. However, studies in different populations and even meta-analyses show inconsistent results. For example, polymorphisms in the SERT gene promoter were also shown to predict a specific subgroup of IBS with diarrhea (IBS-D) [19]. However, the *5-HTTLPR* mutation was associated with IBS with constipation (IBS-C), but not with IBS-D or IBS-mixed (IBS-M). This association was only demonstrated in the East Asian groups in one meta-analysis [20]; a separate meta-analysis suggested a reduced risk of IBS in both American and Asian populations [21];

- *5-HTTLPR* polymorphism was also found to be associated with intermediate phenotypes in IBS, with LS/SS genotype being associated with increased pain sensation [22] and L/S and S/S genotypes of the *5HTTLPR* polymorphism with greater symptom severity [23];

- Polymorphisms in the serotonergic pathways were also shown to be associated with symptom severity in IBS. Examples include the association of T/T genotype at position 102 of *HTR2A* (5-HT2A receptor gene) associated with more severe pain [24] and C/C genotype of the c. -42C>T polymorphism in *HTR3A* with amygdala responsiveness in IBS [25];

- Another potential role for 5-HT_3 polymorphisms in FGIDs is related to the genes' interactions with microRNAs, which are short noncoding RNA molecules involved in post-translational regulation of expression of mRNAs [26]. Such microRNAs have been studied as potential biomarkers and therapeutic targets in IBS by using

microRNA inhibitors or precursors. A variant in the *HTR3E* subunit (c. *76G>A) was found to be associated with IBS-D in females. This variant of the receptor subunit was resistant to the inhibitory effect of microRNA-510 in IBS-D, leading to an increased expression of the 5-HT_{3E} protein [27]. This information suggests that precursors for microRNA-510 might have a protective effect against IBS-D in individuals without the variant (c. *76G>A), but likely have no significant effect on individuals with this variant;

- G-proteins are essential to transform stimuli from the cellular receptor level into an intracellular signaling pathway leading to a physiological effect. Genetic variations in G-protein β 3 subunit (*GNB3*) were found to be associated with FD in one study conducted in Germany [28], but this was not replicated in a USA cohort of similar ethnic distribution [29];

- Associations between IBS and IBS-C and a polymorphism in *TNFSF15*, the gene encoding for the protein, TL1A, suggest involvement of inflammatory responses [30]. This has been replicated in separate European studies, including a meta-analysis of the available data [31,32]. Association of the *IL-10* gene with IBS [33] is also consistent with the hypothesis that predisposition to immune activation may contribute to IBS. Genes that encode proteins involved in epithelial cell barrier function (e.g., *TLR9*) and the innate immune response to enteric bacteria (e.g., *CDH1*) are associated with development of IBS following acute gastroenteritis (postinfectious IBS) [34];

- The autonomic nervous system plays an important role in GI motility and IBS [35,36]. The adrenergic axis is integral in the regulation of the autonomic nervous system and was shown to be a potential target to modulate gastrointestinal motility by using α2 adrenergic agonists such as clonidine [37,38]. Genetic variations in α2a receptor, *ADRA* (C-1291G), were found to be associated with gastric emptying at 2 and 4 h and with postprandial gastric volume [39,40];

- Polymorphisms in genes controlling adrenoceptors are associated with worse symptoms in FGIDs or quality of life; examples include the α(2A), α(2C) and β2 adrenergic receptors [41,42];

- The cannabinoid pathway and genetic variations in endocannabinoid metabolism and cannabinoid receptors are involved in the pathophysiology of IBS. A single nucleotide polymorphism in the enzyme, fatty acid amide hydrolase, responsible for the inactivation of the endocannabinoid, anandamide, was studied. The genotype fatty acid amide hydrolase CA/AA was found to be associated with IBS-D, IBS-M, chronic abdominal pain and accelerated colonic transit in IBS-D [43]. Furthermore, the polymorphism of *CNR1*, the gene encoding for the cannabinoid 1 receptor, was shown to predict phenotype and quantitative traits. The *CNR1* rs806378 genotype was associated with colonic transit in IBS-D and with symptom rating of gas, but not pain [44];

- Bile acid synthesis, enterohepatic circulation and excretion affect bowel function and are, thus, involved in the pathophysiology of IBS [26]. Klothoβ (KLB) normally interacts with growth factor receptor (FGFR)4 which leads to a negative feedback mediated by fibroblast growth factor (FGF)19, resulting in suppression of bile acid synthesis [45]. A variant of *KLB*, Arg728Gln, results in an unstable KLB protein and impaired negative feedback and, hence, increased bile acid synthesis. This, in turn, leads to accelerated colonic transit and diarrhea. This association between the KLB variant and abnormal colonic transit is mediated by the *FGFR4* genetic variants, rs1966265 (Val10Ile) and rs351855 (Gly388Arg) [46];

- Given the inconclusive evidence of the role of genetic polymorphisms in the association with FGIDs and IBS, specifically, the role of genetics appears to be of greater relevance in the context of the responses to pharmacological agents. In this review, we will focus on the genetic polymorphisms with potential pharmacogenetic implications in FGIDs.

Pharmacogenetics in FGIDs

Pharmacogenetics modulates responses to therapy at two levels in FGIDs: pharmacokinetics – through modulation of drug metabolism; and pharmacodynamics – through changes affecting receptors or transporters involved in the mechanisms of action of medications. Examples of pharmacokinetics include the roles of the variations in functional CYP2D6 in modifying the plasma levels and the efficacy and safety of several drugs such as tricyclic antidepressants [47]. The first gene polymorphism affecting drug action was genetic variation in *5-HTTLPR*, which influences the promoter for the synthesis of SERT (SERT-P), and its effect on the activity of a serotonergic drug, the 5-HT_3 antagonist, alosetron, in IBS-D [48]; this was replicated for the 5-HT_4 agonist, tegaserod [49].

Pharmacogenetics related to pharmacokinetics

Genetic variation in *CYP450*

The effects of genetic variations on enzymes involved in drug metabolism can be very significant, rendering the pharmacokinetics of a drug extremely variable among individuals [50]. This variability in metabolism is usually related to one principal enzyme, which makes the genetic polymorphism of the enzyme of great potential clinical and experimental value. In general, metabolism of a drug involves Phase I reactions such as oxidation, dehydration or esterification of functional groups and Phase II conjugations [51]. The CYP450 enzymes such as CYP2C19 and CYP2D6 plays an important role in Phase I reactions in the metabolism of a multitude of medications used in FGIDs, particularly antidepressants. The CYP2D6 enzyme is highly polymorphic, with more than 100 genetic variants. The frequency of functional versus nonfunctional alleles may explain the differences in responses to several medications in different ethnicities. Functional alleles include *CYP2D*2*, **9*, **10*, **17*, in addition to the wild-type *CYP2D6*1*. Depending on the genotype, an individual may be an ultrarapid, extensive, intermediate or poor metabolizer [52]; 7–10% of Caucasians are poor metabolizers compared with only 1–2% of Asians [53]. CYP2C19 and enzymes involved in the metabolism of frequently prescribed medications such as omeprazole and cimetidine also show polymorphisms that vary depending on ethnicity, with a prevalence of poor metabolizers in 2–6% of Caucasians, 15–20% of Japanese and 10–20% of Africans [54].

Examples of clinical implications of impact of genetic variation on pharmacokinetics in FGIDs

Neuroleptics in IBS: effect of *CYP2D6* polymorphism

Antidepressants, including tricyclics and selective serotonin reuptake inhibitors, are used for the treatment of FGIDs and visceral hypersensitivity [55]. Metabolism of the tricyclic antidepressant, nortriptyline, correlated with the number of functional *CYP2D* genes [47]. The effect of the variability in the metabolism of antidepressants on the response to therapy has not been studied extensively for FGIDs. However, a better understanding of the pharmacogenetics of drug metabolism may help tailor the choice of antidepressant and its dose for each patient, depending on their genetic makeup, and thereby minimize toxicity and maximize benefit [53]. Future studies are needed to understand the role of *CYP2D* variability on the efficacy of antidepressants specifically in FGIDs.

Proton pump inhibitors & H2 receptor blockers in functional dyspepsia: effect of *CYP2C19* polymorphism

Genetic variation in *CYP2C19* results in lower inactivation of most proton pump inhibitors (PPIs), thus leading to an increased efficacy of the inhibition of gastric acid secretion by the PPIs that undergo metabolism by CYP2C19; this genetic variation is most prevalent in people of Asian lineage who would theoretically require a lower dose to achieve efficacy. The PPI, rabeprazole, is metabolized by CYP3A4, not by CYP2C19, and may offer an option to avoid potential interaction of the *CYP2C19* genotype with PPI function.

A study of 100 patients with FD who were treated with cimetidine until the dyspepsia resolved showed that the mean duration of treatment was the shortest for the variant homozygote type *CYP2C19* [56]. This is consistent with a prior study that showed a lower failure rate in poor metabolizers of on-demand therapy with pantoprazole after successful treatment for esophagitis [57]. This can be explained by a more sustained and significant effect of those drugs in poor metabolizers. Larger trials specifically targeting FD are needed to study the clinical relevance of *CYP2C19* polymorphism on the response to PPIs and H2 blockers. Furthermore, genetic tests lack widespread availability, and FD is usually treated with therapeutic trials of medications such as PPIs or H2 blockers. The genetic tests may still have a role in refractory cases or in cases where potential toxicity is a concern.

Pharmacogenetics & pharmacodynamics

Pharmacogenetics of serotonin pathways

Serotonin receptors are therapeutic targets in IBS, such as with the use of 5-HT_3 receptor antagonists in IBS-D and 5-HT_4 agonists in IBS-C or functional constipation. In addition to the influence of *5-HTTLPR* on SERT function, the genes for 5-HT_3 receptors are also polymorphic, and these variants are thought to affect the response to treatment [58].

Alosetron & tegaserod: effects of *5-HTTLPR* polymorphism

The polymorphism in *5-HTTLPR* was shown to possibly predict the response to the 5-HT_4 agonist, tegaserod, with higher response rate in S/S and L/S genotypes (which are both associated with reduced SERT function [59], and poor response rate in the L/L genotype in patients with IBS-C. Li *et al.* suggested that an increased serotonin uptake in LL subjects may lead to a decreased serotonergic neurotransmission, altering 5-HT_4 receptor affinity to endogenous serotonin or exogenous tegaserod [49]. In theory, the S allele is associated with more synaptic serotonin and,

potentially, more contractile response with the use of 5-HT_4 agonist. Ismair *et al.* showed that tegaserod may also inhibit SERT, which may further explain the variable efficacy of this drug in association with different *5HTTLPR* gene variants [60]. Conversely, individuals with the L/L genotype have more effective SERT function resulting in less synaptic serotonin, which may explain the better response observed with the 5-HT_3 antagonist, alosetron, in IBS-D [48]. The *5-HTTLPR* polymorphism shows the complexity of the pharmacogenetics of IBS, where genetic variation in one pathway can alter response to therapy.

5-HT_3 receptor polymorphisms & treatment of gastrointestinal symptoms

A study of the pharmacogenetics of 5-HT_{3B} receptors in chemotherapy-induced nausea and vomiting suggested a lower efficacy of antiemetic therapy with 5-HT_3 antagonists in patients homozygous for the *HTR3B* -100_-102delAAG deletion variant [61]. To date, no trials have studied the effects of such 5-HT_{3B} receptor polymorphisms on responses to drugs in FGIDs. Celli *et al.* summarized the role of the different 5-HT_3 receptor variants (*CHTRA-E*), provided an electronic database where genetic and pharmacogenetic data will be gathered as a reference for potential clinical use, and postulated that polymorphisms in 5-HT_3 receptor genes may have clinical utility in the management of FGIDs [58].

Ramosetron (5-HT_3 antagonist): effect of *TPH1* polymorphism

A pilot study showed that Single nucleotide polymorphisms in the genes encoding for tryptophan hydroxylase 1 (*THP1*), the rate-limiting enzyme in the synthesis of 5-HT, predicted response to the 5-HT_{3R} antagonist, ramosetron, in IBS-D. The frequency of the genotypes, *TPH1* rs4537731 T/T, rs7130929 C/C and rs211105 T/T, was significantly higher in responders compared with nonresponders [62]. This finding has potential clinical utility to identify subgroups of patients with IBS-D with a greater likelihood of response to new agents such as ramosetron. Furthermore, the genetic polymorphism in *THP1* helps further elucidate the role of serotonin as a biomarker involved in one of the complex mechanisms involved in the etiology of IBS.

The identification of these genetic variations in the serotonergic pathway can offer a unique opportunity to target therapy based on prediction of response. Before these findings can be applied in clinical practice, more research is required to establish the effects of such polymorphisms in diverse populations, given the differences in the prevalence of the genetic variations in different ethnicities.

Pharmacogenetics of cannabinoid pathways

Dronabinol: effect of CNR1 polymorphism

Dronabinol is a nonselective cannabinoid receptor agonist that was shown to inhibit gastric emptying and colonic motility [63,64]. A trial of dronabinol in IBS-D showed a modest delay in colonic transit in patients with *CNR1* rs806378 CT/TT compared with CC [65].

Despite the lack of observations in large cohorts, this preferential effect of dronabinol observed in a subgroup of IBS patients can have a significant implication in an era when the use of medicinal cannabinoids is increasing and with the need to minimize toxicity.

Pharmacogenetics of adrenergic pathways

Clonidine: effect of α2A polymorphism

Clonidine is an α2 receptor agonist that can modulate colonic tone and pain perception [37]. Genetic variation in *ADRA2A* (C-1291G) was associated with improvement in rectal sensation of gas and urgency in response to clonidine in IBS patients [66]. Future research on adrenergic receptor polymorphisms and their effects on responses to specific medications is needed. Clonidine is not considered a first-line therapy in FGIDs. Future pharmacogenetics studies may help identify a subcategory of patients with IBS who would benefit from α2 receptor agonists.

Pharmacogenetics of bile acid modulation

Chenodeoxycholic acid & colesevelam: *KLB* & *FGFR4* polymorphisms

A study on chenodeoxycholic acid in IBS-C showed that polymorphisms in *KLB* and *FGFR4* can influence the response to therapy. Furthermore, genetic variations in KLB and FGFR4 may predict a more beneficial response to the bile acid sequestrant, colesevelam, on ascending colon half-emptying time and overall colonic transit in patients with IBS-D [67,68]. This is an example of the potential utility of pharmacogenetics in IBS. Learning more about the genetic variations involved in bile acid metabolism and effects of the genetic polymorphisms in *FGFR4* and *KLB* on the responses to specific IBS therapy targeting the bile acid pathway may predict the patients who are more likely to respond to bile acid directed therapy in the future.

Conclusion, future perspective & a note of caution

Though, there are both appeal and potential benefits of precision medicine, the use of pharmacogenetics in FGIDs is still challenged. First, there is a lack of profound understanding of the different pathophysiological mechanisms in FGIDs and of the role of the genetic factors in those mechanisms. Second, genetic testing remains relatively expensive, not widely available, and may at times

Table 1. Summary of associations of genetic polymorphisms with pharmacokinetics and pharmacodynamics in functional gastrointestinal disorders.

Pathway	Gene	Mechanism	Drug	Clinical applicability	Study (year)	Ref.
Genetic polymorphism and effect on pharmacokinetics						
CYP450 and drug metabolism	*CYP 2D6*	Number of functional *CYP2D6* gene copies determines phenotype (ultrarapid, extensive, intermediate or poor metabolizer)	Tricyclic anti-depressants	*CYP2D6* genotype may predict clearance rate, efficacy, safety and dosing of nortriptyline	Dalen *et al.* (1998)	[47]
	CYP 2C19	Variant *CYP2C19* associated with lower inactivation of most PPIs in Asians	Proton pump inhibitors	Variant *CYP2C19* in poor metabolizers may predict better response to pantoprazole	Sheu *et al.* (2012)	[57]
			H2 blockers	Variant *CYP2C19* in poor metabolizers may predict shorter duration of cimetidine therapy needed to achieve resolution of symptoms in FD	Kim *et al.* (2012)	[56]
Genetic polymorphism and effect on pharmacodynamics						
Serotonergic pathway	*5-HTTLPR*	Short (S) variant of *5-HTTLPR* associated with reduced SERT function, reduced 5-HT reuptake, increased synaptic 5-HT, compared with long (L) variant	Tegaserod (5-HT_4 agonist)	S/S and L/S genotypes may predict better response to tegaserod in IBS-C	Li *et al.* (2007)	[49]
			Alosetron (5-HT_3 antagonist)	L/L genotype may predict better response to alosetron in IBS-D	Camilleri *et al.* (2002)	[48]
	5-HT receptor	Homozygosity for the –100_-102delAAG deletion affects function of 5-HT_3 receptor	Tropisetron and ondansetron (5-HT_3 antagonists)	Homozygosity for the –100_-102delAAG may predict decreased efficacy of antiemetic therapy with tropisetron and ondansetron	Tremblay *et al.*(2003)	[61]
	TPH1	Polymorphism predicts response to 5-HT_{3R} antagonists	Ramosetron (5-HT_{3R} antagonist)	Genotypes rs4537731 T/T, rs7130929 C/C, and rs211105 T/T may predict higher response to ramosetron in IBS-D	Shiotani *et al.* (2015)	[62]
Cannabinoid pathway	*CNR1*	*CNR1* rs806378 genotype associated with colonic transit in IBS-D and with symptom rating of gas	Dronabinol (nonselective CB receptor agonist)	Genotypes rs806378 CT/TT may predict more delay in colonic transit in response to dronabinol in IBS-D	Wong *et al.* (2012)	[65]
Adrenergic pathway	α*2A receptor*	(C-1291G) associated with gastric emptying and postprandial gastric volume	Clonidine (α2 receptor agonist)	C-1291G may predict better response to clonidine in patients with IBS	Camilleri *et al.* (2009)	[66]
Bile acid pathway	*KLB* and *FGFR4*	Variants in *KLB* and *FGFR4* modulate negative feedback on hepatocyte bile acid synthesis	Chenodeoxy-cholic acid	Genetic variations in *KLB* and *FGFR4* may predict response to chenodeoxycholic acid in IBS-C	Rao *et al.* (2010)	[67]
			Colesevelam (bile acid sequestrant)	Genetic variations in *KLB* and *FGFR4* may predict response to colesevelam in IBS-D	Wong *et al.* (2012)	[68]

pose an ethical dilemma that requires counseling unless specifically related to pharmacokinetics. Third, a lack of demonstrated cost–effectiveness is a major limitation, especially given that one of the goals in the management of FGIDs is to minimize testing and cost. Recent reviews have questioned the impact of precision medicine on public health [69] and on individualization of therapy [70].

Despite these limitations, we believe there is a role for further study of pharmacogenetics in FGIDs in those cases that do not respond to conventional therapy, given the opportunity to tailor treatment to each individual based on genetic predictors of response. With further validation, it is conceivable that genetic testing may have diagnostic utility by subcategorizing patients based on mechanisms or intermediate phenotypes, and thus, acting as actionable biomarkers. The study of pharmacogenetics in FGIDs has the potential to lead to better understanding of the pathophysiology of FGIDs and to propose hypotheses for future research. In the future, a management approach based on pharmacogenetics may become cost–effective since a personalized therapy that targets patients who are more likely to respond by using the lowest effective dose of a specific medication will help achieve better outcomes and will help avoid more invasive testing and more harmful and costly adverse events related to application of nontargeted therapy.

Precision medicine involves a multilayered approach to patient management, and pharmacogenetics is only one part of the equation. Environmental factors and their dynamic interactions with the genetic factors are key elements in individualized medicine, especially in FGIDs, given their complex pathophysiology. Hence, for the management of FGIDs, physicians need to consider other factors apart from pharmacogenetics, including environmental changes, drug-to-drug interactions, patient preferences and availability of drugs and tests. The role of environmental factors led to consideration of an epigenetic model of IBS [71], whereby DNA modifications, variations in gut microbiota and gene expression alteration by microRNAs can affect the pharmacogenetics of FGIDs and vice-versa [72]. Finally, despite the complexity added by these gene–environment interactions, the study of pharmacogenetics in FGIDs has the potential to lead to new therapies and future research opportunities in FGIDs.

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Executive summary

- Genetics of FGIDs: genetic variants are possible biomarkers involved in underlying mechanisms in FGIDs.
- Serotonergic pathway, e.g., 5-HT transporter long polymorphic region (5-HTTLPR), and genes for 5-HT receptors HTR2A HTR3A, HTR3E.
- G-proteins are essential to transform stimuli from the cellular receptor level into an intracellular signaling, e.g., G-protein β3 subunit (GNB3).
- Inflammatory responses, including TNFSF15, the gene encoding for the protein, TL1A, and *IL-10* gene.
- Innate immune response to enteric bacteria (e.g., CDH1).
- Epithelial cell barrier function (e.g., TLR9).
- Adrenergic pathway, such as α2a receptor, ADRA (C-1291G).
- Cannabinoid pathway including *FAAH*, the gene for fatty acid amide hydrolase, which inactivates the endocannabinoid, anandamide, and *CNR1*, the gene encoding for the cannabinoid 1 receptor.
- Bile acid feedback regulation, e.g., KLB and FGFR4.
- Pharmacogenetics: genetic variants modulate responses to therapy at two levels in FGIDs:
  - Pharmacokinetics – drug metabolism e.g., CYP 450 variants.
  - Pharmacodynamics – through changes affecting receptors or transporters involved in the mechanisms of action of medications e.g., 5-HTTLPR and serotonergic drugs alosetron and tegaserod; TPH1 and ramosetron; CNR1 and dronabinol; ADRA2A (C-1291G) and clonidine; KLB and FGFR4 and chenodeoxycholic acid or colesevelam.

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