Pharmacogenomics for the efficacy and side effects of antihistamines

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Abstract

Antihistamines are widely used in allergic diseases such as urticaria and allergic rhinitis, mainly by reverse excited histamine and anti-allergic effects. Antihistamines are generally safe, but there may be some adverse reactions like cardiotoxicity, central inhibition, anticholinergic effects, etc. And there are also individual differences in clinical practice. The concept of individualized medicine has been deeply rooted in people's minds since it was put forward. In recent decades, pharmacogenomics has been developing rapidly, which provides new ideas for the occurrence of individual medication. Gene polymorphism in the metabolic enzyme, transports, and target receptors have been shown to affect the application of antihistamines. Besides, recent evidence suggests that genetic polymorphisms influence urticaria susceptibility and antihistamine therapy. Here, we summarize current reports of this area, aim to contribute to the future research and clinical guidance of antihistamine personalized medicine.

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Conflict of interests

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Abstract

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transports, and target receptors have been shown to affect the application of antihistamines. Besides, recent evidence suggests that genetic polymorphisms influence urticaria susceptibility and antihistamine therapy. Here, we summarize current reports of this area, aim to contribute to the future research and clinical guidance of antihistamine personalized medicine.

Key words: Antihistamines, Pharmacogenomics, Individualized medication, Urticaria, Adverse reactions

| Introduction

1.1 | Histamine and histamine receptor

Histamine, an important biogenic amine in the human body, is mainly found in central nervous system neurons, gastric mucosa B cells, mast cells, basophils, and other cells[1]. It is synthesized from L-histidine by histidine decarboxylase. Histamine exerts its biological effects as a neurotransmitter and local mediator via four histamine receptor (HR) subtypes(H1,H2,H3,H4) that belong to the superfamily of G-protein-coupled receptors (GPCRs)[2, 3]. HR is a very important drug target and plays an important role in human health, such as immune regulation and anaphylactic inflammation[4-7]. In sensitized patients, histamine is released after the activation of IgE-mediated mast cells and basophils, causing inflammation and playing an important role in the pathogenesis of allergic diseases such as urticaria, asthma, allergic rhinitis, etc[7]. Histamine H1 receptors are mainly distributed on the surface of vascular endothelial cells, smooth muscle cells, neurons, and immune cells in the skin and mucosa. It's involved in the regulation of vascular dilatation, vascular permeability, blood pressure, headache, tachycardia, sleep, memory, etc[8]. The histamine H2 receptor is mainly distributed on the cell surface of the gastric wall, to participate in regulating gastric acid secretion, vascular permeability, blood pressure, tachycardia, bronchiectasis, airway mucus secretion reaction, and so on[9]. Histamine H3 receptor is mainly distributed on the surface of histaminergic neurons, work on the regulation of histamine and the neurotransmitter release like acetylcholine [10]. Histamine H4 receptor is a newly discovered receptor and is mainly involved in cell differentiation, probably mediated chemotaxis of mast cells and eosinophils[11, 12].

| Antihistamines and their adverse reactions

Currently, H1 and H2 antihistamines are widely used in clinical practice. Antihistamines are commonly referred to histamine H1 receptor antagonists. H1-antihistamines act as inverse agonists that interfere with the actions of histamine at H1-receptors by combining with and stabilizing the inactive conformation of H1-receptors[13]. H1-antihistamines also have anti-allergic effects by decreasing antigen presentation, expression of proinflammatory cytokines and cell adhesion molecules. Moreover, through transcription factor nuclear factor -KB, it inhibits mast cell activation and histamine release in a concentration-dependent manner [14-16]. It is widely used in the treatment of allergic rhinitis, urticaria, and other allergic diseases. Since the successful development of the first antihistamine in 1937[17], antihistamines have experienced the development of the first generation, the second generation, and the second generation of improved varieties.

1.2.1 | First generation H1 antihistamines

Classic H1 receptor antagonists before the 1970s are commonly referred to the first-generation H1 antihistamines, such as chlorphenamine, diphenhydramine, promethazine, tripelennamine, and so on. First-generation H1 antihistamines are used to treat allergic reactions such as urticaria, allergic rhinitis, bronchial asthma, antipruritic, and antiemetic, etc [18]. The curative effect is definite. However, because of its short half-life, it must be given many times and the dosage is larger compared with the second-generation H1 antihistamines. First-generation H1 antihistamines, also known as sedating antihistamines, penetrate well through the blood-brain barrier and bind to the histamine receptors of the central nervous system. Then it can produce inhibitory and excitatory effects on the central nervous system, manifested as hallucinations,

drowsiness, decreased alertness, or restlessness, tension, insomnia, etc[19]. Almost all the first-generation antihistamines have a sedative effect, especially hydroxyzine, cyproheptadine, and diphenhydramine. Due to poor selectivity for H1 receptors, as well as block cholinergic receptors and serotonin activity, the incidence of dry mouth, tachycardia, gastrointestinal disorders, dementia, and other adverse reactions is high [20, 21]. Therefore, in recent years, except for a few local applications or recurrent applications, most first-generation H1 antihistamines have withdrawn from the market.

| Second generation H1 antihistamines

Second-generation H1 antihistamines include loratadine, imidazoline, terfenadine, and so on. In addition to their high histamine H1 receptor selectivity, they also have other anti-allergic effects, such as antagonizing intercellular adhesion molecules (ICAM). Compared with the first-generation H1 antihistamines, Second-generation H1 antihistamines have obvious advantages. It has lower lipotropy, rarely through the blood-brain barrier, and not a competitive priority and peripheral H1 receptor [22, 23]. Because of its long half-life, the dosage used is relatively small. What's more, with low or no sedation, there are fewer side effects such as sedation, drowsiness, and dry mouth, so they are also called non-sedating antihistamines[24]. However, they also have some defects. The second-generation H1 antihistamines like ketotifen, cetirizine, nitrogen, and acrivastine, still have a relatively light central sedative effect. Astemizole, azelastine, and ketotifen can stimulate increased appetite and lead to increased weight, of which astemizole is the most serious. The most serious adverse reaction is cardiotoxicity especially induced by terfenadine and astemizole, followed by loratadine, Ketotifen, and cetirizine, etc[25, 26]. Among the adverse reactions of the cardiovascular system, arrhythmia was the most common clinical picture. Although the incidence of such adverse reactions is relatively low, the consequences are severe.

| New H1 antihistamines

In recent decades, new second-generation antihistamines[27]—a modified version of a second-generation antihistamine have been introduced. The new second-generation antihistamines are derived from the active metabolites or optical isomers of second-generation antihistamines, such as desloratadine, levocetirizine, and fexofenadine. It is effective and has few adverse reactions, and no serious adverse reactions have been reported so far.

H2 antihistamines

Histamine H2 receptor antagonists include cimetidine, ranitidine, and famotidine, etc [28]. The H2 receptor antagonist can selectively block the H2 receptor on the cell membrane, resulting in the production of cAMP in the cell wall and the decrease of gastric acid secretion. It can also partially block the secretion of gastric acid caused by histamine, pentagastrin, cholinergic drugs, and stimulation of the vagus nerve[29]. Mainly used for the treatment of gastric and duodenal ulcers[30],Some studies have found that histamine H2 receptor antagonist (H2RA) can also improve the symptoms of heart failure (HF) patients[31, 32]. Histamine H2 receptor antagonists are safe drugs with a low incidence of serious adverse reactions. For the patients who are old age, with kidney function or other diseases is easy to produce adverse reactions like common diarrhea, headache, lethargy, fatigue, myalgia, constipation, and so on[33, 34].

| Pharmacogenomics of antihistamines

Pharmacogenomics is a science to study the relationship between gene sequence polymorphism and drug effect diversity[35]. Pharmacogenomics aims at drug effect and safety, it has contributed not only to the acknowledgment of gene polymorphism responsible for variation in drug response but also to the new drugs or new drug delivery methods development process [36]. In recent decades, the rapid development of pharmacogenomics has endowed a new connotation and brought new opportunities for individualized drug use, which makes today's clinical individualized drug use more far-reaching [37].

Antihistamine is a drug with a marked therapy effect that is widely used in allergic diseases, while individual variability in drug use has been reported. Individual differences may be mainly manifested as differences in pharmacodynamics and adverse reactions. Antihistamine pharmacogenomics has found that gene polymorphism plays an important role in its application (Fig 1). The genetic variation of metabolic enzyme, transporters, and targeted molecules influences the distribution, metabolism, and excretion of antihistamines through molecular mechanisms. Also, genes variation related disease like urticaria or allergic rhinitis may affect the application of antihistamine. A summary of the effect of drug metabolism enzyme, transporters, and receptors polymorphism on antihistamine is listed in Table 1. This paper summarizes the current researches of pharmacogenomics on antihistamines, hoping to have a certain significance for further research in this field and guiding clinical medication in the future.

| Drug metabolism enzyme polymorphism

The cytochromes P450(CYPs) is the main enzyme system of drug metabolism, which contains many subgroups. Human CYPs are mainly membrane-associated proteins that are widely expressed in most tissues, especially in liver tissue with specific CYPs types distributed[38, 39]. The gene variation of CYPs can change its susceptibility to induction and inhibition, then influence the pharmacokinetics of drugs. Therefore, CYPs play an important role in inter-individual drug response that is closely linked to the efficacy and side effects of drugs [40]. Most antihistamines are metabolized by the liver CYP450 enzyme system.

Cytochrome P450 (CYP) 3A is an important group of the CYP450 enzyme system, which is most abundant in the liver and gastrointestinal tract[41]. However, previous studies have shown that due to the single nucleotide polymorphisms (SNPs) in gene sequences, the enzyme encoded by the CYP3A allele has little or no activity[42]. The members of the CYP3A subfamily mainly include four genes that lie within a 231 kb region of chromosome 7q22.1, namely CYP3A4(MIM124010), CYP3A5(MIM605325), CYP3A7(MIM605340), and CYP3A43(MIM606534)[41]. Human cytochrome P450(CYP)3A4 is involved in the metabolism of about 50% of commonly used drugs [43, 44], among which the relationship between genetic polymorphism of CYP450 and antihistamines has been reported. Rupatadine (RUP) is an oral antihistamine and platelet activator antagonist that metabolizes desloratadine and 3-Hydroxydesloratadin primarily through CYP3A4 mediated metabolism. *CYP3A5*3* can reduce the expression of CYP3A5, and the polymorphism of the CYP3A5 gene may significantly affect the activity pattern of CYP3A[42]. Yuqing Xiong et al[45] found that *CYP3A5*1/*1* carrier had high metabolic activity and low transporter activity, while *CYP3A5*1 /*3* carriers had the opposite effect, which may lead to different concentrations of rupatadine (RUP) in the gastrointestinal tract and blood. Differences in concentration will lead to various treatment effectiveness and toxicity. The underlying mechanism of CYP3A5 polymorphism in individual differences in antihistamine application needs to be further demonstrated. Maekawa et al found that variants of CYP3A4 such as CYP3A4*16 and CYP3A4*18 alleles showed different catalytic activities for different CYP3A4 substrates[46]. In another study, possible genetic variants of CYP3A4, such as CYP3A4*2, *7, *16, and *18, may lead to drug-drug interaction individual-mediated variation by CYP3A4 inhibitor cimetidine[47]. Therefore, when antihistamines are used together with other drugs, the polymorphism of CYP3A4 in patients may be taken into account and the drug should be reasonably applied.

The CYP2 family is the largest group of the human P450 enzyme family. The CYP2J subfamily contains a single human gene, CYP2J2, which was originally proposed by Kikuta and his colleagues[48]. Human cytochrome CYP2J2 is highly expressed in the heart and is involved in a variety of metabolic reactions, including oxidation of important drugs and epoxidation of endogenous arachidonic acid[49, 50]. It is involved in the metabolism of a variety of antihistamine drugs, including ebastine, terfenadine, and astemizole [51, 52]. But the contribution of CYP2J2 to overall clearance is not clear and may strongly depend on the tissue[53, 54]. At least 10 genetic variants of CYP2J2 have been listed on the CYP alleles website. Jeong et al[55]used the antihistamine terfenadine as a substrate to analyze the biochemical characteristics of *CYP2J2*8, *9,* and **10* alleles (G312R, P351L, and P115L) containing non-synonymous SNPs and biochemical characteristics of P351L and P115L. It was found that the metabolic activity of the two mutant enzymes P351L and P115L

was similar to that of the wild type, and the changes of G312R amino acids affect the structural stability of the P450 heme environment. This may affect the metabolism of antihistamines like terfenadine and cause corresponding adverse reactions, but the specific mechanism of influence and the manifestation of adverse reactions are not described in the paper.

CYP2D6 is highly correlated with drug metabolism. CYP2D6 is involved in the metabolism of about 25% of clinically used drugs, and its gene polymorphism changes the pharmacokinetics of those with poor or extensive metabolism [56, 57]. CYP2D6 is encoded by a highly polymorphic gene [58]. Based on the activity of CYP2D6 isozymes, it identifies four types of carriers with different gene polymorphisms: normal (extensive), poor, intermediate, and hypertrophic metabolites[59]. Extensive metabolite (EM): The main alleles were **1* and **2* ; Poor metabolite (PM): The main allele was **3˜*6* ; Intermediate metabolite (IM): The primary alleles were **10* and **41* . Wild-type allelic hypervelocity metabolites included individuals with gene variants *(CYP2D6*1)xN* and *(CYP2D6*2)xN* duplication and multiplication[60]. The most common allelic variants associated with the poor phenotype of metabolites were *CYP2D6*3, CYP2D6*4, CYP2D6*5,* and *CYP2D6*6*[60]. People with poor metabolism are more likely to be affected by poor substrate metabolism. CYP2D6 is the main metabolic pathway for many sedative drugs in the central nervous system[56, 61]. Antihistamine effects are also known to occur with antidepressants and antipsychotic drugs[62], such as mirtazapine, esmirtazapine, mianserin, and meclizine. Mirtazapine and mianserin have an H1 antagonist effect obviously, studies have shown that people with dysmetabolic CYP2D6 phenotypes are more sensitive to the potential damage of esmirtazapine and are more likely to be exposed to high levels of drugs or metabolites[63]. Besides CYP2D6, another study has found that mirtazapine metabolism may also be influenced differently by the CYP3A5 genotype and by multiple combinations (three or more)[64], so there may also be a greater chance of adverse reactions. Meclizine has long been a widely accepted antihistamine used in the preventative treatment and management of nausea, vomiting, and dizziness associated with exercise disorders [65]. Zhijun Wang et al [65]found that CYP2D6 was the dominant enzyme in meclizine metabolism, and its polymorphism might be related to the elimination of variation of meclizine.

| Polymorphism of drug transporters

Drug transporters are integral membrane proteins localized to tissue and cellular membrane domains in the human body, mediating the transport of drug molecules through active and passive mechanisms[66]. Influx and efflux transporters play an important role in the absorption, tissue distribution, and excretion of drugs[67]. It has been reported that non-sedating antihistamines are characterized by the efflux function of P-glycoprotein(P-gp) through the blood-brain barrier [68]. P-glycoprotein is an ATP-dependent carrier protein first discovered in tumor cells and expressed by multi-drug resistance genes[69]. It exists in a variety of tissues in the human body, such as the liver, kidney, brain, and so on [69-73]. P-gp is encoded by the MDR1(ABCB1) gene[74]. P-gp gene polymorphism, including *1236C>T, 2677G>A/T,* and *3435C>T* mutation produced, and conflicting results have been obtained in the study of the pharmacokinetics of fexofenadine. Persons with *2677AA/3435CC*genotype of MDR1(ABCB1) have lower plasma concentrations of fexofenadine after a single oral taking compared to the person with other genotypes[75]. On the contrary, Drescher et al found that there was no significant correlation of*C3435T* polymorphism with the H1 receptor occupancy by the P-glycoprotein substrate fexofenadine[76]. In addition to P-gp, organic anion transport polypeptide (OATPs) that encoded by the SLCO gene [77] and multidrug resistance protein 2(MRP2) that encoded by the *ABCC2*genes [78] may also work on fexofenadine pharmacokinetics. OATP1B1, 1B3, and 2B1 involved in fexofenadine liver metabolism in OATP drug transporters[79-81] and Akamine et al[82]studied the effect of drug transporter polymorphism on the pharmacokinetics of fexofenadine and found that the pharmacokinetics of S-fexofenadine was related to the single polymorphism of *SLCO2B1* and multiple polymorphism combinations of *ABCB1 C1236T, C3435T,* and *ABCC2 C-24T.* In the small intestine and liver, the binding of multiple transporters involved in OATP, P-GP, and multidrug resistance protein 2(MRP2) may strongly respond to exposure to fexofenadine, resulting in different configurations between enantiomers. In another study, the relationship between *SLCO2B1* , the encoding gene of OATP transporter, and the antihistamine drug fexofenadine was also pointed out. Through in vitro kinetics studies, this study showed that *SLCO2B1*

c.[1457C>T]2 allele reduce OATP2B1 transport function and the bioavailability of fexofenadine[83], which may affect the efficacy and toxicity of the drug.

| Receptor polymorphism

As a drug target for antihistamines, the change of the histamine receptor, especially the polymorphism of the receptor gene, will also affect the effect of drugs and lead to the individual difference. Therefore, the study of the variation of the receptor gene is of great significance. Gu et al[84]found that among HRH4 genes, rs77485247 mutant (TA+AA) and rs77041280 mutant (TA+TT) may reduce the efficacy of H1A orally, which may increase the incidence of adverse reactions. The polymorphism of HRH4 rs77485247 and rs77041280 may affect the therapeutic effect of antihistamines. A study on histamine H1 receptor gene polymorphism and efficacy in Chinese Han patients with allergic rhinitis showed that the efficacy of H1 antihistamines was enhanced in AR patients with HRH1 wild-type gene type, while the heterozygous mutant (CT) and homozygous mutant (TT) genes have a higher risk of AR and may affect the efficacy of antihistamines and increase their adverse reactions[85].

| Disease susceptibility and drug efficacy, side effects

Antihistamines are the first-line therapeutic drugs for urticaria, which is an allergic disease mainly involved with mast cells. The polymorphisms of the genes involved in the development and progression of urticaria may also affect the efficacy and toxicity of antihistamines. In recent years, the research in this field has been increasing and relevant research reports have provided us with some ideas. Reports in this area include *FCER1A, CACNA1C,* ORAI1, C5AR1, and CRTH2, as shown in Table 2. *FCER1A* is an important immune-related gene that encodes ligand-binding subunit a chain (FceRIa) of high-affinity IgE receptor (FceRI) to trigger IgE-mediated allergic reactions, related to the total level of IgE serum[86-88]. High total serum IgE levels are closely correlated with the clinical expression and severity of allergic diseases[89-91]. However, no association between *FCER1A* and allergic rhinitis was found in one study [92]. For urticaria, Guo et al of our group have found that among the rs2298805, rs10908703, and rs2494262 genotypes of *FCER1A* , rs2298805 polymorphism is associated with the risk of CSU and serum total IgE concentration, and CSU patients with rs2298805A allele show a better response to non-sedate H1-antihistamine[93]. Further functional studies are needed to elucidate the mechanism of rs2298805 affecting the pathogenesis of urticaria and the therapeutic effect of non-sedated H1-antihistamine.*CACNA1C* codes for the pore-forming α1C subunit of the L-type voltage-gated calcium channel (LTCC). Our group's study on genetic polymorphism of the *CACNA1C* gene and susceptibility and prognosis of chronic spontaneous urticaria showing that genetic polymorphisms of the *CACNA1C* gene can affect the mast cell activation and degranulation process, thus affecting the onset of the CSU[94]. A/G mutation at rs58619945 in patients may be related to the onset of chronic spontaneous urticaria, different alleles at rs216008 may be related to the efficacy of desloratadine, and mutations at rs7316246 may indicate differences in the severity and prognosis of the disease[94]. The degranulation process of mast cells is mainly mediated by Ca^{2+}influx mediated by calcium channels activated by calcium releasing enzymes. ORAI1 is a plasma membrane protein, encoded by the *ORAI1* gene, and calcium-release-activated calcium (CRAC) channels pore formation subunit[95]. Studies on ORAI1 knockout mice have shown that ORAI1 plays an important role in mast cell degranulation, leukotriene (LTC4) secretion, histamine release, and TNF-a secretion [96, 97]. Our group reported[98] that rs3741595, rs3741596, rs12320939, and rs12313273, especially the rs3741596A allele, were significantly increased in CSU patients and rs12320939T allele was associated with increased expression of the *ORAI1* gene. The *ORAI1* gene allele rs3741596A enhanced the degranulation activity of mast cells and the rs3741595C may be associated with the therapeutic effects of desloratadine. C5a receptor (C5aR) plays an important role in mast cell activation and degranulation by regulating the complement C5a pathway, thus enhancing the release of histamine. C5a/C5aR pathway promotes histamine release and leads to CSU inflammatory response, human C5aR is encoded by *C5AR1* (also known as C5aR) gene, and Yan et al[99] in our group founded that *C5AR1* SNP -1330T/G can be used as an effective pharmacodynamics predictor of the efficacy of non-sedating H1-antihistamine drugs in CSU patient. The

chemoattractant receptor-homologous molecule expressed on Th2 Lymphocytes (CRTH2) is a member of the G protein-coupled, seven-transmembrane receptor family and it has been reported to be associated with mast cell-related allergic diseases [100, 101]. Palikhe NS et al[102] founded that CRTH2 gene polymorphism(*-466T>C* and-*129C>A*) may not be associated with susceptibility in Korean patients with chronic urticaria, but the CRTH2-*466T>C* gene polymorphism was associated with the required antihistamine dose and CU patients with the CRTH2 *-466T*genotype need a higher dose.

There have been a few clear reports on gene polymorphism and the exact adverse effects of antihistamines. Sedating side effects is a major adverse effect of first-generation and some second-generation antihistamines. Juan et al in our team[103] evaluated the association between HRH1 gene rs901865 polymorphism and sedating side effects severity in 114 Chinese CSU patients treated with desloratadine. HRH1 rs901865 G/G polymorphism was found to be associated with an increase in desloratadine induced lethargy but did not affect drug efficacy or increase the risk of CSU. This study will be important for predicting the severity of narcolepsy adverse reactions after the desloratadine application. Cardiotoxicity is a serious adverse reaction induced by antihistamines. Among second-generation antihistamines, terfenadine and astemizole have been reported to cause tip torsion ventricular tachycardia with prolonged QT interval and even death due to drug overdose and drug interactions[104-107]. Antihistamines can cause cardiotoxicity by blocking the current of a human Etherago-go-related gene (HERG). A614v-HERG mutations have been shown to cause syncope in patients with a first-generation H1 receptor antagonist and hydroxyzine can inhibit the channel current of the gene[108]. The correlation between gene polymorphism and adverse cardiotoxicity induced by antihistamines is scarce, more research needs to be done in the future.

| Discussion

Antihistamines are safe drugs that are widely used in various allergic diseases and its clinical application has been shown to have good efficacy. However, there have been some reports of adverse reactions and differences in efficacy, some of which are rare and potential. Previous studies have reported that gene polymorphisms are responsible for differences in antihistamine use. They include metabolic enzymes, drug transporters, and drug target gene polymorphisms. In addition, genes associated with the disease itself have been shown to correlate with individual differences in antihistamines.

Once the concept of individualized drug use was put forward, it was widely concerned and recognized. The core of rational drug use is individual drug administration, no unified drug administration. Personalized medicine remains a major challenge for healthcare decision-makers. The study of pharmacogenomics will provide us with an important idea of personalized medicine. It can provide people with personalized health guidance, personalized medication guidance, and personalized physical examination services through analyze the risk or efficacy of patients by determining their genotypes.

The study of pharmacogenomics is of great significance. Disease susceptibility genes are continuously discovered by people, people can infer the possible risk of developing certain diseases through genetic tests and to conduct health guidance. The in vivo processes of drugs include absorption, distribution, metabolism, and excretion. Drug response varies among individuals due to disease heterogeneity, environmental and genetic factors: doses that are effective in some patients inevitably become ineffective or cause adverse drug reactions (ADRs) in others. Gene polymorphism can influence the pharmacokinetics and pharmacodynamics of drugs, leading to changes in local and systemic drug exposure and/or changes in drug target function that alter drug responses. For patients, the occurrence of adverse events may mean longer hospital stays, higher disease treatment costs, and even higher mortality rates. Pharmacogenomics will help reduce these potential adverse events, improving the efficacy, shortening the course of the disease, and reducing the cost of treatment. Through genetic testing, doctors can infer the likelihood of adverse reactions, and pharmacogenomics provides powerful support for doctors' prescribing decisions, guiding drug selection and administration. Besides, pharmacogenomics, which classifies genes according to different drug effects, has the potential to greatly accelerate the process of new drug development. Drugs with the goal of human

genetic validation are more likely to be marketed successfully than those without such evidence[109, 110]. The identification of rare sequence variations associated with important human phenotypes also provides a basis for new drug development.

In conclusion, variability in response, especially the risk of adverse reactions, is an almost inevitable feature of modern drug therapy. Pharmacogenomic science, such as exome or genome sequencing, provides new tools for understanding variability in drug responses. Although to date here have been limited published studies on antihistamines pharmacogenomics, related antihistamine genomics research has contributed to the rational drug use of patients to a certain extent. Previous studies mainly focus on metabolic enzyme genes, while studies on the coding genes of drug-binding receptors, drug-transport-related membrane channels, and signal-transduction-related proteins are lacking. According to the previous research reports, the specific mechanism, type, and degree of adverse reactions caused by gene polymorphism after the application of antihistamines are not fully understood. Therefore, further studies are needed to elucidate these unknown areas to better guide the rational clinical application of antihistamines, realize individualized drug administration and treatment, and to avoid the adverse consequences caused by individual differences.

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Figure legends

FIGURE 1. Gene polymorphism affects the efficacy and adverse reactions of antihistamines. As a reverse agonist, antihistamine acts on the histamine receptor to antagonize the histamine effect, exerting the antihistamine and anti-allergic effect. Antihistamines complete the process of absorption, distribution, metabolism and excretion under the action of drug transporter and the cytochromes P450(CYPs). Mast cells, one of the

main histamine-releasing cells, express multiple receptors on the surface. Polymorphisms of these receptor-related genes, histamine receptor, transporter and metabolic enzyme related genes may affect drug efficacy and adverse reactions.

Table 1. Effects of metabolic enzymes, drug transporters, and drug target receptor gene polymorphisms on antihistamine drug therapy and adverse reactions.

	Gene	**Variants**	**Variant effect**	**Related anti-histamines**	**Ref.**
Metabolic enzyme	CYP3A5	*1/*1	High metabolic activity, low transport activity	Rupatadine	[45]
		*1/*3	Low metabolic activity, high transport activity		[45]
	CYP3A4	*2	May lead to drug-drug interaction	Cimetidine	[47]
		*7			
		*16			
		*18;-392A>G (rs2740574)			
	CYP2J2	*8(G312R)	Affects the structure of P450 heme	Terfenadine	[55]
		*9(P351L)	No effects No effects		
		*10(P115L)			
	CYP2D6	*1,*2	Extensive metabolizers	Asmiranzapine Mirtazapine Methiazine	[60, 63-65]
		*3~*6	Poor metabolizers		
		*10,*41	Intermediate metabolizers		
		(CYP2D6*1)xN (CYP2D6*2)xN”	Ultrarapid metabolizers		
Transport molecules	ABCB1	1236C>T,2677G>A/T, 3435C>T	Contradictory results	Fexofenadine	[75, 76]
	SLCO	2B1 (SLCO2B1c.[1457C>T])	Reduced transport function	Fexofenadine	[82 83]
		1B1	Not reported		
		1B3			
Receptors	HRH1	CT, TT	Increase the incidence of AR and affect the curative effect		[85]

Gene	Variants	Variant effect	Related anti-histamines	Ref.
HRH4	rs901865 G/G	Increase sleepiness	Desloratadine	[103]
	rs77041280(TA+TT)	Reduce the efficacy of H1A orally		[84]
	rs77485247(TA+AA)			

Table 2. Effects of gene polymorphism on susceptibility to urticaria and antihistamine use.

Gene	Coding target and functions	Variant/SNPs	Risk of urticaria	Influence on antihis-tamines efficacy(Drugs)	Affects prognosis and severity	Ref.
FCER1A	FcRIα: Initiating IgE mediated allergic reactions	rs2298805 (rs2298805A)	+	Increase	No reports	[93]
		rs10908703	—	—	No reports	
		rs2494262	—	—	No reports	
CACNA1C	Alpha 1 c subunits in LTCC: Mediates Ca2+ influx	rs58619945,A/G	+	—	No reports	[94]
		RS216008	—	+(Desloratadine)	No reports	
		RS7316246	—	—	+	
ORAI1	ORAI1: Mediates Ca2+ influx	rs3741596A	Increase	No reports	No reports	[98]
		rs12320939T	Increase	No reports	No reports	
		rs3741595C	Increase	+(Desloratadine)	No reports	
C5AR1	C5aR: Regulate the complement C5a pathway	rs11673309 (—1330T/G)	Increase	+(Desloratadine)	No reports	[99]
CRTH2	G-protein-coupled, seven-transmembrane receptor family	-466T>C	Increase	Increase dose	No reports	[102]

+: Related

—:Not related to