



Histamine pharmacogenomics

Genetic polymorphisms for histamine-metabolizing enzymes are responsible for interindividual variation in histamine metabolism and are associated with diverse diseases. Initial reports on polymorphisms of histamine-related genes including those coding for the enzymes histidine decarboxylase (HDC), diamine oxidase (ABP1) and histamine *N*-methyltransferase (HNMT), as well as histamine receptor genes, often have pointed to polymorphisms that occur with extremely low frequencies or that could not be verified by later studies. In contrast, common and functionally significant polymorphisms recently described have been omitted in many association studies. In this review we analyze allele frequencies, functional and clinical impact and interethnic variability on histamine-related polymorphisms. The most relevant nonsynonymous polymorphisms for the *HDC* gene are rs17740607 Met31Thr, rs16963486 Leu553Phe and rs2073440 Asp644Glu. For *ABP1* the most relevant polymorphisms are rs10156191 Thr16Met, rs1049742 Ser332Phe, and particularly because of its functional effect, rs1049793 His645Asp. In addition the *ABP1* polymorphisms rs45558339 Ile479Met and rs35070995 His659Asn are relevant to Asian and African subjects, respectively. For *HNMT* the only nonsynonymous polymorphism present with a relevant frequency is rs1801105 Thr105Ile. For *HRH1* the polymorphism rs7651620 Glu270Gly is relevant to African subjects only. The *HRH2* rs2067474 polymorphism, located in an enhancer element of the gene promoter, is common in all populations. No common nonsynonymous SNPs were observed in the *HRH3* gene and two SNPs were observed with a significant frequency in the *HRH4* gene: rs11665084 Ala138Val and rs11662595 His206Arg. This review summarizes relevant polymorphisms, discusses controversial findings on association of histamine-related polymorphisms and allergies and other diseases, and identifies topics requiring further investigation.

KEYWORDS: ABP1 ■ allergy ■ HDC ■ histamine ■ HNMT ■ polymorphism ■ receptor

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Histamine (2-[4-imidazole]ethylamine) is one of the most important biogenic amines and was first identified as a mediator in biological functions in the early 1900s. Histamine is involved in the regulation of numerous physiological and pathophysiological processes including gastric acid secretion, hypersensitivity reactions, bronchial asthma, multiple elements of immune regulation and tumorigenesis [1–3]. In the CNS histamine may act both as a neuromodulator and as a classical transmitter regulating several brain functions such as learning, sleep/wake cycles, hypothalamic responses or food and water intake [4–7]. Several diseases are claimed to be associated with histamine metabolism and/or its receptors because of its widespread biological significance.

Histamine is synthesized by decarboxylation of its precursor histidine, in a one-step reaction carried out solely by the enzyme L-histidine decarboxylase (HDC; E.C. 4.1.1.22). Two enzymes are known to participate in the degradation of histamine: histamine *N*-methyltransferase

(HNMT; E.C. 2.1.1.8) to tele-methylhistamine and diamine oxidase (DAO; ABP1, E.C. 1.4.3.6) to imidazole acetaldehyde. Tele-methylhistamine is further metabolized to tele-methylimidazoleacetaldehyde by mono- and di-amine oxidase enzymes and the aldehyde is metabolized to tele-methylimidazoleacetic acid by the aldehyde dehydrogenase enzyme. The DAO metabolite, imidazole acetaldehyde, is metabolized by the aldehyde dehydrogenase to imidazole-4-acetic acid, which is further metabolized in two sequential steps by imidazoleacetic acid phosphoribosyltransferase and 5' nucleotidase and acid phosphatase to imidazoleacetic acid-riboside [8].

Histamine performs its action via different types of histamine receptors [9]. Four metabotropic histamine receptor types have been cloned so far. All histamine receptors belong to the rhodopsin-like family of G protein coupled receptors. Histamine H₁ receptor (HRH1) is involved in hypersensitivity reactions, smooth muscle contraction and vascular permeability. The H₂

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receptor (HRH2) modulates gastric acid secretion. Both HRH1 and HRH2 are involved in numerous processes of immune response [10]. The H_3 receptor (HRH3) acts as an autoreceptor in the nervous system by inhibiting histamine synthesis and its release. HRH3 also acts as a heteroreceptor, modulating the release of other neurotransmitters, including acetylcholine, dopamine and noradrenaline [11]. HRH4, initially identified by an *in silico* approach [12], has a higher affinity for histamine compared with HRH1 and appears to be more selectively expressed, found mainly on hematopoietic cells. HRH4 is involved in chemotaxis and inflammatory mediator release by eosinophils, mast cells, monocytes, dendritic cells and T cells [13], and it has been implicated in the immune system control mechanism in different organs and tissues such as the spleen, the thymus and leukocytes [12,14]. Also, there is evidence of HRH4 expression in synovial cells of rheumatoid arthritis patients [15]. In addition to classical histamine receptors, histamine modulates ionotropic receptors such as GABA A and NMDA receptors by interacting at receptor sites for allosteric modulators [7,16,17].

The sequences of genes coding for enzymes involved in histamine synthesis and degradation and histamine receptors have been elucidated in recent years. Considering the biological significance of histamine, polymorphisms of histamine-related genes were soon considered as potential genetic factors likely to have an influence on disease outcome and therapy. Initial reports pointed to a number of potentially relevant polymorphisms in these genes [18–20] and in recent years several studies on the putative association between these polymorphisms and different diseases have been performed. Many of the polymorphisms initially proposed as relevant were not confirmed in further studies. On the other hand, newly described polymorphisms have proved to be common in most human populations and have a prominent functional and clinical significance. In this review we analyze polymorphisms of histamine-related genes including enzymes HDC, HNMT and ABPI, and receptors HRH1 to HRH4 and we present an overview of the present knowledge of the clinical significance of these gene variations.

Histidine decarboxylase

Histidine decarboxylase is a homodimeric enzyme composed of two 55-kDa subunits. It is a decarboxylase pyridoxal phosphate-dependent and it is highly specific for the substrate histidine [8]. HDC can be stimulated by

cyclic AMP-dependent protein kinase [21] and Ca^{2+} -calmodulin-dependent protein kinase II pathways [22]. Cells of neuroepithelial and hematopoietic origin have histamine synthesis capability [7,23]. Mast cells and basophilic granulocytes are major sources of histamine. Biochemical, biophysical and immunological studies have suggested the occurrence of HDC isoenzymes that may result from either post-translational modification of the protein or allelic variants [24].

The human *HDC* gene is located on chromosome 15q21-q22, is composed of 12 exons (FIGURE 1) and has a size of about 2.4 Kb [25]. SNPs for the *HDC* gene are detailed in TABLE 1. Three of these SNPs cause amino acid substitutions and have been detected in human populations. The most relevant nonsynonymous polymorphisms for the *HDC* gene are presented in FIGURE 1. Among Caucasian and Asian subjects only two nonsynonymous SNPs have been detected: those causing the amino acid changes Met31Thr and Asp644Glu. For African subjects an additional SNP, which causes the amino acid change Leu553Phe, has been observed.

In agreement with the HapMap data shown in TABLE 1, the Met31Thr variant allele frequency for other Caucasian populations is 0.917 for the AFD European panel [101]. Regarding Asian subjects, the frequency is 0.938 for Chinese subjects in the AFD Chinese panel, and 0.978 for Japanese subjects in HapMap [101]. For African subjects, the Met31Thr variant allele frequency is 0.978 in the AFD African–American Panel, which is close to that shown in TABLE 1. The Leu553Phe variant allele has been consistently detected in African populations. In addition to the sub-Saharan African HapMap population (TABLE 1) it has been observed in the AFD African–American Panel with a frequency of 0.109 and in an African–American population from the Coriell Cell repository with a frequency of 0.054 [102]. Besides the frequencies shown in TABLE 1, the Asp644Glu variant has been observed with a frequency of 0.021 for the AFD European panel, 0.062 for the AFD Chinese panel, and 0.152 for the AFD African–American Panel. For Japanese individuals the HapMap frequency is 0.056, which is lower than that reported for Chinese subjects [103]. To date, no studies have investigated the functional effect of *HDC* SNPs.

In addition to the mutations shown in TABLE 1, two mutations in a colorectal cancer sample have been described to cause the amino acid changes Glu49Val and Glu285Lys [26]. These gene variations, however, have not been observed in further studies.

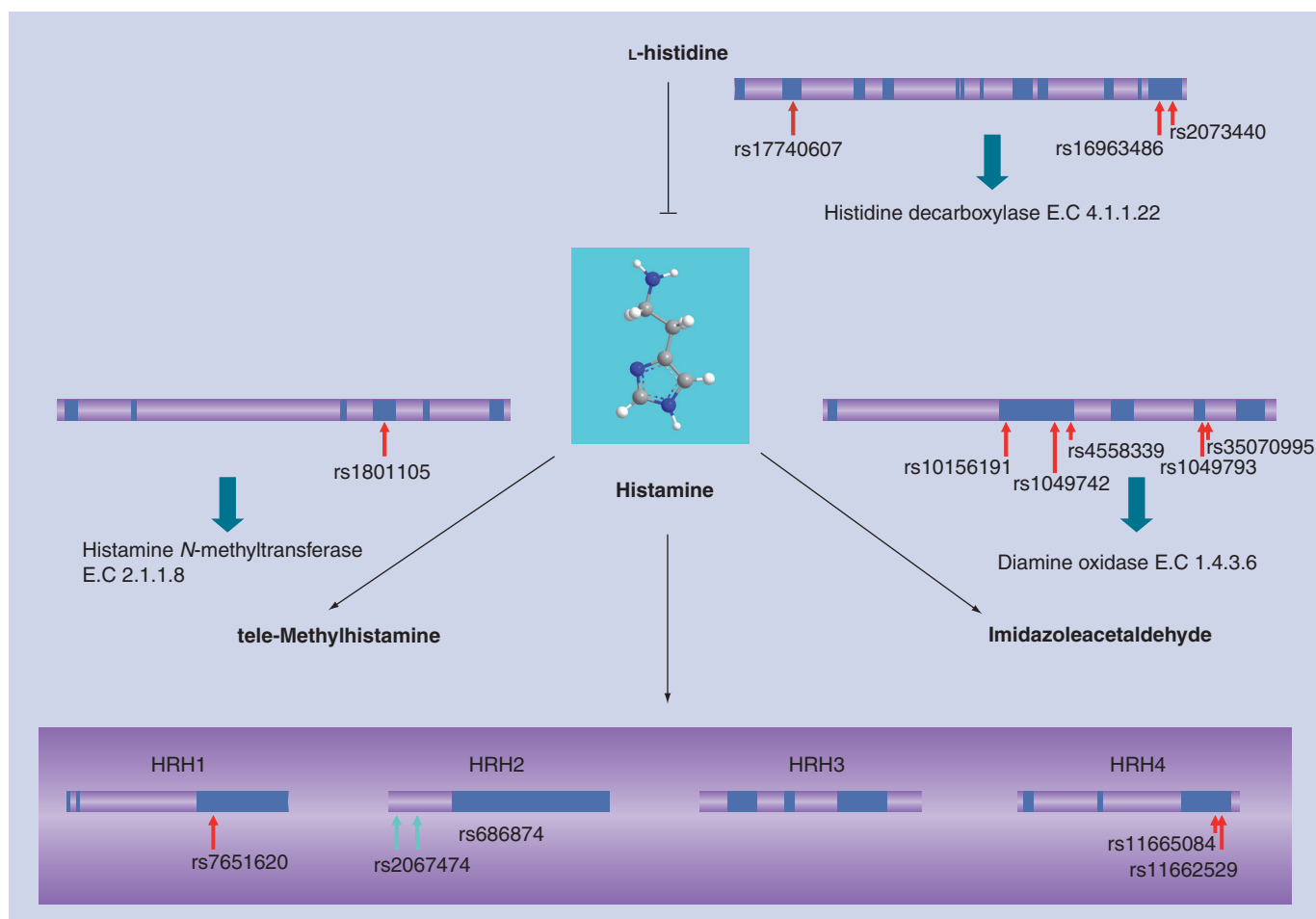


Figure 1. Relevant histamine-related polymorphisms. Red arrows mark nonsynonymous polymorphisms and green arrows mark promoter polymorphisms.

Studies on the potential association of *HDC* polymorphisms with human disease are scarce due to the recent description of most gene variants. A recent report suggests that the *HDC* gene polymorphism rs854163, located on the boundary between exon 1 and intron 1 of the *HDC* gene, is significantly associated with age at natural menopause in Caucasian women [27]. Some studies focusing on the biological functions of histamine at the hypothalamus have suggested that histamine influences the secretion of the gonadotropin-releasing hormone, and plays an important role in the regulation of gonadal hormone release [28]. These findings support the hypothesis that histamine may play a role in the regulation of the reproductive system. Although the authors propose that the association of the *HDC* SNP rs854163 may be due to a linkage disequilibrium with genes that influence age at natural menopause, further studies are required to fully elucidate such putative association [27]. Surprisingly the potential role of *HDC* polymorphisms on diseases of immune origin has

not been analyzed to date. Since histamine plays a key role in such diseases and *HDC* is the only enzyme capable of synthesizing histamine, the occurrence and effects of genetic variations at the *HDC* gene in patients with histamine-related disorders is an interesting topic which deserves further study.

Besides genetic variability due to the presence of SNPs, variability in *HDC* gene regulation has also been described, although the potential role of common polymorphisms in the *HDC* gene promoter with regard to *HDC* expression remains to be elucidated. It has been shown that upregulation of *HDC* expression colocalizes with histamine in superficial cortical nephrons during pregnancy [29], thus suggesting that increased *HDC* expression may lead to high histamine levels. Gastrin activates *HDC* promoter activity in human gastric cancer cell line through three overlapping downstream promoter elements [30,31]. Kruppel-like factor 4 is a nuclear factor that binds to the gastrin responsive elements in the *HDC* promoter and

Table 1. SNPs reported for the human *HDC* gene.

dbSNP	Polymorphism	Amino acid change	Variant allele frequency			Position
			European	Asian	African	
rs854163	C/T	–	0.198	0.116	0.088	Intron 1
rs17740669	A/G	–	0.892	0.989	1.000	Intron 1
rs11856059	C/G	–	0.125	0.011	0.000	Intron 1
rs854160	C/T	–	0.442	0.556	0.475	Intron 1
rs17740607	A/G T/C	Met31Thr	0.892	0.956	1.000	Exon 2
rs854159	C/T	–	0.798	0.856	0.929	Intron 2
rs860526	A/G	–	0.467	0.778	0.567	Intron 2
rs3784295	A/G	–	0.958	0.956	0.942	Intron 2
rs16963523	C/T	–	0.000*	0.000*	0.043*	Intron 2
rs854158	A/G	–	0.317	0.244	0.108	Intron 2
rs7182203	A/G	–	0.696	0.927	0.816	Intron 2
rs854157	A/G	–	0.475	0.795	0.825	Intron 2
rs16963519	A/G	–	0.000*	0.000*	0.043*	Intron 2
rs1894236	A/G	–	0.792	0.944	0.892	Intron 2
rs10518836	A/C	–	0.892	0.944	1.000	Intron 2
rs2238292	A/C	–	0.669	0.611	0.883	Intron 2
rs17796788	A/G	–	0.892	0.956	1.000	Intron 2
rs8029889	C/T	–	0.208	0.056	0.108	Intron 2
rs34505468	G/T A/C	Ile91Leu	ND	ND	ND	Exon 3
rs2853766	A/G	–	0.817	0.756	0.992	Intron 4
rs16963517	A/G	–	0.017	0.000	0.050	Intron 4
rs1677254	–/A/G	–	0.227	0.535	0.259	Intron 4
rs35806322	A/G	Ala187Ala	ND	ND	0.987 [†]	Exon 5
rs16963514	C/T	–	0.000	0.000	0.050	Intron 5
rs2070595	A/C	–	0.642	0.922	0.525	Intron 7
rs2070596	A/T	–	0.282	0.062	ND	Intron 7
rs34406040	A/G	Ala296Ala	ND	ND	0.985 [†]	Exon 8
rs854151	A/G	–	0.233	0.267	0.158	Intron 9
rs854150	C/G	–	0.667	0.756	0.875	Intron 9
rs552379	A/T	–	0.026	0.000	0.067	Intron 9
rs16963498	A/G	–	1.000	1.000	1.000	Intron 9
rs2081629	A/G	–	0.017	0.000	0.214	Intron 10
rs8042671	A/G	–	1.000	1.000	0.95	Intron 10
rs2238294	A/G	–	1.000	0.911	0.833	Intron 10
rs16963496	C/T	–	1.000	0.911	0.833	Intron 10
rs7164386	C/T	–	0.000	0.089	0.161	Intron 10
rs7163895	A/G	–	1.000	0.911	0.850	Intron 10
rs7163360	C/T	–	0.000	0.089	0.158	Intron 10
rs16963493	C/T	–	0.992	0.911	ND	Intron 10
rs1573594	C/T	–	0.000	0.000	0.000	Intron 10
rs35490626	–/G	–/453Glu	ND	ND	ND	Exon 12
rs1549521	A/G	Asn538Asn	0.017	0.089	0.353	Exon 12
rs16963486	A/G	Leu553Phe	0.000	0.000	0.067	Exon 12
rs16963485	A/G	Thr581Thr	0.000	0.089	0.033	Exon 12
rs35670478	C/T	Val590Val	ND	ND	0.066	Exon 12

Allele frequencies correspond to those described by HapMap unless specified [112]. For details of the populations analyzed see [113].

*Samples obtained from the Coriell Cell Repository [114–116].

[†]African–American population obtained from Coriell Cell Repositories [117].

[‡]Population obtained from the Centre d'Etude du Polymorphisme Humain [118].

dbSNP: SNP database; ND: Not determined.

Table 1. SNPs reported for the human *HDC* gene (cont.).

dbSNP	Polymorphism	Amino acid change	Variant allele frequency			Position
			European	Asian	African	
rs2073440	A/C	Asp644Glu	0.017	0.089	0.158	Exon 12
rs16963481	G/T	–	1.000	0.909	0.831	Exon 12, 3'-UTR
rs1042447	G/T	–	0.990 [§]	ND	ND	Exon 12, 3'-UTR
rs7167784	C/T	–	0.983	0.909	0.825	3' near gene
rs7166052	C/T	–	0.017	0.091	0.175	3' near gene
rs7183971	A/G	–	1.000	0.900	0.825	3' near gene

Allele frequencies correspond to those described by HapMap unless specified [112]. For details of the populations analyzed see [113].

[†]Samples obtained from the Coriell Cell Repository [114–116].

[‡]African–American population obtained from Coriell Cell Repositories [117].

[§]Population obtained from the Centre d'Etude du Polymorphisme Humain [118].

dbSNP: SNP database; ND: Not determined.

inhibits *HDC* promoter activity in a specific and dose-dependent manner [32]. The specific oncoprotein BCR/ABL of chronic myeloid leukemia induces expression of *HDC* and the synthesis of histamine in leukemic cells, and it has been shown that certain histamine-receptor targeting drugs such as loratadine and terfenadine exert antileukemic effects on these cells [33].

It has been demonstrated that certain skin disorders are related to increased *HDC* expression levels. Skin with chronic urticaria in particular expresses high levels of *HDC* as compared with normal foreskin, breast skin and cultured human keratinocytes [34]. Whether *HDC* expression levels correlates with local histamine concentrations remains to be studied in detail.

Diamine oxidase

Diamine oxidase also designated as amiloride-binding protein 1 (ABP1) catalyzes the degradation of histamine and the other compounds such as putrescine, spermine and spermidine, substances involved in allergic and immune responses, cell proliferation, tissue differentiation, tumor formation and possibly apoptosis. DAO activity is mainly expressed in the kidney and colon, as well as in the placenta, thymus and seminal vesicles [35,36] and it is responsible for scavenging extracellular histamine after mediator release [21]. DAO is also considered a regulating enzyme in rapidly proliferating tissues and it has been suggested that it is involved in regulating cell division or differentiation and that it may act as a neurotrophic ligand [36]. Determination of DAO activity in blood has become a useful marker of gut mucosal integrity. In fact, serum DAO enzyme activity is modified by certain disorders including severe burns, gut injury, diverse enteropathies and abdominal surgery, chemotherapy and kidney injury [37–39]. In addition, gender is a determinant factor in serum

DAO activity because women display a wide range of interindividual variability in enzyme activity whereas men show little interindividual variability in enzyme activity and have a lower mean activity than women [40].

The human *ABP1* gene, which codes for the DAO enzyme, is located on chromosome 7q34–q36. Several nonsynonymous SNPs have been reported in this gene. TABLE 2 shows the *ABP1* SNPs reported, and FIGURE 1 summarizes the situation of the most relevant SNPs. Three common nonsynonymous SNPs, which bring about the amino acid substitutions Thr16Met, Ser332Phe and His645Asp have been detected in Caucasian subjects. Two additional SNPs causing the amino acid changes Ile479Met and His659Asn have been reported to occur at low frequencies in Asian and African subjects, respectively. The three most common polymorphisms, Thr16Met, Ser332Phe and His645Asp, are in partial linkage disequilibrium [41].

Thr16Met has been described as occurring in Caucasians with allele frequencies of 0.300 in a HapMap population composed of 60 individuals (TABLE 2), 0.295 in a population of 24 individuals from the Coriell Cell repository [103], and 0.254 in a population composed of 134 healthy Caucasian individuals [41]. The frequencies reported for Asian subjects, besides that shown in TABLE 2, are 0.042 for Chinese subjects [104] and 0.089 for Japanese subjects [104]. For African–Americans, frequencies of 0.397 and 0.600 have been reported, whereas for sub-Saharan Africans the frequencies reported are 0.567 (TABLE 2) and 0.625 [104].

The Ser332Phe has been detected with a frequency of 0.068 in 22 Caucasian subjects [105]. This frequency was further confirmed in a larger study involving 134 subjects that had a frequency of 0.063 [41]. Among Asian subjects, the Ser332Phe variant allele is rare, with

Table 2. SNPs reported for the human *ABP1* gene.

dbSNP	Polymorphism	Amino acid change	Variant allele frequency			Position
			European	Asian	African	
rs2373876	A/G	–	0.273*	0.116	0.620	5' near gene
rs10273148	C/T	–	1.000*	1.000*	0.833*	5' near gene
rs45600938	A/G	–	0.932*	1.000*	1.000*	5' near gene
rs10273373	C/T	–	0.727*	0.867	0.361	5' near gene
rs2052130	C/T	–	0.159*	0.024	0.000	5' near gene
rs2052129	A/C	–	0.738*	0.867	0.708*	5' near gene
rs2301256	C/T	–	0.000	0.056	0.000	5' near gene
rs8180720	A/G	–	1.000	1.000	1.000	Intron 1
rs7786420	A/C	–	0.75*	0.933	0.792*	Intron 1
rs7786526	A/C	–	0.75*	0.886	0.75*	Intron 1
rs7786439	A/G	–	0.273*	0.000	0.250*	Intron 1
rs10281706	A/T	–	1.000	1.000	0.667*	Intron 1
rs45476794	A/G	–	1.000*	1.000*	0.875*	Intron 1
rs45601031	–/TATGAAAA	–	0.775*	0.952*	0.438*	Intron 1
rs10441176	A/G	–	0.000*	0.000*	0.333*	Intron 1
rs2268998	C/T	–	0.295*	0.114	0.625*	Intron 1
rs10441169	A/G	–	0.000	0.000	0.108	Intron 1
rs2268999	A/T	–	0.308	0.111	0.600	Intron 1
rs2071513	G/T	–	0.250*	0.105	0.333*	Intron 1
rs10156189	C/T	–	0.000	0.000	0.207	Intron 1
rs10156191	C/T	Thr16Met	0.300	0.167	0.567	Exon 2
rs34502771	–/A	-160Lys	ND	ND	ND	Exon 2
rs45568935	C/T	Ser298Ser	0.000*	0.000*	0.000*	Exon 2
rs35929142	C/T	Gly321Asp	ND	ND	ND	Exon 2
rs1049742	C/T	Ser332Phe	0.068*	0.011	0.150	Exon 2
rs41465145	A/G	Gly342Gly	0.941	0.967	1.000	Exon 2
rs2071514	A/G	Ala443Ala	0.853	0.511	0.771	Exon 2
rs45558339	A/G	Ile479Met	1.000*	0.979*	1.000*	Exon 2
rs56280448	–/G	-494Gly	ND	ND	ND	Exon 2
rs2301257	C/T	–	0.150	0.489	0.356	Intron 2
rs45455308	A/G	–	0.786*	0.932*	0.875*	Intron 2
rs10893	A/G	Pro545Pro	0.322	0.522	0.667	Exon 3
rs1049748	C/T	Pro574Pro	0.669	0.389	0.458	Exon 3
rs6943147	C/G	Thr592Arg	ND	ND	ND	Exon 3
rs13235592	C/G	–	1.000	1.000	1.000	Intron 3
rs13235597	C/G	–	1.000	1.000	1.000	Intron 3
rs45453396	A/G	–	0.738*	0.739*	0.958*	Intron 3
rs11981415	C/G	–	ND	0.912	ND	Intron 3
rs10952294	C/T	–	0.262*	0.604*	0.750*	Intron 3
rs4725968	A/G	–	0.738*	0.396*	0.250*	Intron 3
rs45615934	A/G	–	0.800*	0.932*	0.875*	Intron 3
rs2071515	C/G	–	0.700*	0.350*	0.125*	Intron 3
rs11771771	A/G	–	0.848	0.989	0.951	Intron 3
rs12179	A/G	Ser630Ser	0.723	0.488	0.382	Exon 4
rs1049793	C/G	His645Asp	0.300	0.522	0.667	Exon 4
rs35070995	G/T	His659Asn	1.000	1.000	0.975	Exon 4
rs3735076	C/T	–	0.295*	0.604*	0.750*	Intron 4
rs45498500	C/G	–	0.000*	0.000*	0.083*	Intron 4

Allele frequencies correspond to those described by HapMap unless specified [112]. For details of the populations analyzed see [113].

*Samples obtained from the Coriell Cell Repository [114–116].

dbSNP: SNP database; ND: Not determined.

Table 2. SNPs reported for the human *ABP1* gene (cont.).

dbSNP	Polymorphism	Amino acid change	Variant allele frequency			Position
			European	Asian	African	
rs12539	C/T	–	0.178	0.111	0.167	Exon 5, 3'-UTR
rs2071517	A/G	–	0.850	0.511	0.692	3' near gene
rs34090933	–/CA	–	0.476*	0.667*	0.875*	3' near gene
rs4725969	C/T	–	0.250	0.115	0.556	3' near gene
rs4725374	C/T	–	0.182	0.115	0.167	3' near gene
rs4725970	C/T	–	0.178	0.102	0.150	3' near gene

Allele frequencies correspond to those described by HapMap unless specified [112]. For details of the populations analyzed see [113].

*Samples obtained from the Coriell Cell Repository [114–116].

dbSNP: SNP database; ND: Not determined.

frequencies of 0.011 and 0.000 for Chinese and Japanese individuals, respectively [105]. In contrast, in African subjects the variant allele is common, with frequencies of 0.033 and 0.064 for African-Americans and 0.150 and 0.167 for sub-Saharan Africans [105]. Ile479Met variation has been observed only in Asian subjects, with a frequency of 0.979 for the Met variant. In the rest of the populations analyzed, including Caucasians, Hispanic, African-Americans and sub-Saharan Africans, only the 479Met variant was observed [106]. The His645Asp variant is common in all populations analyzed. For Caucasian subjects, in addition to the frequency shown in TABLE 2 frequencies of 0.318 and 0.306 have been observed in samples of 22 [116] and 134 individuals [41]. For Asian subjects the frequencies range 0.522 in Chinese subjects to 0.605 in Japanese subjects [107]. For African-Americans, reported frequencies are 0.382 and 0.600, and for sub-Saharan Africans the frequencies are 0.667 and 0.750 [107]. His659Asn is a rare allelic variant that has been described only in African subjects, with frequencies of 0.947 and 0.967 for African-Americans and 0.975 and 1.000 for sub-Saharan Africans. In the rest of the populations studied, only the Asn allele is present and therefore the variant allele frequency is 1.000 [108].

The functional effect of common *ABP1* gene variations in DAO serum enzyme activity has been studied recently. The variant alleles Thr16Met and His645Asp cause changes in enzyme kinetics by increasing the K_m of the enzyme [41]. Individuals heterozygous and homozygous for 645Asp have V_{max}/K_m values of 66 and 51%, respectively, as compared with noncarriers of the variant allele. The effect of the 16Met variant allele is similar, since individuals heterozygous and homozygous for 16Met have V_{max}/K_m values of 79 and 42%, respectively, as compared with noncarriers of the variant allele, and that of the rarest allele 332Phe

is negligible [41]. In a study analyzing the role of the polymorphisms Thr16Met, Ser332Phe and His645Asp in intestinal biopsy samples of patients with food allergy, no major differences in enzyme activity regarding *ABP1* genotypes were detected [42]. Unfortunately, this study did not investigate the effect of SNPs on the K_m of the enzyme or putative differences in intestinal enzyme activity between individuals with food allergy and healthy subjects, a topic that deserves further investigation.

Regarding the analysis of whether *ABP1* polymorphisms may affect disease risk or clinical outcome, few studies on this have been performed and these are limited to the most common variant allele His645Asp which is, in fact, the most relevant in enzyme function [41]. It has been shown that ABP1 enzyme activity in bowel mucosa was lower among patients with inflammatory bowel disease (IBD), as compared with healthy individuals [43–45], thus supporting the hypothesis that individuals carrying mutations in the *ABP1* gene may show altered susceptibility to ulcerative colitis and greater activity of the disease. A preliminary study involving 17 patients with ulcerative colitis and 34 patients with Crohn's disease indicated an increased frequency of individuals carrying variant *ABP1* alleles among patients with IBD [46]. However, none of the *ABP1* gene variations analyzed in this study are located within the coding region of the gene, and no evidence of a relevant effect of these mutations in ABP1 enzyme activity or expression has been published. After the identification of the relevant variant alleles of *ABP1*, a study involving 229 IBD patients revealed that the gene variant 645Asp was linked to parameters closely related to the severity of the disease, that is to say the need for immunosuppressant therapy and/or the need for surgery [47].

The variant allelic His645Asp of the *ABP1* gene was studied in patients with asthma and allergic rhinitis [48]. This study shows that

the 645Asp polymorphism may influence the clinical presentation of asthma or allergic rhinitis. Individuals who are carriers of 645Asp alleles tend to develop clinical symptoms even though IgE levels were not severely altered, thus suggesting that individuals with altered histamine biodisposition may display atopic symptoms even in the absence of a high release of histamine [48].

Although the number of studies on the effect of *ABPI* variations in clinical outcome is still low, overall findings are promising and suggest that the clinical course of allergic and other diseases related to high histamine levels may be altered in patients with genetically-determined impaired histamine metabolism, and therefore *ABPI* gene variations could be a determinant in such diseases.

Histamine *N*-methyltransferase

Histamine *N*-methyltransferase is an *S*-adenosyl-methionine (AdoMet)-dependent enzyme that catalyzes the *N*-methylation of histamine, one of the two main pathways for the biotransformation of histamine in mammals, and is the primary enzyme responsible for inactivating histamine in the mammalian brain [24]. HNMT can be inhibited or induced by a variety of drugs [49]. Hence, HNMT has not only a physiopathologic importance, but also a pharmacologic importance. Over two decades ago it was observed that inheritance was a determinant in HNMT activity in human tissues [50–52], and therefore gene polymorphisms were expected to play an important role in phenotypic variation of HNMT activity.

The *HNMT* gene is located on chromosome 2q22.1. Early biochemical studies reported that the only product of the 50-Kb human *HNMT* gene was a single mRNA of approximately 1.6 Kb with six exons [52], although recent studies have revealed a new brain mRNA product of *HNMT* of about 1.0 Kb. This species, named HNMT-short (HNMT-S), encodes a 126 amino acid protein and has been detected in brain and placenta but not in other human tissues. HNMT-S cDNA does not result in histamine-methylating activity and its physiological role remains unknown [53].

Only two nonsynonymous *HNMT* SNPs have been described (TABLE 3). Among these, the most common is the Thr105Ile variant allele [54]. The 105Ile variant enzyme is associated with reduced thermal stability and decreased HNMT activity, probably related to a tighter packing of the enzyme that results in a re-orientation

of cosubstrate-binding sites [54,55]. The other nonsynonymous SNP, Ile199Val (TABLE 3), was reported in a Japanese subject [56], although it was not identified again among 352 Chinese individuals [57] or among 90 ethnically anonymous samples from the Coriell Cell Repository [58]. In addition to these nonsynonymous SNPs, diverse mutations at the 5' flanking region of the *HNMT* gene have been described, although none of these seems to have a relevant effect on HNMT enzyme activity [58].

Besides HapMap data on Thr105Ile variant allele frequency (TABLE 3), several studies have analyzed this frequency in diverse human populations. Among healthy Caucasians, the variant allele frequency ranges from 0.08 to 0.170 [59,60], although most studies report allele frequencies between 0.100 and 0.120 [61–63]. For healthy Asian subjects, the variant allele frequencies range from 0.035–0.060 [57,64–66]. The variant Thr105Ile allele seem to be absent in African subjects (TABLE 3).

Due to the fact that histamine is an important mediator of asthma and HNMT is the primary enzyme for histamine metabolism in bronchial epithelium, the role of *HNMT* gene polymorphisms in the pathogenesis of asthma has been studied. Promising findings indicating the association of the Thr105Ile variant allele with asthma were initially reported [60] although further independent studies failed to identify such an association either for patients with asthma or with bronchial hyper-responsiveness [48,60,67,68]. A lack of association between the Thr105Ile polymorphism and aspirin-induced hypersensitivity has been also reported [65,69]. These findings taken together suggest that the *HNMT* Thr105Ile polymorphism is not a relevant factor *per se* in the development of allergic disease. However, a recent study that needs confirmation suggests that the Thr105Ile variant allele may confer increased risk of developing atopic dermatitis [61].

Inflammatory bowel disease has been also investigated for the *HNMT* Thr105Ile polymorphism. The basis for these studies is that increased mucosal histamine levels are observed in patients with IBD [70] and increased levels of tele-methylhistamine, the HNMT-specific metabolite of histamine, have been detected in the urine of patients with IBD [71]. However, no differences in the *HNMT* allele frequency were observed in two independent studies [46,47]. These findings suggest that variation in HNMT activity in the bowel may be related to factors unrelated to the Thr105Ile

Table 3. SNPs reported for the human *HNMT* gene.

dbSNP	Polymorphism	Amino acid change	Variant allele frequency			Position
			European	Asian	African	
rs3113201	A/T	–	0.000	0.000	0.050	5' near gene
rs6430764	C/T	–	0.600	0.659	0.314	5' near gene
rs2071048	C/T	–	0.600	0.678	0.517	5' near gene
rs11569722	A/G	–	1.000	1.000	0.925	5' near gene
rs12995000	C/T	–	0.133	0.144	0.059	5' near gene
rs11569723	C/T	–	1.000	1.000	0.925	5' near gene
rs1471004	A/G	–	0.000	0.000	0.142	Intron 1
rs1471003	A/G	–	0.000	0.000	0.108	Exon 2, 3'-UTR
rs1471001	G/T	–	1.000	1.000	0.892	3' near gene
rs1471000	C/G	–	1.000	1.000	0.892	3' near gene
rs1801105	C/T	Thr105Ile	0.125	0.044	0.000	Exon 4
–	A/G	Ile199Val	ND	0.000*	ND	Exon 6

Allele frequencies correspond to those described by HapMap unless specified [112]. For details of the populations analyzed see [113].
 The SNP Ile199Val was reported in [56].
 *Absent in a study involving 352 Chinese individuals [57].
 dbSNP: SNP database; ND: Not determined.

polymorphism. In this regard, it is interesting to note that differences in the transcription of *HNMT* between patients with IBD and control subjects have been observed [72], thus suggesting that factors affecting gene expression, rather than nonsynonymous polymorphisms, may be relevant in IBD.

Histamine is involved in neuronal degeneration [52] and neurotoxicity [73], and changes in the morphology and increase in density of histaminergic fibers in the substantia nigra have been described in the brain of Parkinson's disease (PD) patients [74]. An association between the *HNMT* Thr105Ile polymorphism and PD has been reported. Patients with PD showed an increased frequency of homozygous *HNMT* 105Thr genotypes as compared with healthy subjects, and this increased frequency is more evident among patients with late-onset PD [75]. Similar results were observed among patients with essential tremor [76]. These results combined suggest that alterations of histamine homeostasis in the CNS are associated with the risk of movement disorders. However further studies are required to confirm this hypothesis.

Another putative effect of the *HNMT* Thr105Ile in the CNS is related to alcoholism. In an initial study it was observed that the *HNMT* Thr105Ile polymorphism was related to alcoholism in two independent populations, non-mutated alleles (Thr105) leading to increased vulnerability to alcoholism [59]. However another study was unable to reproduce these findings and observed an association confined to patients with positive family history [63]. Therefore, the putative association

of *HNMT* with alcoholism remains controversial and deserves further studies to definitively confirm or discount this association.

Other diseases that have been investigated with regard to the *HNMT* Thr105Ile polymorphism, although with negative findings, are gastric ulcer [64,66] schizophrenia [77] or migraine [62].

Histamine receptors

Studies involving SNPs in histamine receptors are scarce and controversial. Some genetic polymorphisms have been described, although no relationship between these polymorphisms and receptor function has yet been found (TABLES 4–7).

The *HRH1* gene, located in chromosome 3p25, shows diverse SNPs, five of which are non-synonymous (TABLE 4). All of these polymorphisms are located in exon 3 and are extremely rare in Caucasians. In fact the polymorphism Ser449Leu, initially described as a relatively common polymorphism [78], was not detected in 231 healthy Caucasian subjects and in only two out of 195 patients with PD, and therefore the allele frequency is extremely low [79]. The synonymous polymorphism Gln356Gln was detected in only one out of 58 Caucasian subjects [109] and the rest of nonsynonymous polymorphisms were not detected (TABLE 4). In a recent study which analyzed the polymorphism Glu270Gly in 426 Caucasian subjects no such polymorphism was observed [79]. Among Asian subjects, only one nonsynonymous *HRH1* gene polymorphism, Glu270Gly, was identified in one out of 44 subjects, whereas the rest of the polymorphisms were not identified (TABLE 4). Among African subjects

Table 4. SNPs reported for the human *HRH1* gene.

dbSNP	Polymorphism	Amino acid change	Variant allele frequency			Position
			European	Asian	African	
rs346076	A/G	–	0.325	0.344	0.633	5' near gene
rs12490160	C/T	–	0.867	0.967	0.725	5' near gene
rs13064530	A/G	–	0.733	0.733	0.650	5' near gene
rs184700	A/G	–	0.675	0.714	0.483	5' near gene
rs346075	A/C	–	0.675	0.667	0.367	5' near gene
rs346074	A/G	–	0.688*	0.683	0.363	5' near gene
rs17034206	C/T	–	0.000*	0.000*	0.048*	Intron 2
rs1018111	C/G	–	0.300	0.295	0.175	Intron 2
rs13087946	C/T	–	0.000	0.000	0.000	Intron 2
rs447378	G/T	–	0.000	0.000	0.000	Intron 2
rs901865	A/G	–	0.825	0.933	0.675	Exon 3, 5'-UTR
rs2067466	C/G	Asn19Lys	1.000	0.989	1.000	Exon 3
rs7651620	A/G	Glu270Gly	1.000	1.000	0.914	Exon 3
rs17855034	A/T	Glu308Val	ND	ND	ND	Exon 3
rs2067467	G/T	Glu349Asp	1.000	1.000	1.000	Exon 3
rs2067468	A/G	Gln356Gln	0.009	0.000	0.008	Exon 3
rs2067470	C/T	Ser449Leu	1.000	1.000	1.000	Exon 3
rs1809049	A/G	–	0.875	0.678	0.708	Exon 3, 3'-UTR
rs346068	A/G	–	0.831	1.000	0.975	Exon 3, 3'-UTR
rs346070	C/T	–	0.175	0.000	0.125	Exon 3, 3'-UTR
rs3732941	C/T	–	0.875	0.633	0.708	Exon 3, 3'-UTR

Allele frequencies correspond to those described by HapMap unless specified [112]. For details of the populations analyzed see [102].

*Samples obtained from the Coriell Cell Repository [103–105].

dbSNP: SNP database; ND: Not determined.

the polymorphism Glu270Gly was consistently detected in African–American and sub-Saharan African individuals, with allele frequencies of 0.955 and 0.914, respectively, and the polymorphism Gln356Gln was detected in three out of 22 African–American individuals but in only one out of 60 sub-Saharan Africans. Therefore,

genetic variations in the *HRH1* gene seem to be common in African subjects only. A study reports splice variation of novel 5' terminal exons of *HRH1* gene and three main separate novel promoters that show tissue-specific expression [80]. The occurrence of splicing variants of *HRH1* is an interesting issue that deserves investigation.

Table 5. SNPs reported for the human *HRH2* gene.

dbSNP	Polymorphism	Amino acid change	Variant allele frequency			Position
			European	Asian	African	
rs2517950	G/T	–	0.025	0.000	0.000	5' near gene
rs594623	A/G	–	1.000	1.000	0.974	5' near gene
rs2067475	A/G	–	1.000	1.000	1.000	5' near gene
rs2067474	A/G	–	0.958	0.756	0.810	5' near gene
rs686874	C/T	–	0.958	0.756	0.600	5' near gene
rs6868411	A/G	–	1.000	1.000	0.990	Exon 1, 5'-UTR
rs2067473	A/G	–	0.000	0.000	0.000	Exon 1, 5'-UTR
rs17065306	C/T	Thr15Thr	0.000	0.000	0.065	Exon 1
rs34310687	–/T	–82Cys	ND	ND	ND	Exon 1
rs1800689	A/G	Val181Val	0.933	0.967	1.000	Exon 1
rs1800690	C/T	Leu276Leu	ND	ND	ND	Exon 1
rs7729139	A/G	–	1.000	1.000	1.000	3' near gene
rs2241562	C/G	–	0.000	0.078	0.000	3' near gene

Allele frequencies correspond to those described by HapMap unless specified [112]. For details of the populations analyzed see [102].

dbSNP: SNP database; ND: Not determined.

Table 6. SNPs reported for the human *HRH3* gene.

dbSNP	Polymorphism	Amino acid change	Variant allele frequency			Position
			European	Asian	African	
rs41284986	T/C	Ser178Ser	ND	ND	ND	Exon 3
rs3787430	C/T	Pro326Pro	0.121	0.200	0.140	Exon 3
rs3787429	C/T	Ser332Ser	0.375	0.444	0.525	Exon 3
rs2067476	A/G	Ser405Ser	ND	ND	ND	Exon 3

Allele frequencies correspond to those described by HapMap unless specified [112]. For details of the populations analyzed see [102].

dbSNP: SNP database; ND: Not determined.

Regarding the SNPs mapped to the *HRH2* gene, which is located in chromosome 5q35.2, TABLE 5 shows that none cause amino acid changes. In addition to these, a variant allele causing the Asn217Asp amino acid change were initially described by Orange *et al.* [19,20] but this was not confirmed by independent studies [81,82]. In fact, many of the *HRH2* polymorphisms initially described, including that causing the amino acid exchange Val133Ala among others [19,20], were not identified in further studies. The functional significance of the SNP rs2067474, a G1018A transition located in an enhancer element of the gene promoter remains unknown, although it is conceivable that it may induce changes in the expression of receptors [79]. This polymorphism occurs with a relevant allele frequency in diverse human populations [62,78,82,83].

The gene *HRH3* is located on chromosome 20q13.33. In contrast to *HRH1* and *HRH2*, the *HRH3* gene has many splice variants, yielding a large number of receptor isoforms [6,84–86]. It has been shown that functional isoforms are generated by deletion of a pseudo-intron that varies in length and is located in the third intracellular loop of *HRH3* [6]. The distribution and pharmacology of these isoforms are different, and their respective functions in the brain remain unknown, but they might generate heterogeneity of cerebral *HRH3* [86]. Besides the SNPs for *HRH3* summarized in TABLE 6, two nonsynonymous *HRH3* variants have been described. These are those causing the amino acid changes Asp19Glu [18] and Ala280Val, which was observed in a patient suffering from Shy–Drager syndrome [87]. None of these have been confirmed in subsequent studies.

HRH4 is the latest identified member of the histamine receptor subfamily. The *HRH4* gene is located on chromosome 18q11.2. SNPs for *HRH4* are summarized in TABLE 7. A total of four nonsynonymous polymorphisms have been reported. Two of these occur in all the populations analyzed, although that causing the Ala138Val amino acid exchange was consistently observed in European and Asian

subjects, but was not consistently observed in African subjects since the polymorphism was identified in one out of 60 sub-Saharan Africans but not among African–Americans [110]. In contrast, the polymorphism causing the His206Arg amino acid exchange was consistently observed in all populations [111], and the frequencies for the rest of the nonsynonymous *HRH4* polymorphisms are unknown. In addition to these shown in the TABLE 7, another nonsynonymous SNP causing the amino acid substitution Arg252Gln was described [18], but has not been identified in further studies. Recently, the cloning of two alternatively spliced *HRH4* isoforms from CD34⁺ cord blood-cell-derived eosinophils and mast cells has been reported, although the authors failed to detect ligand binding or constitutive activity for these *HRH4* splice variants [84]. Therefore, the functional significance of these alternatively-spliced *HRH4* receptors remains unknown.

Unlike polymorphisms of histamine-metabolizing enzymes, polymorphisms of histamine receptors are rare and their functional and clinical relevance is unknown. *HRH1* mediates the proinflammatory actions in the cytokine release and adhesion processes [10,88,89], while *HRH2* is involved in Th1/Th2 balance [85]. In an attempt to investigate whether *HRH1* and *HRH2* polymorphisms contribute to allergic diseases, two studies carried out on a Japanese and a Korean population have reported a lack of association between *HRH* polymorphisms and salicilate-induced urticaria/angioedema [65,81].

In individuals suffering from schizophrenia, the *HRH2* variant allele causing the Asn217Asp amino acid change was found to be more prevalent than in the normal population [20]. However this finding could not be replicated [82]. Another *HRH2* polymorphism, the promoter polymorphism rs2067474, was found to be associated to obesity and the effect of clozapine [78,90], although these findings await confirmation.

The expression of histamine receptors is linked to a protective role against toxic-induced neurodegeneration [91]. Since alteration in

Table 7. SNPs reported for the human *HRH4* gene.

dbSNP	Polymorphism	Amino acid change	Variant allele frequency			Position
			European	Asian	African	
rs9944755	C/T	–	0.050	0.011	0.217	5' near gene
rs10163596	A/C	–	1.000	1.000	0.975	5' near gene
rs670327	A/C	–	ND	0.333	0.091	5' near gene
rs615283	A/G	–	0.833	0.967	0.942	5' near gene
rs9748607	A/C	–	1.000	1.000	1.000	Intron 1
rs628764	C/T	–	0.825	0.967	0.942	Intron 1
rs17187605	A/C	–	0.033	0.156	0.000	Intron 1
rs1791517	A/C	–	0.000	0.000	0.000	Intron 1
rs1362819	A/G	–	1.000	1.000	1.000	Intron 1
rs2848556	A/G	–	1.000	1.000	1.000	Intron 1
rs17187605	A/C	–	0.967	0.844	1.000	Intron 1
rs880263	C/T	–	0.121	0.033	0.025	Intron 1
rs1421119	C/T	–	0.733	0.689	0.667	Intron 1
rs623590	A/C/T	–	0.092	0.278	0.192	Intron 1
rs9963453	C/T	–	0.051	0.011	0.308	Intron 1
rs4483927	G/T	–	0.733	0.644	0.667	Intron 1
rs16940762	A/G	–	0.949	0.989	0.683	Intron 1
rs17797945	C/T	–	0.254	0.167	0.000	Intron 1
rs16940765	C/T	–	0.950	0.989	0.675	Intron 1
rs17797951	A/G	–	0.750	0.833	1.000	Intron 2
rs8088140	A/C	–	0.775	0.678	0.325	Intron 2
rs17187619	C/T	–	0.808	0.867	0.942	Intron 2
rs8092706	C/T	–	1.000	1.000	0.933	Intron 2
rs13381219	A/G	–	0.000	0.000	0.114	Intron 2
rs681807	C/T	–	1.000	1.000	1.000	Intron 2
rs7505887	A/C	–	1.000	1.000	1.000	Intron 2
rs9962663	A/G	–	1.000	1.000	1.000	Intron 2
rs104000	A/G	–	0.117	0.044	0.192	Intron 2
rs17203328	C/T	–	0.966	0.989	1.000	Intron 2
rs643552	C/T	–	0.783	0.922	0.783	Intron 2
rs8098979	A/G	–	0.068	0.134	0.093	Intron 2
rs17187626	G/T	–	0.271	0.439	0.192	Intron 2
rs657132	A/G	–	0.883	0.711	0.933	Intron 2
rs1626398	C/T	–	1.000	1.000	1.000	Intron 2
rs11083069	G/T	–	1.000	1.000	1.000	Intron 2
rs684167	C/G	–	0.000	0.000	0.000	Intron 2
rs536468	C/T	–	0.058	0.011	0.161	Intron 2
rs17259800	C/T	–	0.312*	0.500*	0.087*	Intron 2
rs11665084	C/T	Ala138Val	0.092	0.033	0.008	Exon 3
rs11662595	A/G	His206Arg	0.092	0.033	0.008	Exon 3
rs58154316	C/G	Ser284Cys	ND	ND	ND	Exon 3
rs34682566	–/G	–379Leu	ND	ND	ND	Exon 3
rs1421126	A/G	–	0.625	0.833	0.883	Exon 3, 3'-UTR
rs9945837	C/T	–	0.058	0.011	0.117	Exon 3, 3'-UTR
rs1421125	A/C	–	0.638	0.844	0.881	Exon 3, 3'-UTR
rs45572832	C/T	–	0.028 [‡]	ND	ND	Exon 3, 3'-UTR

Allele frequencies correspond to those described by HapMap unless specified [112]. For details of the populations analyzed see [113].

*Samples obtained from the Coriell Cell Repository [114–115].

[‡]French Canadian population [119].

[§]WICGR1 Caucasian population [120].

dbSNP: SNP database; ND: Not determined.

Table 7. SNPs reported for the human *HRH4* gene (cont.).

dbSNP	Polymorphism	Amino acid change	Variant allele frequency			Position
			European	Asian	African	
rs1791266	A/C	–	0.000	0.000	0.000	Exon 3, 3'-UTR
rs472407	A/G	–	0.731 [§]	ND	ND	Exon 3, 3'-UTR
rs475997	A/G	–	0.925	0.878	0.833	Exon 3, 3'-UTR
rs17797975	C/T	–	0.892	1.000	1.000	Exon 3, 3'-UTR
rs4800573	A/G	–	0.792	0.689	1.000	Exon 3, 3'-UTR
rs8085246	C/T	–	0.915	0.967	0.992	3' near gene

Allele frequencies correspond to those described by HapMap unless specified [112]. For details of the populations analyzed see [113].
[§]Samples obtained from the Coriell Cell Repository [114–115].
[†]French Canadian population [119].
[§]WICGR1 Caucasian population [120].
dbSNP: SNP database; ND: Not determined.

histaminergic transmission is observed in patients with PD [74], a study analyzed *HRH1* and *HRH2* polymorphisms in patients with PD [79]. Although the authors conclude that the polymorphisms analyzed are not a major risk factor for PD, the study was not conclusive because of the low frequency of *HRH* polymorphisms.

From the analysis of TABLES 4–7 and of recent literature, we conclude that only a few nonsynonymous *HRH* polymorphisms actually occur and have potential clinical implications. Many studies have analyzed *HRH* polymorphisms initially believed to be common though these have not been identified in further studies. Therefore, even negative and nonconclusive studies on *HRH* polymorphisms should be replicated, the appropriate polymorphisms selected and the allele frequencies summarized in the present review should be taken into consideration.

Future perspective

The widespread significance of histamine and the initial description of a few polymorphisms in histamine-related genes, including enzymes and receptors, has been the basis for several studies focusing on histamine genomics. However, in the last few years the knowledge of histamine-related polymorphisms has increased dramatically and today it is evident that many polymorphisms thought to be common and relevant actually do not occur and, conversely, relevant polymorphisms have been overlooked in several studies.

Igaz *et al.* reviewed histamine genomics *in silico* in 2002 and they identified several putative polymorphisms as potential targets for histamine pharmacogenomic studies [18]. For *HDC*, they reported three nonsynonymous polymorphisms Ser148Gln, Ile400Asn and Arg617Trp, which have not been detected in HapMap or in further

studies (TABLE 1). None of the nonsynonymous polymorphisms shown in TABLE 1 were included in the review by Igaz *et al.* [18]. For the ABP1 enzyme, they reported five nonsynonymous polymorphisms that were not confirmed, namely Pro280Ala, Asp290Thr, Ser592Thr, Arg632Gly and Asp664His (TABLE 2). Only one polymorphism, Phe332Ser, was confirmed and two major polymorphisms, Thr16Met and the one with the highest frequency and functional impact, His645Asp (TABLE 2), were missing [18]. In addition, other nonsynonymous polymorphisms relevant to Asian subjects, Ile479Met, or to African subjects His659Asn were also missing in this review [18].

Regarding histamine receptors, Igaz *et al.* included the nonsynonymous *HRH1* Glu252Val polymorphism, which has not been identified in further studies, as well as the following *HRH2* polymorphisms: Val133Ala, Lys175Asn, Lys207Arg, Asn217Asp, Lys231Arg and Val268Met [18]. For *HRH3*, the variant Asp19Glu was described and for *HRH4*, the variant Arg252Gln was reported. None of these were detected in further studies (TABLES 5–7). Only two *HRH4* polymorphisms, Val138Ala and Arg206His, remain from the study by Igaz *et al.* [18]. In addition, several polymorphisms, particularly those for histamine receptors, were initially described as common and in subsequent studies have not been identified, or have occurred with extremely low frequencies. This has created considerable confusion and has caused a waste of effort in studies focused on extremely rare or even nonexistent target polymorphisms. As a consequence of such confusion, and because most of the relevant information on histamine pharmacogenomics has evolved in the last few years, the knowledge of the clinical implications of histamine pharmacogenomics is still in its infancy.

Experimental validation of putative polymorphisms is always necessary and failure to validate these polymorphisms is frequent with *in silico* methods. Today we have enough information to design future studies including relevant polymorphisms taking into consideration allele frequencies, interethnic variability and functional effect. In addition, available data point to the occurrence of intra-ethnic variability for some polymorphisms at least. This is a common feature for drug-metabolizing enzymes [92,93] and requires further investigation. Hopefully in the next few years information on allele frequencies in several human populations will be available, the functional effects of the existing *HDC* and *HRH* polymorphisms

will be elucidated, and well-designed studies will provide relevant and clinically useful information on the promising topic of histamine pharmacogenomics.

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Executive summary

Initial studies pointed to extremely rare or nonexistent polymorphisms

- Several polymorphisms for histamine-metabolizing enzymes and histamine receptors, which were initially proposed as relevant were not identified in subsequent studies. Conversely, many relevant polymorphisms were ignored.

All histamine metabolizing enzymes, including L-histidine decarboxylase (*HDC*), histamine N-methyltransferase (*HNMT*) & diamine oxidase (*DAO*), as well as two histamine receptors present common nonsynonymous polymorphisms

- These polymorphisms are present in all human populations, although interethnic variability in allele frequencies exists.
- Information on intra-ethnic variability in allele frequency for these polymorphisms is scarce, but it is enough to suggest that it may be a relevant issue requiring further investigation.

The number of studies on the functional & clinical effect of histamine-related polymorphisms is still low & incomplete

- More studies are required to analyze the functional effect of *HDC* and *HRH* gene variations.
- Many studies analyzing clinical associations have focused on nonexistent polymorphisms or analyzed only a few relevant polymorphisms.
- Further studies should be undertaken to obtain a complete view of all histamine-related gene variations with regard to human disease.

Functionally relevant polymorphisms of histamine-metabolizing enzymes are related to allergic diseases

- Studies analyzing functionally relevant and common histamine-related polymorphisms, particularly for *HNMT* and *DAO*, have reported promising findings with regard to association with allergic diseases.
- Such studies, however, should be replicated and should include analyses of interactions with polymorphisms of *HDC* and *HRH*.

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