Genetic Polymorphisms in the Histamine Receptor Family

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Abstract:

Histamine is a biogenic amine which has an inherent biological importance in many physiological functions, both in the central nervous system and in the periphery. With the new genomic era we are facing, personalised care and treatment is becoming one of the major focal points in research. This chapter focuses on the genetic variations and polymorphisms localised on genes encoding for human histamine receptors (HRHs) where it provides an up to date collection of polymorphisms found on genes encoding HRHs and their association to diseases. There is a clear need to highlight the specific implications polymorphisms have on this family of G-protein coupled receptors. This book chapter collates recent and other important publications related to polymorphisms and genetic linkage of histamine receptors. New association studies have been published for the gene encoding the HRH4, linking SNPs to asthma, cancer and atopic dermatitis. For example, rs17187619, rs527790, rs487202, rs1421125 and rs615283 have been associated with infection-induced in asthma patients. Other SNPs were found to harbour a link in breast cancer rs623590, rs11662595, rs1421125. With the increasing interest in cancer research, a polymorphism (rs2607474) discovered on the gene encoding for HRH2 was also found to have an association to gastric atrophy leading to gastric cancer. Looking into pharmacogenetics, a linkage was found between risperidone treatment and histamine receptor 3 (HRH3), where rs3787430 could be a potential biological marker for treatment. With these significant genetic variations recently discovered and their potential contribution to the common diseases, this chapter gathers the knowledge to date for SNPs identified on the human histamine receptors.

Key words: Histamine receptors, genetic polymorphisms, single nucleotide polymorphisms, association studies, linkage analysis, human histamine 1 receptor, human histamine 2 receptor, human histamine 3 receptor, human histamine 4 receptor

Single nucleotide polymorphisms can show an effect at a phenotypic level. In humans, these SNPs occur in at least 1% of the population with at a frequency of 1 every 100 to 300 bases along the 3 billion-base human genome [1]. Understanding the genetic basis of receptors generates better comprehension of underlying diseases leading to novel strategies for improved therapeutic agents. Hence, considering the biological significance of histamine, polymorphisms of histamine-related genes represent potential genetic factors that are likely to influence a disease or a therapy. In this chapter we look into the genetic composition of the histamine receptor family and identify genetic variants associated with disorders and how they impact on gene function.

The oldest family members of the amine subtype are histamine H₁ and histamine H₂ receptors. They were the first histamine GPCRs discovered and they were first cloned in 1991 [2]. The existence of a third histamine receptor was known pharmacologically but the histamine H₃ receptor was first cloned only in 1999, with the discovery that cells transfected with GPCR97 were able to inhibit adenylate cyclase in response to histamine [3]. Homology and phylogenetic analysis of the H₃ receptor showed it to be markedly different from the previously cloned H₁ receptor and H₂ receptors, which suggests that these histamine receptors evolved from different ancestor sequences [2]. This discovery also led to the identification of a fourth receptor, the human histamine H₄ receptor in the year 2000/2001 by several research groups [4-10].

All four histamine receptors belong to the rhodopsin-like family of the G-protein coupled receptors [11]. Even though they form part of the same family, they exhibit different genomic and amino acid organization. Using the bioinformatics tool GenomeNet and multiple sequence alignment CLUSTALW, homology for the genes can be estimated. Comparing the DNA sequence alignment between all HRH genes the homology seems to be in the same range (18-20%) between human histamine receptors (HRHs) (Table 1) [12].

Table 1 *Gene and protein homology for the histamine receptor subtypes*

Homology for HRHs		Gene %			
		HRH1	HRH2	HRH3	HRH4
Protein %	HRH1		18.60	20.20	20.60
	HRH2	21.50		20.70	18.95
	HRH3	25.70	19.50		18.30
	HRH4	23.00	22.00	37.00	

However, the translated genomic sequences for the HRH family into amino acids give a different picture. An amino acid sequence resemblance can be seen between two GPCR family members, namely the H₃ receptor and the H₄ receptor. The histamine H₃ receptor displays a 37% homology to the H₄ receptor, but when compared to H₁ and H₂ receptors the similarity drops to 23% and 22%, respectively (Table 1) [12]. Looking at the transmembrane domains, the similarity between the H₃ receptor and H₄ receptor increases up to 54% and if the physiochemical properties of the amino acids is taken into account this similarity increases even more to 68% [13]. This similarity between the H₃ receptor and H₄ receptor also led to the development of imidazole-containing ligands that have a dual action on histamine H₃ and histamine H₄ receptors [14]. Similarly, ligands targeting H₁ and H₂ receptors were also investigated using a series of cyanoguanidines compounds were synthesized by linking mepyramine-type H₁ receptor antagonist substructures with roxatidine-, tiotidine-, or ranitidine-type H₂ receptor antagonist moieties [15]. However, these need to be further improved to provide an enhanced affinity binding profile. The combination of H₁ and H₄ receptor antagonists was also studied, where benefit was observed by inhibiting both receptors in histamine-induced scratching. This study suggested that combined H₁ and H₄ antagonists provided to be more effective than monotherapy [16]. The dual antagonistic benefit was also identified when the H₁ antagonist, olopatadine, and H₄ antagonist, JNJ17777120, were used in allergic dermatitis mice models. The combined effect proved to be as effective as prednisolone. Glucocorticoids such as prednisolone are known for atrophy of the skin and systemic side effects. The H₄ antagonist is currently in phase II clinical study and is proving to have a safe drug profile [17]. These results indicate a promising future for the treatment of these allergic conditions.

Important cellular processes such as DNA binding, protein interactions and enzyme activity are highly impacted by conserved domains in proteins [18]. Alignment of the amino acid sequences of the GPCR family provides further evidence of the similarities and conserved domains between these receptors. Figure 1 represents the alignment of H₁ and H₂ receptors on the amino acid level. The dark grey highlights conserved amino acids between the two receptors, while the light grey regions represent strong similarities between conserved domains. The yellow highlight on the other hand represents the seven transmembrane domains of the GPCRs. Even though the homology is significant between these proteins, the H₁ receptor is characterized by a large intracellular loop 3 (ICL3) unlike the receptor H₂ receptor subtype, with a small ICL3 and a longer

C-terminal. The asterisks (*) showed in Figure 1 represents amino acids which are singly fully conserved residue.

[Figure 1]

Figure 2 shows a similar representation for the newer histamine receptors, histamine H₃ and H₄ receptors; noticeably, both show a large intracellular loop 3 (ICL3), comparable to the ICL in histamine H₁ receptor. GPCRs are known to interact with a wide variety of protein domains through the intracellular loops, transmembrane and C-terminal domains. The most abundant interaction is with the C-terminus of the GPCR [19]. Both histamine H₃ and H₄ receptors show a longer C-terminus which is comparable to the histamine H₁ receptor.

[Figure 2]

Studies on the crystalline structures of GPCRs identified common similarities between class A receptors. The extracellular loops (ECL) are considered as peptide linkers that hold together functionally important transmembrane domains. This link also keeps these helices in a stable position in the cell membrane. The ECL have also the important role of receptor activation and ligand binding [20]. The first extracellular loop (ECL1) is generally small and made up of only a few amino acids. This is also represented in all 4 histamine receptors. Despite this, it was identified in different publications that the ECL1 affects the binding pockets, as with the help of other ECL this loop can provide rigidity and structure essential for receptor activation [20].

Histamine H₁ receptor and H₂ subtypes have proven to be excellent drug targets, and the more recently discovered histamine H₃ and H₄ receptors remain under investigation as future drug targets. First and second generation antihistamines are widely used to relief symptoms of allergic rhinitis, urticarial and other allergies and can cost between \$8 to \$200 per month per patient [21], hence the search for histamine ligands is appealing for the pharmaceutical industry. Ligands for histamine H₃ receptor are currently in clinical studies. Antagonists for this receptor are currently in Phase 1 and Phase 2 clinical trials under review that indicate there is a potential treatment for Alzheimer's disease, ADHD, schizophrenia, epilepsy, narcolepsy, obesity, neuropathic pain and allergic rhinitis [22]. The histamine H₃ receptor antagonist pitolisant is in Phase 3 clinical trial for treatment of narcolepsy and excessive daytime sleepiness associated with Parkinson's disease. The recently discovered H₄ receptor is still undergoing intense preclinical research, with some

novel H₄ receptor antagonists having entered clinical trials, such as; UR-63325 which recently completed Phase 2 clinical trial for allergic rhinitis [23], JNJ-39758979 completing Phase 2 clinical trial for patients suffering from asthma and PF-3893787 which is in Phase 1 clinical trial for asthmatic patients subjected to allergen change [24].

Human Histamine H₁ Receptor

The human histamine H₁ receptor is the largest protein in the histamine receptor family [2] and is expressed primarily in smooth muscle, endothelial cells, the adrenal medulla, the heart, and also in the central nervous system (CNS). The H₁ receptor is predominantly involved in smooth muscle contraction and increased vascular permeability [7]. The main therapeutic target for H₁ receptor antagonists are allergic conditions and sleep disorders [4].

Histamine H₁ gene (HRH1) is located on chromosome 3; 3p25. Figure 3 shows the complete organisation of this receptor. In (A) the genomic organisation is seen where it is characterised by a large intron between the UTR region at the 5'-end and has only one exon [12]. The amino acid sequence of this receptor (B) in turn shows a large intracellular loop (ICL3) similar to the H₃ and H₄ receptor. The snake plot for the amino acid sequence is represented in (C) which illustrates the structural formation of the receptor [25].

[Figure 3]

Histamine H₁ receptor polymorphisms in CNS disorders

The histaminergic system has proven to be one of the aminergic systems present in the mammalian CNS. The discovery that histamine is one of the major neurotransmitters in the CNS, encouraged studies that proved it is involved in a wide range of physiological functions such as cognition, emotion, feeding behavior and sleep-wake cycle [26]. Studies on schizophrenia observed that the levels of N-tele-methylhistamine, a major brain histamine metabolite, were elevated in the cerebrospinal fluid of schizophrenia patients and H₁ receptor binding sites were decreased [27-29]. The role of this receptor in psychiatric conditions was further evidenced by showing that antidepressants and antipsychotics exhibit a high binding affinity to H₁ receptor with a very pronounced antagonistic effect [30]. High binding affinity to the H₁ receptor in antidepressants has been linked to a higher incidence of metabolic syndrome in patients with

bipolar disorder [31]. The histaminergic system may also be a target for the prevention of obesity and metabolic syndrome through histamine H₁ and H₃ receptors with combined activity compounds displaying agonism at H₁ receptors and antagonism at H₃ receptors [32].

Genetic variations in histamine H₁ receptors were studied due to its interesting role in CNS disorders. Single nucleotide polymorphisms (SNPs) were found to play a role in depression in bipolar disorder, where the SNPs in the dopamine D₃ receptor and histamine H₁ receptor genes indicated a significant association to the improvement of the condition following olanzapine and fluoxetine treatment [33]. Studying SNP variations can also be of interest in predicting side effects of medications and developing personalized medicines. Antipsychotic medication such as clozapine and olanzapine are associated with an increased risk of obesity. Clozapine, the atypical antipsychotic, has a diverse binding profile to all four aminergic systems (serotonergic, dopaminergic, histaminergic and noradrenergic) [34]. A study on antipsychotic affinity for the histamine H₁ receptor and the muscarinic M₃ receptor has been linked to side effects such as weight gain. A significant association was also identified between patients using antipsychotics with high affinity for the H₁ receptor (clozapine, olanzapine and quetiapine) in obesity and BMI; where haplotype for rs346074-rs346070 A-T associated with obesity $P = 0.025$ and haplotype A-T associated with BMI $P = 0.005$ [35]. In another study, however, looking into a polymorphism on exon 1 which leads to a change in Glu349Asp on this receptor (which lies on ICL3), found no association for antipsychotic induced weight gain in a Chinese population diagnosed with schizophrenia [36].

Variations found on the promoter region of Histamine H₁ Receptor were investigated for association for psychiatric disorders. A significant Linkage Disequilibrium (LD) ($P < 10^{-6}$) was found in the excess of C allele but no strong association with schizophrenia was identified in multiple testing. However, the polymorphism for G/C allele may represent a marker for more functional polymorphisms located further upstream [37].

The histamine receptors are also of interest in Parkinson's disease patients (PD) as histamine is involved in neuronal degeneration and neurotoxicity. The expression and density of histamine receptors was observed to change in PD patients [38] and histamine receptor antagonists were noticed to improve motor symptoms. However, a study that looked into the a C/T polymorphism in Exon 1 which results in a Leu449Ser amino acid substitution was not able to link this SNP to PD [39].

Histamine H₁ receptor polymorphisms in inflammation

Histamine levels have been studied in various inflammatory diseases suggesting an association of these conditions to histamine receptors. Histamine levels are found to be elevated in bronchoalveolar fluids extracted from asthma patients, in the skin and plasma of patients with atopic dermatitis, in chronic urticaria biopsies, in both plasma and synovial fluid of patients with rheumatoid arthritis and in the plasma of patients with psoriatic arthritis [40]. The major receptors shown to be linked to inflammation and immune response are H₁, H₂ and H₄ receptors [41]. Activation of H₁ receptors increases histamine release and the release of other mediators, while also augmenting the pro-inflammatory activity of the immune system by promoting migration to the area of inflammation.

To date the H₁ receptor has been the major target in the treatment of allergic conditions. Histamine H₁ receptor antagonists have been used for decades to treat allergies, and although they provide symptomatic relief for most allergic conditions, they are not as effective for allergic asthma [42]. A study in a Korean population looked into associations between aspirin-induced urticarial/angioedema to polymorphisms on H₁ receptor. The polymorphisms studied were a C/T change in the promoter region and a G/A change in Exon 1 that leads to D349A amino acid change. However, no association was found between these genetic variations and the allergic response [43].

Histamine H₁ receptor polymorphisms in cancer

The HRH1 gene was investigated for a potential link in various types of cancer. In a study conducted by Wang et al, 88 SNPs were identified that may cause an impact of histamine on H₁ receptor. Out of these 88 SNPs, 84 led to a missense mutation and 4 alleles that disrupt an exon splicing enhancer. From 153 tests carried out on the HRH1 gene, 23 tests proved an association between microarray expression in the HRH1 gene and cancer prognosis (including bladder, blood, brain, breast, colorectal, eye, lung, ovarian, soft tissue cancers) with 5% level of significance. It is also worth noting that the level between HRH1 expression and the different types of cancer prognosis varied, suggesting that the function of HRH1 gene varies between cancers [44].

In a large population study to determine genetic variability, polymorphisms were selected to identify opioid efficacy in cancer patients. Experience has shown that opioid doses and efficacy vary in cancer patients and studies in small populations samples were not found to be reliable. This study conducted by Klepstad et al, included polymorphisms from H₁ receptor (rs2606731

rs346076 rs901865 rs346070). However, Opioid efficacy in cancer patients for pain is not genetically associated with these SNPs [45].

A summary of the above mentioned polymorphisms and their respective SNP location is shown in Table 2 below.

Table 2. *HRH1* polymorphisms in diseases

rs number	SNP	Location on gene	Condition	PubMed ID
NA [†]	G/C	Promoter (intron)	Schizophrenia	12429384 [37]
rs346074 rs346070	A/G C/T	Intron 1 3' UTR	Schizophrenia	21336576 [35]
rs2067467	G/T	Exon 1	Schizophrenia	21937795 [36]
rs2067470	C/T	Exon 1	Parkinson's disease	18366640 [39]
NA*	C/T	Promoter	Aspirin-induced	15953854 [43]
NA*	G/A	Exon 1	urticaria/ angioedema	
rs2606731	G/T	Intron 1	Opioid use in cancer pain	21398039 [45]
rs346076	A/G	Intron 1		21570824 [46]
rs346070	C/T	3'UTR		
rs901865	G/A	5'UTR		

*NA** denotes rs number was not assigned and *NA[†]*denotes rs number could not be identified

Human Histamine H₂ Receptor

The human histamine H₂ receptor is mostly expressed in gastric parietal cells, vascular smooth muscle, suppressor T cells, neutrophils, the CNS and the heart. Its main involvement is in stimulation of gastric acid secretion and hence an important therapeutic target for gastric ulcers

[7]. The Histamine H₂ receptor is located in Chromosome 5 and contains two introns and two exons. Similar to the H₁ receptor, HRH2 gene has intron 1 located in the 5'-UTR region, however, this region is much smaller in length with 24,561 base pairs compared to 121,910 base pairs in the H₁ receptor gene [12]. Looking into the translated amino acid sequence, this member displays a different structure when compared to the other family members (Figure 4). The receptor is characterised by a small ICL3 and a larger C-terminal with around 54 amino acids, compared to 4, 18 and 20 amino acids for H₁, H₃ and H₄ receptors, respectively.

[Figure 4]

Histamine H₂ polymorphisms in CNS disorders

Human Histamine 2 receptor has also been localized in the neocortex, hippocampus, caudate and putamen regions of the brain [37]. However, studies focusing on the H₂ receptor and schizophrenia so far have been controversial. The amino acid exchange of Asn217Asp was suggested to be more common in schizophrenia patients [47, 48], however this could not be replicated in other studies [49]. To date no strong association has been linked between the H₂ receptor and the disease, yet famotidine, a selective H₂ receptor antagonist, has been successfully used to treat the negative symptoms of schizophrenia [50]. Low brain distribution of available H₂ receptor antagonists/inverse agonists most probably contribute to the missing significance of data. The interactions between antipsychotics and the four histamine receptor subtypes generate an interesting perspective for the involvement of HRHs and the disease.

A study for the H₂ polymorphism -1018-G/A was carried out on 164 patients treated with clozapine and diagnosed with schizophrenia showed a strong linkage disequilibrium (LD) between -1018-G/A and -592-A/G (LD $P < 10^{-6}$). This relationship was not observed in multiple testing possibly due to small patient sample and due to the differences in diagnostics methods employed to assess drug response. However, due to limitations in the study there could still be a potential role in patient outcome to clozapine treatment upon further studies [37]. This same polymorphism (-1018-G/A) was also looked into for association with Parkinson's disease (PD), since this genetic variation lies in the promoter region of the receptor. Variations in the promoter region may contribute to changes in expression of the receptor. Nevertheless, no major risk factor was observed for the risk of PD to this SNP [39]. This promoter polymorphism was included in multiple studies which are summarized in Table 3.

Histamine H₂ polymorphisms in inflammatory disorders

The histamine H₂ receptor works by suppressing inflammation by decreasing eosinophil and neutrophil chemotaxis; decreasing IL-12 by dendritic cells; increasing IL-10 and inducing the development of Th2 or tolerance-inducing dendritic cells [51]. This receptor also became pharmacologically important in gastric acid production. Studies observed that histamine-evoked gastric acid secretion were not blocked with classical antihistamines, hence, this led to the conclusion that histamine H₂ receptors were involved in gastric acid secretion [52].

The same polymorphism mentioned earlier, -1018-G/A, located in the promoter region of the H₂ receptor was identified to be associated with gastric mucosal atrophy [53], which is interesting considering that H₂ receptor blockers are the major therapeutic strategy used against gastric acid disorders. Atrophic gastritis is a chronic inflammation in the mucosal lining and together with *H. pylori* infections, can even result in gastric cancer if left untreated [54, 55]. The GG genotype of rs2607474 proved to give a significant increase in the risk of gastric mucosal atrophy, especially in *H. pylori* infected patients. The minor allele frequency for the GA genotype in gastric atrophy patients compared to controls was 8.02% and 13.3% respectively ($P = 0.057$), with the GG genotype being significantly increased in the patient group ($P = 0.055$) [53]. As a result, this polymorphism in particular seems to provide a biological marker for this condition and can be used as a tool to identify the risk and severity of gastric mucosal atrophy in combination with *H. pylori* infection.

Genetic variation on the exon of Histamine H₂ receptor were also studied in relation to aspirin induced urticaria/angioedema. The polymorphisms located on Exon 1, G543A and C826T, however did not show any significant difference in allele and genotype frequencies of their SNPs, which indicated that these genetic variations are not related with the development of aspirin induced urticaria/angioedema phenotype [43].

Histamine H₂ polymorphisms in cancer

Histamine seems to play a role in cell proliferation in malignant cells, where high histamine biosynthesis was reported in different human neoplasias [56, 57]. It has been shown that H₁ and H₂ receptors are expressed in normal and malignant cells lines, and that H₃ and H₄ receptors are expressed in cell lines of human mammary gland [57]. Analysis carried out on the H₂ receptor in gastric carcinoma identified promoter polymorphism rs2607474 (-1018-G/A) to be associated with

the disease. The homozygous GG genotype was found to be associated with gastric mucosal atrophy ($P = 0.0052$) with a subsequent development of gastric cancer (mostly intestinal, $P = 0.0047$) especially at an advanced age [58]. This polymorphism was also identified by the same group to be associated with gastric mucosal atrophy as mentioned in the previous section. And this association with gastric cancer was even higher at an advanced age where the atrophy and metaplasia scores were found to be higher [58]. Due to the location of this SNP in an important region for gene regulation, it seems like it has an important implication in gene transcription, but further analysis are needed to prove this biological significance. Another recent study also investigated the potential impact this polymorphism has in breast cancer. Two hundred and one Chinese Han women were genotyped for rs2607474, however no significant difference in the frequencies of genotypes ($P = 0.174$) or alleles ($P = 0.054$) between breast cancer patients and health controls [59]. Hence, while this SNP indicates a potential role in gastric cancer, it might not be a risk factor in breast cancer. However further investigations need to be conducted to confirm this is not ethnic or population related.

The polymorphisms rs1800689 which is located on Exon 1 (G/A; codon 181) was included in a study in UV-susceptibility in non-melanoma skin cancer. However it was concluded that there was no association between this SNP with UV-induced immunosuppression and risk of non-melanoma skin cancer [60].

The Table below (Table 3) shows all polymorphisms related to histamine H₂ receptor and associated diseases.

Table 3. HRH2 polymorphisms in diseases

rs number	SNP	Location on gene	Condition	PubMed ID
rs2067474	G/A	Promoter	Schizophrenia	12429384 [37]
rs2067474	G/A	Promoter	Parkinson's disease	18366640 [39]
NA* NA*	G/A C/T	Exon 1 Exon 1	Aspirin-induced urticaria/ angioedema	15953854 [43]
rs2607474	G/A	Promoter	Gastric mucosal atrophy	22720301 [53]

rs1800689	G/A	Exon 1	Non-melanoma skin cancer	21760883 [60]
rs2607474	G/A	Promoter	Gastric cancer	22615049 [58]

NA denotes rs number was not assigned*

Human Histamine H₃ Receptor

The histamine H₃ receptor, first cloned in 1999 by J&J [3], is a presynaptic autoreceptor on histamine neurons and heteroreceptor on various neurotransmitter neurons, and is expressed in the CNS and peripheral nerves [7]. The genomic organization of this receptor is slightly different from the previous two receptors. It is similar to histamine H₂ where both have two introns. Though, intron two is the largest with 1549 base pairs, unlike histamine H₂ where intron one was the largest intron with 24561 base pairs. The histamine H₃ gene also has three exons with exon 3 being the largest with 941 base pairs [12]. These exons are translated into amino acids forming the seven transmembrane domains with a large ICL3, similar to Histamine H₁ and H₄ receptors. Exon 1 translates the N-Terminal to mid of TM2, exon 2 translates to mid of TM2 to beginning of ICL2, while exon 3 of histamine H₃ receptor translates into ICL2 to the C-terminal. Figure 5 shows these levels of structural organization leading to the GPCR.

[Figure 5]

Histamine H₃ polymorphisms in CNS disorders

Migraine is a neurovascular disorder and histamine is thought to participate in the pathophysiology of the disease, where the frequency of migraine is more pronounced in patients with allergic diseases and an increase in histamine levels was also observed in patients susceptible to migraine attacks [61, 62]. A polymorphism located in the third intracellular loop of histamine H₃ receptor (A280V), which leads to the amino acid exchange from alanine to valine was found to be a risk factor for migraine [62]. The V allele for this SNP was found to be higher in patients when compared to controls, and especially the genotype VV or VA was found to be 12.92% when compared to controls with 3.22% ($P = 0.001$). This same polymorphism was also

reported to influence the signaling of the histamine H₃ receptor without affecting the binding characteristics in the Shy-Drager syndrome study. This SNP was initially noticed in one patient when HRH3 was originally cloned (shown in Table 4) [63]. This syndrome is marked with multiple system atrophy with orthostatic hypotension. In this publication a functional implication of the amino acid exchange of alanine to valine was suggested it reduces signaling efficacy in H₃ receptors when expressed in CHO-K1 cell line [64]. This was suggested to be of relevance in the pathophysiology of conditions linked to this A/V mutation such as migraine and multiple system atrophy with orthostatic hypotension, however further research is needed to confirm this hypothesis [64].

This third member of the histamine family was also studied for its impact in schizophrenia. A publication by Southam *et al* identified a possible role for the histamine H₃ receptor in schizophrenia. A histamine H₃ receptor antagonist, GSK207040, was found to exhibit a behavioral and neurochemical profile on this receptor and beneficial to treat the cognitive and sensory gating deficits of schizophrenia [65]. The polymorphism found in exon 3, giving a C/T allele exchange was investigated in risperidone response in Chinese Han population. Strong association was identified between rs3787430 ($P = 0.024$, 0.010) and a positive response to risperidone treatment in a Chinese Han population after 4 and 8 weeks respectively. This polymorphism could be a potential genetic marker for treatment. Association for rs3787429 was only noted after 4 weeks ($P = 0.013$) [66]. The histaminergic system has been linked to the pathophysiology of schizophrenia and with histamine H₃ receptor being mostly located in the central nervous system, will continue to encourage research in this area.

Histamine H₃ polymorphisms in inflammatory disorders

Allergic asthma is an inheritable condition and many genetic variations were investigated in order to establish a link to the disease and its treatment. The histamine H₃ receptor was not excluded from these investigations. The study by Ferreira *et al* aimed to establish a link between candidate genes and the disorder, including eight SNPs on HRH3. The SNP rs6062144, located 8 kbp upstream to the gene was the most associated ($P = 0.036$), but there was no overall evidence for association [67]. The evidence for a strong link between asthma and histamine H₃ receptor is still far from being confirmed, and as seen from Table 4, the majority of association studies between this third receptor and diseases are mostly related to CNS disorders.

The role of histamine and histamine receptors in experimental autoimmune encephalitis has been looked into. This third histamine receptor and its polymorphisms were investigated for a potential role in multiple sclerosis pathogenesis. The functional polymorphism G293D located in the third intracellular loop of the GPCR was studied by expressing the two alleles in mice models and compare the pharmacological properties of H3 receptor ligands. Overall, no significant difference in affinity was observed, however, this polymorphism seems to have an impact in the HRH3 isoform for this receptor. This study indicates the HRH3 polymorphism isoform has a role in regulating neurogenic control in experimental autoimmune encephalitis and T cell response in mice [68]. With further research into this role, we might be a step closer into identifying pharmacological targets in preventing the development of new lesions in multiple sclerosis.

Histamine H₃ polymorphisms in cancer

Unlike the other family members of this GPCR family, the histamine H₃ receptor is less investigated in its impact in cancer. The SNPs located on this gene were genotyped in a Chinese Han population together with histamine decarboxylase (HDC) and histamine N-methyltransferase (HNMT) were genotyped for an association in breast cancer. Two hundred and one patient samples were analysed for a potential role in this condition. The SNPs rs3787429 and rs3787430 were identified as the only two tag-SNPs for HRH3 gene. However, even though, as mentioned earlier these two polymorphisms were identified to contribute to risperidone treatment, no significant association was identified in the risk of breast cancer in this group [69]. Further to this finding, a larger population study would be required to omit the role of these SNPs in breast cancer.

Table 4. HRH3 polymorphisms in diseases

rs number	SNP	Location on gene	Condition	PubMed ID
rs3787430	C/T	Exon 3	Schizophrenia	21652606
rs3787429	C/T	Exon 3		[66]
rs752380770	C/T	Exon 3	Migraine	21376262
				[62]

rs752380770	C/T	Exon 3	Shy-Drager syndrome	23713487 [64, 63]
rs6062144	C/G	Upstream 5'UTR	Asthma	19824886 [67]

Human Histamine H₄ Receptor

Several research groups cloned and identified the new member of the histamine receptor family, the human histamine receptor 4 [70, 2, 7, 4]. To date, only two isoforms have been identified for the HRH4. However when compared to the other member HRH3, 20 naturally occurring isoforms have been identified so far, where some display differential expression patterns in various brain areas and functionalities compared with its respective full-length isoform [22]. Investigations of potential therapeutic use for this receptor are strongly related to its localization and expression. The HRH4 is preferentially expressed in various cells of the immune system and mast cells. It also induces chemotaxis of eosinophils, mast cells and monocyte-derived dendritic cells. Other involvement of HRH4 was also reported in the control of interleukin (IL)-16 release from human lymphocytes and it has been speculated that H₄ selective antagonists might be useful in the treatment of asthma [70, 26]. Various research groups suggest that this receptor can also be a potential therapeutic target for other inflammatory diseases, such as chronic allergy, atopic dermatitis and inflammatory bowel disease. Other possible roles for HRH4 are rheumatoid arthritis and colorectal cancer since this receptor has been detected in the primary synovial fluid of these tissues [70].

The HRH4 gene is located in chromosome 18 in section q11.2 close to the centromere. On comparing the four receptors, the H₃ receptor and H₄ receptor genes (HRH3 and HRH4, respectively) share a similar genomic organization, consisting of three exons and two introns, and in both receptors intron 2 is the largest with 7804 base pairs for HRH4 [12]. Similar to H₁ and H₄ receptors, the intracellular loop 3 large and is the largest for this family member. The gene, amino acid and GPCR organization are shown in Figure 6 respectively.

[Figure 6]

Histamine H₄ polymorphisms in CNS disorders

The histamine H₄ receptor was also studied for associations with CNS disorders. Immunological and pharmacological studies have suggested that HRH4 is expressed on fibers emanating from brain regions, most likely the hippocampus or thalamus [71]. It was also suggested that it is expressed in subpopulations of neurons within the sensory dorsal root ganglia and dorsal horn of the spinal cord and in restricted cortical thalamic areas of the brain [72]. So far, the expression of HRH4 in the brain is still controversial. Several groups could not detect mRNA of this receptor in the CNS [4, 6], while other research groups reported the presence in various parts of the CNS, including amygdala, cerebellum, hippocampus, caudate nucleus, substantia nigra, thalamus and hypothalamus [9, 10].

Evidence was put forward for the role in the schizophrenia and this was also seen by the different binding affinity that therapeutic drugs have for this condition. Clozapine and amitriptyline were found to bind to the H₄ receptor in the low micromolar range where clozapine showed partial agonism for the H₄ receptor and a high binding affinity to the H₂ receptor, both in a clinically relevant concentration [30]. An association study was conducted to identify a link between a polymorphism (rs4483927) with histamine H₄ and the efficacy of risperidone, an antipsychotic drug used in schizophrenia. A significant association for risperidone efficacy where the TT genotype predicts poor response to treatment both on the positive, negative, and general subscales and on the total scale of PANSS scores ($P = 0.017, 0.019, 0.021, 0.002$ respectively). The SNP could be used as a biological marker for therapeutic response in personalized medicine [73].

Histamine H₄ polymorphisms in inflammatory disorders

Histamine H₁, H₂ and H₄ receptors are the three main receptors shown to be linked to inflammation and immune response [41]. The H₄ receptor promotes the accumulation of inflammatory cells at sites of allergic inflammation by increasing calcium flux in human eosinophils; increasing eosinophil chemotaxis and increasing IL-16 production [51, 74].

The main focus for this new receptor was with inflammatory disorders. Only few genetic variations on this gene have been associated so far with asthma and underlying conditions, as shown in Table 5. These SNPs (rs17187619, rs527790, rs487202, rs1421125, rs615283) do not give a missense mutation since they are not located in an exon leading to an amino acid exchange, yet they still seem to contribute to the condition.

Other polymorphisms found on the H₄ receptor have also been linked to infections in asthma patients. The recent SNPs described in the study by Simon et al identified an association to conjunctivitis in asthma patients for the polymorphism rs615283 in the GG genotype ($P = 0.008$). An association was also identified in polymorphisms rs17187619, rs487202, rs527790 in patients with or without infection-induced asthma ($P = 0.002$, 0.0002 , 0.00007 respectively). Haplotypes from polymorphisms, rs487202 and rs574913, where the CC allele combination for these SNPs was found to be associated with infection-induced asthma ($P = 0.0009$) [75]. The CA haplotype for these polymorphisms was also more common in infection-induced asthma patients ($P = 0.0006$). SNPs located downstream to the HRH4 gene, rs1421125, rs487202, rs527790, have shown to be linked to asthmatics with or without allergic rhinitis ($P = 0.005$, 0.006 , 0.006 respectively) [75], which enhances the concept that this receptor could play a role in this condition.

The histamine H₄ receptor was also associated to allergic atopic dermatitis (AAD). This receptor has been found expressed in dendritic epithelial cells with a role in regulating histamine levels. It was suggested that H₄ receptor agonists can be beneficial in downregulating inflammation in AAD [76]. One of the SNPs identified in this linkage study was rs77485247, located 51 bp upstream to the gene in the 5'UTR [41], representing the potential promoter region of the gene. A variation in this part of the gene could be responsible for gene expression [77], but further investigations need to be done to confirm. Two other polymorphisms located in exon 3 were also investigated in systemic lupus erythematosus and atopic dermatitis. The nonsense mutation of SNP rs74604924 leads to a stop codon, whereas rs77041280 results in a missense mutation leading to an amino acid exchange. These SNPs suggest a genetic linkage to Atopic Dermatitis where rs74604924 gives a functional amino acid exchange Lys376Ter[*] and rs77041280 gives an amino acid exchange Ile376Lys (rs77485247, rs74604924, rs77041280 where $P = 0.002$, $P < 0.001$, $P < 0.001$, respectively) [41]. However, these SNPs were found to show no significant association between rs77485247, rs74604924, rs77041280 in lupus erythematosus ($P < 0.694$, 0.439 , 0.561 respectively) [78], however copy number variants found on the H₄ receptor were identified as a significant link to the disease [78]. These copy number variations (CNVs) were recently found to be associated with Allergic Atopic Dermatitis. Variations included in the study were both deletions (CNVs less than 2) and amplifications (CNVs more than 4). Amplification on the HRH4 gene were found to be significantly associated to AAD ($P < 0.05$) whereas deletions on the HRH4 were not found to be linked to the condition ($P = 0.3$). The HRH4 mRNA levels were also found to be higher in CNV amplifications, suggesting that HRH4 expression is regulated by inflammatory stimuli from this autoimmune disease [79].

This potential linkage between SNPs to AAD, encourages studies to identify ligands that can treat or prevent this condition. The H₄ receptor antagonists, JNJ7777120 and JNJ28307474, were investigated for their potential use when compared to H₁ receptor antagonists, cetirizine and hydroxyzine but it was shown that there was no impact on the skin lesion prevention for AAD [80]. Interactions between H₄ receptor and this antagonists, JNJ3975879, is to date the most studied and published as it is a potent selective H₄ antagonist that proved effective in preclinical models of pruritus, dermatitis, asthma, and arthritis [81]. A recent study found that co-administration of histamine H₁ and H₄ receptor antagonists had potent inhibitory effects that were equal to those of steroids in a chronic allergic dermatitis mouse model, and JNJ39758979 exhibited anti-pruritic effects in moderate AD patients [82]. This encourages further investigations for H₄ receptor antagonists in this allergic inflammatory conditions.

Histamine H₄ polymorphisms in cancer

This new member of the histamine receptor family has been recently associated with malignancy of breast cancer. Evidence was shown in the analysis of genotypes and haplotypes of a Chinese Han population. This study showed that SNPs rs623590, rs11662595, rs1421125 had a significant association with the risk and malignancy of breast cancer. The T allele in rs623590 had a decreased risk of breast cancer ($P = 0.012$), while A allele of rs1421125 had an increased risk of cancer ($P = 0.008$) [83]. Furthermore, the haplotype C-A-A of rs623590- rs11662595- rs1421125 was found to be more common in breast cancer patients ($P = 0.003$) [83]. More investigations need to be performed to understand if these results are replicable in other populations and if this association is ethnicity-based or not.

The potential link between histamine H₄ receptor and gastric carcinoma was also studied. However, no significant difference was found between copy number variations on H₄ receptor genes and patients with gastric carcinoma, but there was a substantial correlation between copy number deletions and H₄ receptor down regulation. This suggests that abnormalities in H₄ receptor have a potential role in histamine-mediated regulation of tumor growth in gastric cancer [84].

The summary of the polymorphisms in histamine H₄ receptor and associated diseases are presented in Table 5 below.

Table 5. HRH4 polymorphisms in diseases

rs number	SNP	Location on gene	Condition	PubMed ID
rs4483927	G/T	Intron 1	Schizophrenia	23422377 [73]
rs17187619	T/C	Intron	Asthma	22653292 [75]
rs527790	G/A	After H4		
rs487202	C/G	After H4		
rs1421125	C/A	3'UTR		
rs615283	G/A	promoter		
rs77485247	A/T	5'UTR	Atopic dermatitis	20199554 [41]
rs74604924	A/T	Exon 3		
rs77041280	A/T	Exon 3		
rs77485247	A/T	5'UTR	Lupus erythematosus	20618322 [78]
rs74604924	A/T	Exon 3		
rs77041280	A/T	Exon 3		
rs623590	A/C/T	Intron 1	Breast cancer	23481304 [83]
rs16940762	A/G	Intron 1		
rs11662595	A/G	Exon 3		
rs1421125	A/C	3'UTR		

Pharmacogenetics is progressively becoming important aspect for patient's health, where the drug targets more efficiently and effectively the disease and provides personalized care. The biogenic amine histamine plays an essential role in controlling many physiological functions, both in the central nervous system (CNS) and the peripheral nervous system (PNS) [22, 70], hence genetic variation in the four receptor subtypes becomes an important focal point. The knowledge to date on polymorphisms for the histamine receptor family encourages further interest in identifying novel genetic variations that contribute to a disease; especially with the importance histamine has in biological processes. The studies mentioned in this book chapter encourage the continued quest for personalized care to patients. However, more genomic research in the context

of on biogenic amines, here histamine, is needed to establish a direct association between diseases, biological markers and drug treatments in this new era of personalized medicine.

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Figure 1. Protein sequences alignment between H₁ receptor and H₂ receptor. Yellow highlighted sequences refer to the seven transmembrane domains. The dark grey indicates the conserved domains and the light grey refers to similarities between amino acids between the two GPCRs. (*) indicates positions which have a single, fully conserved residue. (:) indicates conservation between groups of strongly similar properties. (.) indicates conservation between groups of weakly similar properties.[85]

Figure 2. Protein sequences alignment between H₃ receptor and H₄ receptor. Yellow highlighted sequences refer to the seven transmembrane domains. The dark grey indicates the conserved domains and the light grey refers to similarities between amino acids between the two GPCRs. (*) indicates positions which have a single, fully conserved residue. (:) indicates conservation between groups of strongly similar properties. (.) indicates conservation between groups of weakly similar properties.[85]

Figure 3. Histamine H₁ Receptor molecular organization. (A) Genomic organization of HRH1. (B) Amino acid organization; where TM is transmembrane domain, ICL is intracellular loop and ECL is extracellular loop. (C) GPCR snake plot.

Figure 4. Histamine H₂ Receptor molecular organization. (A) Genomic organization of HRH2. (B) Amino acid organization; where TM is transmembrane domain, ICL is intracellular loop and ECL is extracellular loop. (C) GPCR snake plot.

Figure 5. Histamine H₃ Receptor molecular organization. (A) Genomic organization of HRH3. (B) Amino acid organization; where TM is transmembrane domain, ICL is intracellular loop and ECL is extracellular loop. (C) GPCR snake plot.

Figure 6. Histamine H₄ Receptor molecular organization. (A) Genomic organization of HRH4. (B) Amino acid organization; where TM is transmembrane domain, ICL is intracellular loop and ECL is extracellular loop. (C) GPCR snake plot.

HRH1_HUMAN	1	MSLPNS---SCLLEDKMC EGNKTTMASPQLMP	57
HRH2_HUMAN	1	-MAPNGTASSFC LDSTAC-----KITITVVLAVLILITVAGN VVVCLAVGLNRR	48
		* * * * * : : * * * * * : * * * * * : * * * * *	
HRH1_HUMAN	58	LHTVGILYIVSLSVADLIVGAVVMPN ILYLLMSKWSLGRPLCLFWLSMDYVASTASIFS	117
HRH2_HUMAN	49	LRNLTNCFIVSLAITDLLLGLLVLPFSATYQLSC KNSFGKVFCN IYTSLDVMLCTASILN	108
		* : * : * * * * * : * * : * * : * : * : * : * * * * *	
HRH1_HUMAN	118	VFILCTDRYRSVQOPLRYLKRYTKTRASATILGANFLSFL--WVIPILGWNHFMQOTS-V	174
HRH2_HUMAN	109	LFMISLDRYCAVMDPLRYPVLVTPVRVAISLVLINVISITLSFLSIHLGWN SRNETSKGN	168
		: * : * * * * : * : * * * * : * : * : * : * * * * : *	
HRH1_HUMAN	175	RREDKCETDFYDVTWFKVMTA IINFYLP TLLMLWFYAKTIYKAVROHCOHRELINRSLPSF	234
HRH2_HUMAN	169	HTTSKCKVQVN--EVYGLVDGLVT FYLP LLLIMCITYYRIFKVARDAQRI-----	216
		: * * : * : : : : : * * * * * * * : * : * * * : * : *	
HRH1_HUMAN	235	SEIKLRPENPKGDAKKPGKESPWEVLKRKPKDAGGGSVLKSPSQTPKEMKSPVVSQEDD	294
HRH2_HUMAN	217	-----NHISS-----	221
		: *	
HRH1_HUMAN	295	REVDKLYCFPLDIVHMQAAAEGSSRDYVAVNRSHGQLKTDEQGLNTHGASEISEDQMLGD	354
HRH2_HUMAN	222	-----	221
HRH1_HUMAN	355	SQSF SRTDSDTTETAPGKGKLRSGSNTGLDYIKFTWKRLRSHSRQYVSGLHMNRERKAA	414
HRH2_HUMAN	222	-----WKA-----ATIREHKAT	233
		* *	
HRH1_HUMAN	415	KQIGFIMAAFILCWIPYFIFFMVIAFC-KNCCNEHLHMFTIWLGYINSTLNPLIYPLCNE	473
HRH2_HUMAN	234	VTLAAVMGAFIICWFPYFTAFVYRGLRGDDAINEVLEAIVLNLGYANSALNPILYAALNR	293
		* : * : * * * * * * * : : * * * * * * * * * * * * * * *	
HRH1_HUMAN	474	NFKKTFKRILHIRS-----	487
HRH2_HUMAN	294	DFRTGYQQLFCRLANRNSHKTSLRSNASQLSRTQSREPRQEQEEKPLKLQVWSGTEVTAP	353
		: * : : * * * * *	
HRH1_HUMAN	488	-----	487
HRH2_HUMAN	354	QGATDR	359

HRH3_HUMAN	1	MERAPPDGPLNASGALAGEAAAAGGARGFSAAWTAVLAA	60
HRH4_HUMAN	1	-----MPDTNSTINLSLSTRVTLAFFMSLVAFAIMLGNALVILAFV	41
		: : : * : .. ** :*,*: . * :*****:****	
HRH3_HUMAN	61	ADSSLRTONNFFLLNLAISDFLVGAFCIPLYVPYVLTGRNTFGRGLCKLWLVDYLLCTS	120
HRH4_HUMAN	42	VDKNLRHRSSYFFLLNLAISDFVGVISIPLYIPHTLF-ENDFGKEICVFWLTDDYLLCTA	100
		. ** :...*:*****:***:..****:***: * ** : * : **..*****:	
HRH3_HUMAN	121	SAFNIVLISYDRFLSVTRAVSYRAQQGDTRRAVRKMLLVWVLAFLLYGPAILSWEYLSGG	180
HRH4_HUMAN	101	SVYNIVLISYDRYLSVSNVSYRTQHTGVLLIVTLMVAVWVLAFLVNGPMILVSESWKD-	159
		*.:*****:***:..*****:*. : * * : *****: ** ** *	
HRH3_HUMAN	181	SSIPEGHCYAEFFYMYFLITASTLEFFTFFLSVTFFNLSIYLNIQRRTRLRLDGAREAA	240
HRH4_HUMAN	160	---EGSECEPGFFSENYILAITSFLEFVIPVILVAYFNMNIYWSLWKRDLHLSRCQSHP--	214
		. * ** :***: * ** . * : :***:..* : * : * : :	
HRH3_HUMAN	241	GPEPPPEAQSPPPPPGCGCNQKGHGEAMPLHRYGVGEAAVGAEGEATLGSGGGGGSV	300
HRH4_HUMAN	215	GL----TAV----SSNICGHSF-----RGRLLSRRSL-----AST	242
		* * * : : * : : * : : * : : * : : * : : * : : *	
HRH3_HUMAN	301	ASPTSSSGSSRGTERPRSLKRGSKPSASSASLEKRMKM-----VSQSFTORFRLSRDR	354
HRH4_HUMAN	243	EVPASF---HSEQRQRKSSLMFSSRTKMNSNTIASKMGSFSQSDSVALHQREHVELLRAR	299
		: * : * : * : * : : * : : * : : * : : * : : * : : *	
HRH3_HUMAN	355	KVAKSLAVIVSIFGLCWAPYTLMIIRAACHG-HCVPDYMYETSFWLLWANSVNPVLYP	413
HRH4_HUMAN	300	RLAKSLAILLGVAFCWAPYSLFTIVLSFYSSATGPKSVMYRIAFWLQWFNSFVNPLLYP	359
		:*****:..*:*****: * : : . * : : *** * * * * :***	
HRH3_HUMAN	414	LCHHSFRRRAFTKLLCPQKPKIIPHSSLEHCWK	445
HRH4_HUMAN	360	LCHKRFQKAFKIFCIKKQPLPSQHSRVSS-	390
		***: *:* * : * : * : : * : .

Chromosome: 3
Location: 3p25

H₁ Receptor

Amino acids: 487

Protein: 56 kDa

(A)

(B)

(C)

Major Function:
Allergic conditions

Chromosome: 5
Location: 5q35.2

H₂ Receptor

Amino acids: 359

Protein: 40 kDa

Major Function:
Gastric acid secretion

Chromosome : 20
Location: 20q13.33

H₃ Receptor

Amino acids: 445

Protein: 49 kDa

Major Function:

Mostly CNS disorders (e.g. narcolepsy, ADHD, alzheimer's disease, schizophrenia).
Also evidence suggesting a role in obesity, pain and rhinitis.

Chromosome: 18
Location: 18q11.2

H₄ Receptor

Amino acids: 390

Protein: 44 kDa

Major Function:

Inflammatory conditions (e.g. rhinitis, pruritis and asthma) and inflammatory pain