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A Genomic Approach to Histamine Function

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ABSTRACT

Genetic variation in histamine pathway has been associated with disease. In a group of 195 patients, many of these with a variety of underlying diseases, three genetic polymorphisms were analyzed in the histamine receptor H1 gene (*HRH1*), the histamine receptor H2 gene (*HRH2*) and the histamine N-methyltransferase gene (*HNMT*), to establish a potential relationship between these polymorphisms and blood histamine levels, white blood cell count, serum cytokines and C reactive protein levels.

Our results show a significantly higher proportion of *HRH1*-17GG genotype in those patients with TNF-alpha levels above the normal value (more than 8.1 pg/mL), whereas in patients with normal levels of serum TNF-alpha (less than 8.1 pg/mL), there is a significant disproportion of the *HRH1*-17GA/AA genotype. The *HRH1*-17GG genotype is associated with high levels of serum TNF-alpha and a high percentage of blood monocytes compared to the GA genotype. The *HRH2*-1018GA genotype is overrepresented in those subjects with hs-CRP levels above 3 mg/dL, while in the group with hs-CRP levels below 3 mg/dL there is a higher proportion of subjects with the *HRH2*-1018 GG genotype. Those subjects with the *HRH2*-1018GA genotype also have significantly higher levels of serum hs-CRP and a lower percentage of blood monocytes compared to the GG genotype. The *HNMT*105 CT/TT genotype is associated with a significant increase in the levels of blood histamine, and the *HNMT*105 CC genotype is associated with increased IL8 serum levels.
In conclusion, the three histamine-related polymorphisms analyzed in the present study are associated with inflammatory mediators and markers of allergic processes.

Keywords: Histamine, Histamine receptors, Polymorphisms, Genomic, Blood cells, Cytokines.

Abbreviations: HRH1: Histamine Receptor H1; HRH1: Histamine Receptor H2; HNMT: Histamine N-Methyltransferase; HA: Histamine; IL1B: Interleukin 1 beta; IL4: Interleukin 4; IL5: Interleukin 5; IL6: Interleukin 6; IL8: Interleukin 8; IL10: Interleukin10; IL13: Interleukin 13; H1: Histamin Receptor 1; H2: Histamin Receptor 2; H3: Histamine Receptor 3; H4: Histamine Receptor 4; HDC: Histidine Decarboxylase; HMT: Histamine N-methyltransferase; DAO: Diamine Oxidase; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M; IgE: Immunoglobulin E; hs-CRP: high sensitive C-Reactive Protein; TNF-alpha: Tumor Necrosis Factor alpha.

INTRODUCTION

Histamine, 4-imidazolyl-2-ethylamine, is an ancestral biogenic amine present in many living tissues as a normal constituent of the body, with multiple effects in several organs of mammals and invertebrates. In humans, HA is found in different concentrations in the majority of the organs of the human body, being synthesized and released by different human cells, especially basophils, mast cells, platelets, neurons, lymphocytes, and enterochromaffin cells, and it is stored in vesicles or granules released on stimulation [1-5]. Histamine exerts its effects on target cells through four different types of receptors: H1, H2, H3 and

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H4. These receptors belong to the G protein-coupled receptor 1 family and they differ in their location, second messengers, and histamine-binding characteristics [6].

The human H1 receptor gene is located on chromosome 3p25 and encodes for a 487 amino acid G protein, being expressed in a wide variety of tissues, including the gastrointestinal tract, central nervous system, airway and vascular smooth muscle cells, endothelial cells, chondrocytes, monocytes, neutrophils, dendritic cells, and T and B lymphocytes. H1 receptor is involved in numerous physiological processes, including thermal regulation, memory and learning, and control of the sleep-wake cycle, food intake, and emotional and aggressive behaviors. It mediates the contraction of smooth muscles, the increase in capillary permeability, the catecholamine release from adrenal medulla, participates in neurotransmission in the central nervous system, and exerts modulatory effects in the immune system [6-9]. Histamine acting through the H1 receptor is involved in the development of various aspects of the antigen-specific immune response and also has a role in autoimmune diseases and malignancy [10]. It is also responsible for many symptoms of allergic inflammation. Antagonists for this receptor exert anti-inflammatory properties and are the first choice to treat allergic conditions [8,9].

Histamine H2 receptor has a widespread distribution, being found in the gastrointestinal tract, in the stomach parietal cells; in cardiomyocytes of the heart; in vascular smooth muscle cells; in endothelial cells; in the central nervous system; and in cells of the immune system. It mediates gastric acid secretion and also appears to regulate gastrointestinal motility, heart contraction, cell proliferation and differentiation, and immune response. The human H2 receptor gene is located on chromosome 5q35 and encodes for a 359 amino acid G protein. H2 activation negatively regulates basophils and mast cells, and inhibits antibody synthesis, T cell production, cell-mediated cytolysis and cytokine production. H2 receptors are present on Th2 cells and their activation increases the synthesis of cytokines such as IL4, IL5, IL10 and IL13. Furthermore, histamine-induced T cell suppressor activity is mediated through H2 receptors [6-9,11].

Histamine H3 receptor is expressed at high levels on histaminergic neurons in the central nervous system, particularly in the basal ganglia, cortex, hippocampus and striatum. It is also expressed at lower densities in the gastrointestinal, bronchial and cardiovascular systems. H3 receptor is a presynaptic autoreceptor, controlling the synthesis and release of histamine in the brain, as well as the release of a variety of other transmitters. H3 receptor has multiple functions, including roles in cognition, sleep-wake status, energy homeostasis and inflammation [6-9,12,13]. The human gene encoding this receptor is localized to chromosome 20q13.33 and encodes for a 445 amino acid G protein.

Histamine H4 receptor is expressed at high levels in spleen, thymus, medullary cells, bone marrow and peripheral hematopoietic cells, including eosinophils, basophils, mast cells, T lymphocytes, leukocytes and dendritic cells. It is also expressed in a wide variety of peripheral tissues, including heart, kidney, liver, lung, pancreas, skeletal muscle, prostate, small intestine, spleen, testis, colon, fetal liver and lymph node. H4 receptors have an important role in inflammation, hematopoiesis and immunity [6-9,14,15]. The human gene encoding the H4 receptor is localized to chromosome 18q11.2 and encodes for a 390 amino acid G protein.

Histamine, through binding to histamine receptors, is the major mediator of the acute inflammatory and immediate hypersensitivity responses, but also seems to be implicated in chronic inflammation and in the regulation of several essential events in the immune response. Histamine and its receptors are also implicated in the pathogenesis of inflammatory and autoimmune diseases. Histamine can selectively recruit the major effector cells into tissue sites and affect their maturation, activation, polarization, and other functions, leading to chronic inflammation. Histamine also regulates monocytes, dendritic cells, T cells and B cells. Several investigations agree that histamine is able to influence T cell response, enhancing T helper 1 type response by triggering the H1 receptor, whereas both T helper 1 and T helper 2 type response is negatively regulated by H2 receptors, through the activation of different biochemical intracellular signals [16-19].

Histamine is synthesized from the amino acid histidine by the enzyme histidine decarboxylase (HDC). In mammals, histamine is metabolized by two major pathways: N(tau)-methylation via histamine N-methyltransferase (HMT), and oxidative deamination via diamine oxidase (DAO). HMT is expressed in human kidney, liver, spleen, prostate, ovary, colon, and spinal cord. Enzymatic activity of HMT has been shown to be regulated by inheritance, and inter-individual variation of HMT activity has been demonstrated in some populations. DAO is the main histamine-degrading enzyme in peripheral tissues (gut, connective tissues) and in invertebrates.

Genetic variation in histamine receptors and histamine-synthesizing and -metabolizing enzymes is associated with differences in histamine metabolism, altered enzyme activities, and risk of disease [20]. Genetic studies have found that polymorphisms in the *HDC* gene are associated with Tourette syndrome, asthma, rhinitis and neoplasms [21]. A common polymorphism in the *HNMT* gene, corresponding to variant rs11558538, results in a Thr105Ile substitution that regulates enzyme activity. The less common T allele (encoding Ile) is associated with decreased HMT enzyme activity [22,23] and with different pathological

conditions [24-26]. Genetic variation in histamine receptors has been associated with diverse diseases and pathological states. Polymorphisms in the *HRH1* and *HRH2* histamine receptor genes have been correlated in several studies with schizophrenia, antipsychotic-induced weight gain, cardiovascular disease, pharmacogenetics of clozapine, Parkinson disease, neoplasms, acetylsalicylic acid hypersensitivity, among others [20,27-32].

To help and advance in the knowledge of histamine genomics, we analyzed in a group of 195 patients three genetic polymorphisms in the *HRH1* gene (rs901865; -17A>G), the *HRH2* gene (rs2067474; -1018G>A) and the *HNMT* gene (rs11558538; Ile105Thr), to establish a potential association between histamine polymorphisms and blood histamine, IgA, IgG, IgM, IgE, hs-CRP, TNF-alpha, IL1B, IL6, IL8, and IL10 serum levels, as well as leukocyte, lymphocyte, neutrophil, monocyte, eosinophil and basophil counts.

MATERIAL AND METHODS

The study sample included 195 unrelated Caucasian patients from the EuroEspes Biomedical Research Centre, in Galicia, Spain. The participants provided written informed consent and the study was performed according to Applicable Regulatory Requirements, the ethical code of the World Medical Association (Declaration of Helsinki) and approved by the EuroEspes Biomedical Research Centre Review Board. The study population was a mixture of healthy subjects and patients with different pathologies (**Table 1).**

Table 1. Characteristics of the study population

VARIABLES	
Number of subjects(n)	195
Female	96
Male	99
Age (years; mean ± S.D)	49.2 ± 22.2
Diagnosis	
Healthy Subjects (n)	28
Patients (n)	
Neurological Disorders	90
Psychiatric Disorders	36
Vascular Disorders	27
Neoplasms	7
Metabolic Disorders	6
Blood histamine (ng/mL; mean ± S.D)	89.9±48.1
IgA (mg/dL; mean ± S.D)	237.2 ± 148.6
IgG (mg/dL; mean ± S.D)	1087.1 ± 302.8
IgM (mg/dL; mean ± S.D)	112.0 ± 58.7
IgE(KU/L; mean ± S.D)	109.9 ± 228.7
hs-CRP- (mg/L; mean ± S.D)	4.0 ± 8.9
Leucocytes (x1000cells/µl; mean ± S.D)	7.1 ± 3.3

Lymphocytes % (mean ± S.D)	32.0 ± 11.9
Neutrophils % (mean ± S.D)	56.7 ± 13.0
Monocytes % (mean ± S.D)	7.4 ± 2.1
Eosinophils % (mean ± S.D)	3.1 ± 2.1
Basophils % (mean ± S.D)	0.6 ± 0.4
TNFA (pg/mL; mean ± S.D)	7.1 ± 2.4
IL1B (pg/mL; mean ± S.D)	8.2 ± 5.1
IL6 (pg/mL; mean ± S.D)	1.6 ± 2.6
IL8 (pg/mL; mean ± S.D)	1.9 ± 1.6
IL10 (pg/mL; mean ± S.D)	2.4 ± 2.7

Venous blood samples were taken from overnight fasting subjects in supine position. Samples for the analysis of serum interleukin 10 (IL-10), tumor necrosis factor-alpha (TNF-alpha), interleukin 1β (IL1β), interleukin 6 (IL6), interleukin 8 (IL8), immunoglobulins (IgA, IgG, IgM, IgE) and high sensitive C-reactive protein (hs-CRP) were collected in BD Vacutainer serum separation tubes. Samples for white cell count (total leukocytes and subpopulations) were collected into EDTA-containing tubes. White blood cells were analyzed immediately after venipuncture. Serum tubes were allowed to clot at room temperature during 30 minutes before processing and centrifuged at 3,000 rpm, at 4°C, for 10 minutes. After refrigerated centrifugation, serum was removed from blood cells and placed in an appropriate sample container to store at -80ºC until analysis.

Determination of serum immunoglobulins (IgA, IgG, IgM) and hs-CRP levels was performed by immunoturbidimetric assay, using an automated biochemical analyzer, Cobas Mira Plus (ABX Diagnostics Inc.). IgE was measured by the immunochemiluminiscence method using an automated immunoassay system, Immulite 1000, Siemens Healthcare Diagnostics.

Determination of the absolute number and percentage of leukocytes, lymphocytes, neutrophils, monocytes, eosinophils and basophils was carried out by the electrical impedance method, using a Coulter ACT5 Diff CP hematology analyzer from Beckman Coulter Inc. (Fullerton, CA, USA). The leukocyte differential count was performed using absorbance cytochemistry and volume technology.

Measurement of TNF-alpha, IL1B, IL6, IL8, and IL10 was performed by immunochemiluminiscent assay, using the automated immunoassay system Immulite 1000, Siemens Healthcare Diagnostics.

Venous blood samples for histamine determination were diluted with water (1:1 v/v), homogenized and centrifuged at 3,000 rpm for 10 min at 4° C. The pellet was discarded and the supernatant was treated with 100 µl/ml 60% perchloric acid and mixed vigorously; then, the mixture was centrifuged for 20 min at 12,500 rpm. The supernatant was stored at -40° C until histamine determination. Histamine was measured by high-performance liquid chromatography (HPLC), as previously described [33]. The chromatographic system consists of four independent isocratic pumps (Agilent 1100 series G13110A), a stainless-steel column packed with a cation exchanger (TSK gel SP-2SW, 5 µm; TosoHaas Corporation) and a fluorometric detection system (Agilent 1100 G1321A FLD). Samples of 20 µl were injected directly into the HPLC column. Histamine is expressed as ng/mL of whole blood. The HPLC method is based on the extraction of histamine with perchloric acid, followed by direct HPLC analysis with on-line derivatization with o-phthaldialdehyde and fluorescence detection, setting the excitation wavelength at 360 nm and the emission at 450 nm.

Molecular genetic analysis was carried out from subjects' blood samples after the appropriate informed consent. DNA was isolated by conventional procedures from a blood leukocyte-rich fraction using a commercial kit, QIAamp DNA Mini Kit (QIAGEN), following the kit handbook recommendations. Genotyping was performed blindly for 3 polymorphisms in 3 genes: *HRH1* rs901865, *HRH2* rs2067474 and *HNMT* rs11558538, all of these reported to be associated with pathological conditions. The polymorphisms analyzed were identified by allelic discrimination, on an ABI PRISM 7300 Sequence Detection System, using a commercially available kit (Applied Biosystems).

Statistical analysis was performed using SPSS® version 20 (IBM Analytics). Subject demographics and mean clinical measurements were calculated by descriptive statistics. The association between polymorphisms and blood and serum biochemical markers was assessed by crosstabs analysis, chi-square test and Fisher's exact test. For this analysis, subjects were divided into two groups, those with biochemical values within normal limits and those with levels above normal values. Differences in biochemical factors as a function of genotypes were performed by non-parametric independent sample Mann-Whitney U Test, assuming that the population does not follow a normal distribution. Given the small observed frequency of the AA genotype in the *HRH1*-17A>G polymorphism and also the TT genotype in the *HNMT* Ile105Thr polymorphism, combined frequencies for these genotypes were used (GA and AA; CT and TT). The level of significance for all statistical tests was α= 0.05.

RESULTS

A total of 195 subjects were included in the study. **Table 1** presents their demographic and clinical characteristics. The majority of the subjects had underlying diseases, including neurological and vascular disorders, neoplasms, psychiatric diseases and metabolic conditions. Only 14% (n=28) of the subjects were considered healthy subjects.

Genotype distribution for rs901865, rs2067474, and rs11558538 was consistent with the Hardy-Weinberg Equilibrium (H-W) (**Table 2**).

Table 2. Genotype distribution and allele frequency for *HRH1*, *HRH2* and *HNMT* polymorphisms and Hardy-Weinberg Equilibrium.

rs901865 (*HRH1* -17A>G)genotype	**Number of subjects; frequency**
AA	7; 3.6%
GA	53; 27.2%
GG	135; 69.2%
H-W: Chi-square=0.39; df=1; p=0.5	
rs901865 (*HRH1 -17A>G*)allele	**Frequency**
A	0.83
G	0.17
rs2067474(*HRH2* -1018G>A)genotype	**Number of subjects; frequency**
GG	182; 93.3%
GA	13; 6.7%
H-W: Chi-square=0.23; df=1; p=0.6	
rs2067474 (*HRH2* -1018G>A) allele	**Frequency**
G	0.97
A	0.03
rs11558538(*HNMT* Thr106Ile)genotype	**Number of subjects; frequency**
CC	156; 80.0%
CT	38; 19.5%
TT	1; 0.5%
H-W: Chi-square=0.7; df=1; p=0.4	
rs11558538(*HNMT* Thr106Ile) allele	**Frequency**
C	0.90
T	0.10

The group of subjects with the *HRH1*-17GG genotype had significantly higher levels of serum TNF-alpha (7.5 ± 2.1 *vs.* 6.0 ± 1.4 pg/mL; p<0.005), and a significant increase in the percentage of blood monocytes (7.6 ± 2.1 *vs.* 7.0 ± 2.0 %; p<0.05) when compared with GA/AA subjects. *HRH1*-17A>G genotype distribution was significantly associated with serum TNF-alpha levels. In this sense, subjects were divided according to biochemical values, those within the normal limits and those above the normal values. A significant over-representation of the GG genotype was observed in subjects with serum TNF-alpha levels over 8.1 pg/mL, considered pathological; conversely, the GA/AA genotype was significantly more frequent in those subjects with serum TNF-alpha levels below 8.1 pg/mL (χ^2 =5.034; p<0.019, df=1) (**Figure 1**).

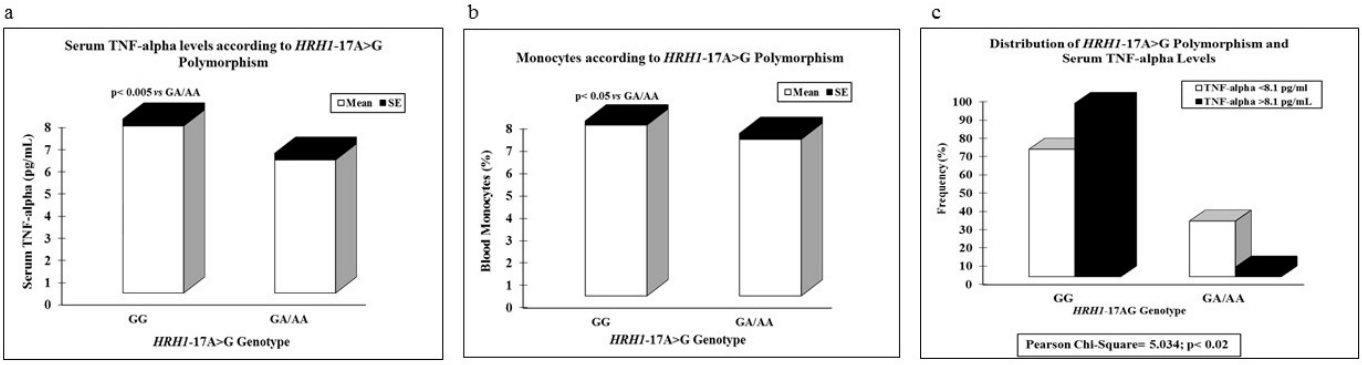

Figure 1. Differences in Serum TFN-alpha levels (a) and percentage of monocytes (b) according to *HRH1*-17A>G polymorphism (rs901865). Frequency distribution of subjects according to serum TNF- alpha levels (normal and pathological serum TNF- alpha values) and *HRH1*-17A>G polymorphism (c).

Statistical analysis of the *HRH2*-1018G>A genotype (**Figure 2**) presents a significantly higher frequency of the GA genotype in subjects with serum hs-CRP above normal values (≥ 3.0 mg/dL), while the GG genotype presents a higher proportion of subjects with hs-CRP below 3.0 mg/dL (χ^2 =13.9; p=0.001, df=1). Subjects with GA genotype have significantly higher levels of serum hs-CRP than subjects with GG genotype (3.8 ± 8.6 *vs.* 6.6 ± 11.2 mg/dL; p<0.02). The percentage of monocytes is increased in the GG genotype in comparison with the GA genotype (7.5 ± 2.1 *vs.* 6.2 ± 1.8 %; p<0.05).

The results concerning the *HNMT* Ile105Thr gene polymorphism (**Figure 3**) showed a significant association of the CT/TT genotype with higher blood histamine levels (CT/TT=107.0 ± 53.9 *vs.* CC=85.6 ± 45.7 ng/mL; p<0.03). Subjects bearing the CC genotype present higher levels of serum IL-8 than subjects with the CT/TT genotype (2.1 ± 1.8 *vs.* 1.2 ± 0.7; p<0.02). A significantly higher frequency of CT/TT genotype was observed in subjects with histamine levels above the normal range (≥90 ng/mL), while the CC genotype is more frequent in subjects with histamine levels within normal values (≤ 90 ng/mL) (χ^2 =5.83; p=0.02, df=1).

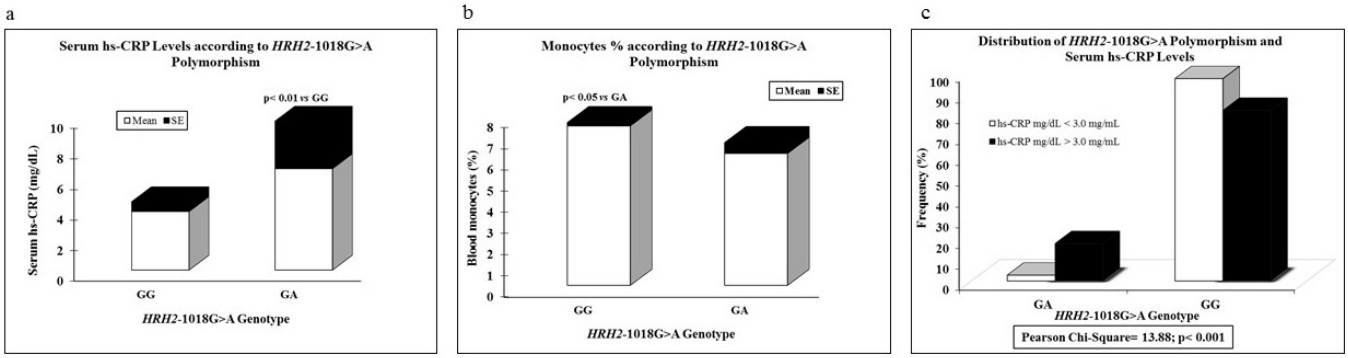

Figure 2. Differences in Serum hs-CRP levels (a) and percentage of monocytes (b) according to *HRH2*-1018G>A polymorphism (rs2067474). Frequency distribution of subjects according to hs-CRP levels (normal and pathological serum hs-CRP levels) and *HRH2*-1018G>A polymorphism (c).

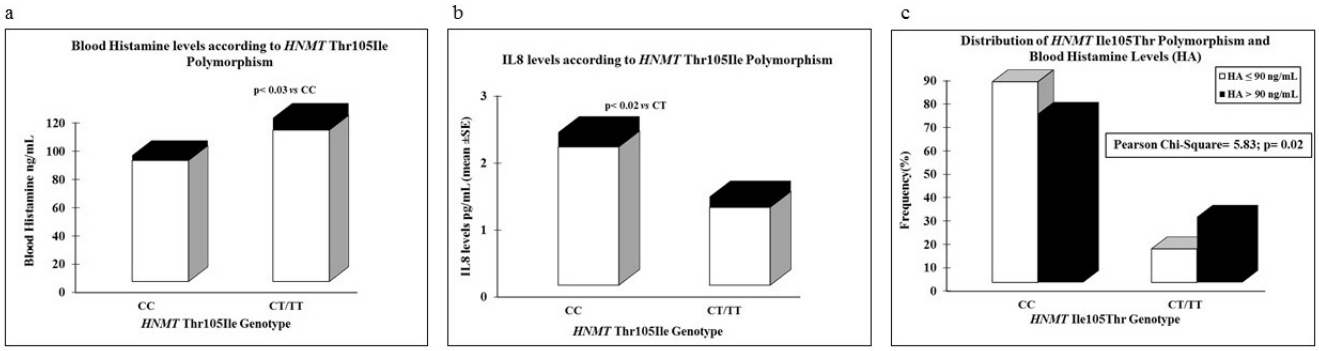

Figure 3. Differences in blood histamine levels (a) and serum IL-8 levels (b) according to *HNMT* THr105Ile polymorphism (rs11558538). Frequency distribution of subjects according to blood histamine levels (normal and pathological blood histamine levels) and *HNMT* THr105Ile polymorphism (c).

DISCUSSION

In this study we show the association of genetic polymorphisms in the histamine pathway with several biological markers related to the immune response. We observed significant associations between genotypes and biochemical and hematological markers. The polymorphism rs901865 in the *HRH1* gene is associated with serum TNF-alpha levels and blood monocytes; the polymorphism rs2067474 in the *HRH2* gene is associated with serum hs-CRP levels and blood monocytes; and the polymorphism rs11558538 in the *HNMT* gene is linked to blood histamine and serum IL8 levels.

Monocytes are circulating white blood cells that are essential components of the innate immune system, and they establish the first line of defense against external or internal danger signals through the initiation of an inflammatory response [34]. Monocytes have the biological property of differentiating into tissue macrophages and dendritic cells, all of these constituting the mononuclear phagocyte system (MPS). The MPS plays crucial roles in development, wound healing, tissue homeostasis and even cancer progression [35]. Blood monocytes express both H1 and H2 histamine receptors, and they exert immunomodulatory effects by influencing the functions of a number of immune cells that play a primary role in initiating and sustaining inflammation [36,37]. In the present study, the polymorphisms rs901865 within the *HRH1* 5'UTR and rs2067474, which is located in an enhancer element of the *HRH2* promoter, are both associated with increased blood monocyte count. The *HRH1* -17GG homozygote is significantly associated with elevated blood monocyte count in comparison with the -17GA/AA genotype. Previous investigations of this polymorphism were focused principally on hypersensitivity to drugs (aspirin, non-steroidal anti-inflammatory agents), response to drugs (clozapine, olanzapine) in schizophrenia and bipolar disorders, antipsychotic medication and obesity, but no conclusive results were found [27-32]. The *HRH2* -1018GG homozygote is significantly associated with elevated blood monocyte count in comparison with the -1018GA genotype. Different studies have linked this polymorphism to different diseases or pathological situations such as Parkinson, schizophrenia, gastric cancer, breast cancer, gastric mucosal atrophy, chronic heart failure, and hypersensitivity to non-steroidal anti-inflammatory agents [27-32].

We found that the *HRH1*-17GG genotype is associated with elevated serum TNF-alpha levels and we observed an increased frequency of subjects with the -17GG genotype and serum TNF-alpha levels above normal values. TNF-alpha is a cytokine thought to be involved in the pathogenesis of asthma and in several other inflammatory conditions. TNF-alpha is mainly secreted by macrophages, a monocyte-derived cell. It has been demonstrated that histamine regulates the production of TNF-alpha by monocytes, and this effect is mediated through H1 and H2 histamine receptors [38,39].

Subjects with the *HRH2* -1018GA genotype present significantly higher levels of hs-CRP protein in comparison with -1018GG subjects, and we observed a higher proportion of subjects with the -1018GA genotype and serum hs-CPR above normal values. CRP is the prototypical acute phase protein in humans; it is an important mediator of host defense and is part of the innate immune response. It is predominantly synthesized in the liver parenchymal cells by cytokines from stimulated leucocytes and released into the circulation. Histamine is able to modulate acute phase proteins through the release of pro-inflammatory cytokines as IL1 and IL6, the latter being the principal inducer of CRP gene expression during the acute phase [40,41].

The third genetic polymorphism analyzed in this study is an amino acid change in the *HNMT* gene. The sequence variation consists of a thr105-to-Ile change in exon 4 (314C-T). This polymorphism has been associated with a decrease in the activity of the HMT enzyme, resulting in reduced histamine metabolism. The enzyme containing Ile at position 105, T allele, was associated with decreased levels of HMT activity and immunoreactivity. The Thr105Ile polymorphism

has been linked to predisposition of more than 30 diseases, such as asthma, Parkinson´s disease, schizophrenia, Alzheimer's disease, atopic dermatitis and cancer [20,22-27]. Our results showed a significant increase in the levels of blood histamine in the *HNMT* 314CT/TT genotype, which is in accordance with the decrease in histamine metabolism due to a lower enzyme activity in 105Ile carriers. We also show that in those subjects with blood histamine levels above normal range, the 314CT/TT genotype is more frequent. A significant increase in IL-8 levels is found in subjects with the *HNMT* 314CC genotype. This effect might indicate a possible relationship between the 314CC genotype and inflammation; although the interrelation between histamine and IL-8 has not been sufficiently studied, it is known that histamine increases the expression of IL-8 via H1 receptors *in vitro*, and enhances the release of IL-8 in different cell types [42]. This cytokine is synthesized by monocytes, macrophages, epithelial cells and smooth muscle cells, and is involved in inflammatory processes. It is also involved in the pathophysiology of several inflammatory-based diseases such as cystic fibrosis, rheumatoid arthritis, inflammatory bowel disease and psoriasis, among others [43].

These results presented here are important in understanding how histamine genetic variation may affect markers of inflammation and allergy. The results provide new data concerning histamine genomics and biochemical and cellular components of inflammatory and immunological processes. Two important inflammatory markers, TNF-alpha and hs-CRP, showed association with genomic markers of the histamine pathway. We also show that the observed increase in blood monocyte count is genotype-dependent. Monocytes are very interesting white blood cells, having the capacity to differentiate into macrophages and dendritic cells, this ability of monocytes being central for the functioning of the immune system. Further investigations are needed in order to clarify some of the genomic associations presented here.

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