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ORIGINAL ARTICLE

Association between two polymorphisms of histamine-metabolising enzymes and the severity of allergic rhinitis in a group of Mexican children

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Abstract
Background: It has been suggested that polymorphisms of histamine metabolising enzymes can be a risk factor for developing histamine-involving diseases. The aim of the present study is to research the possible association between two functional single nucleotide polymorphisms (SNPs): C314T in the Histamine-N-Methyl Transferase gene and C2029G in the Diamine Oxidase gene, with the severity of allergic rhinitis and the number of allergic diseases, in a group of allergic Mexican children.
Methods: We studied 154 unrelated allergic children. SNPs were analysed by RT-PCR. The total serum IgE was measured by chemiluminescence and the serum histamine by ELISA. We used logistic regression analysis to determine OR.
Results: Patients carrying the mutant allele for any SNP had more risk to develop higher rhinitis severity or a bigger number of allergic diseases. Haplotype analysis revealed that this effect is synergistic. In patients carrying one or two mutant alleles, serum histamine levels were higher than those of patients carrying only wild alleles. Serum IgE levels were not associated with the presence of mutant alleles.
Conclusion: The presence of these SNPs in patients with allergic rhinitis can lead to higher serum histamine, therefore to a higher risk of developing more severe symptoms or more associated allergic diseases, even if the serum IgE remains low.
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Background

Allergic rhinitis (AR) is the most common allergic disease. With a prevalence of 20–23%, it affects more than 500 million people worldwide.[1,2] It is characterised by nasal symptoms including sneezing, rhinorrhoea and nasal blockage. AR, as other allergic diseases (AD) (asthma and eczema), is associated with an IgE-mediated immune response against allergens.[3] It is believed that the disease may be the result of the interaction between different genetic alterations, each of which would contribute to a small defect. The heritability of AR has been estimated to be as high as 70–90%.[3,4] Recently, special attention has been given to genes that may be implicated in AR and other AD. A series of genomic researches have been made, yielding different chromosomal associations, the most common being those involving chromosomes 2, 3, 4, 9 and 21. Single-nucleotide polymorphism (SNP) studies related to genes encoding for molecules implicated in the pathogenesis of AR have also been carried out. Such molecules comprise chemokines and their receptors, interleukins and their receptors, eosinophil peroxidase and leukotrienes, among others.[5,6]

As in other AD, histamine plays a principal role in the pathophysiology of AR. Some patients with AR are symptomatic only during the pollen season, while many others are allergic to multiple allergens including indoor allergens, which lead to perennial symptoms. Circulating IgE antibodies bind to the high affinity IgE receptor on mast cells and basophils, then they are crosslinked by allergen, initiating the secretion of inflammatory mediators including histamine.[7] In this way, synthesis, activity and degradation of histamine could impact on the severity of AR or other AD symptoms.

It has been suggested that an over-expression of histidine decarboxylase (HD) gen is associated with rhinitis[8] and that a polymorphism of this enzyme is more common among patients with rhinitis.[9] Another study demonstrated that three SNPs of the H4 Histamine receptor are associated with infection-induced asthma.[10]

Histamine is degraded through two enzymes: histamine N-methyltransferase (HNMT, EC. 2.1.1.8) and diamine oxidase (DAO) or amiloride binding protein 1 (ABP1, EC 1.4.3.6). HNMT is involved in the inactivation of intracellular histamine[11] while DAO is secreted and plays a role in the inactivation of extracellular histamine.[12]

The genes coding for HNMT and DAO are polymorphic. The HNMT gene, located in chromosome 2q22.1, shows eight SNPs, but only one is non-synonymous. This SNP is located in exon 4 and causes the amino acid substitution Thr105Ile (rs11558538).[13] This SNP is unambiguously related to decreased enzyme activity.[14]

Three non-synonymous SNPs have been mapped to the DAO gene, located in chromosome 7q34–36. Functional impairment has been shown on serum DAO activity only for the SNP rs1049793, which codes for an altered protein with the amino acid substitution His645Asp.[15] Because of this, we focused on both SNPs: Thr105Ile for HNMT, and His645Asp for DAO, which will be named C314T and C2029G respectively (for the allelic nucleotide substitution) in this study.

HNMT and DAO SNPs involvement has been investigated in several pathologies implying histamine participation, mainly in AD. The association of the HNMT C314T polymorphism with asthma was initially reported,[16] although further independent studies failed to identify such an association.[17,18] Recently, two studies have supported a positive association between these polymorphisms with asthma.[19,20] On the other hand, two studies suggest that C314T polymorphism is a risk factor for eczema.[21,22] DAO C2029G polymorphism has not been associated with the presence of any histamine related pathology. However, two studies were able to associate the severity of symptoms in Ulcerative Colitis[23] and the intensity of symptoms of asthma and rhinitis[24] with this polymorphism.

The aim of the present study is to investigate the possible association between the functional SNPs C314T in the HNMT gene and C2029G in the DAO gene, with the severity of rhinitis and the number of AD in a group of allergic Mexican children.

Materials and methods

We studied 154 unrelated children from ages 3 to 18 years, with a mean of 7.8 ± 3.84 ($\pm$SD). Patients were recruited from the Paediatric Allergy Department of the Health Secretary in Torreon, Coahuila, Mexico, between March 2013 and May 2014.

The diagnosis of AR was made according to the ARIA workshop.[3] The Hanifin and Rajka Diagnostic Criteria were used for atopic dermatitis, while the GINA criteria were used for asthma. Patients who had a history of antihistaminic drugs within one month prior to the study were excluded from the study. The total serum IgE level was measured by chemiluminescence (kit Cat.LKIE1 IMMULITE IgE Total). The serum histamine was measured by ELISA (kit Cat. IB89128). An immediate hypersensitivity skin prick test was used to detect allergic reactions for a panel of 55 allergens: 4 epithelia, 2 mites, 9 fungi, 13 trees, 5 grasses, 12 weeds and 10 foods. Histamine was used as a positive control and saline solution as a negative control. A flare or induration higher than 3 mm was considered positive.

All patients were invited to participate and signed an informed consent. This study was done according to the principles of the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the Medicine School, University of Coahuila, Mexico.

Polymorphism analysis

DNA was obtained from peripheral blood (5 ml) using the Salting Out method.[25] The polymorphisms were analysed by real-time polymerase chain reaction (RT-PCR). Genotyping was performed using TaqMan assays (supplied by Applied Biosystem®) designed to detect the following SNPs: for DAO, rs1049793 (C_7599774_10) a non-synonymous variant causing the amino acid substitution His664Asp, and for HNMT rs11558538 (C_11650812_20) a non-synonymous variant causing the amino acid substitution Thr105 Ile.

Polymorphisms were carried out by RT-PCR using the RT-PCR equipment (7300 real time PCR system by Applied Biosystem®, with software 7300 system). We used a concentration of 8 ng of DNA. The amplification conditions were: after a denaturation time of 10 min at 95 °C, 40 cycles of 95 °C for 15 s and at 60 °C for 90 s were carried out. 308

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