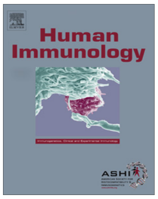
Human Immunology 78 (2017) 88–94

Contents lists available at ScienceDirect

ASHI
American Society for Histocompatibility & Immunogenetics
www.ashi-hla.org

journal homepage: www.elsevier.com/locate/humimm



Association between HLA genes and dust mite sensitivity in a Brazilian population

Marcela Caleffi da Costa Lima Caniatti [a,*], Sueli Donizete Borelli [b], Ana Lúcia Falavigna Guilherme [b], Luiza Tamie Tsuneto [b]

[a] *Post-Graduate Program in Health Sciences, Universidade Estadual de Maringá (UEM), Maringá, PR, Brazil*
[b] *Department of Basic Health Sciences, UEM, Maringá, PR, Brazil*

ARTICLE INFO

Article history:
Received 21 June 2016
Revised 20 October 2016
Accepted 20 October 2016
Available online 22 October 2016

Keywords:
Mites
Sensitive
Genetic association
HLA
Disease susceptibility

ABSTRACT

Background: Type I hypersensitivity, also known as IgE-mediated allergy, is a complex, multifactorial condition whose onset and severity are influenced by both genetic and environmental factors. Mite allergens stimulate the production of humoral response (IgE), especially in children, which is closely involved in atopic asthma and rhinitis.
Objective: This study aimed to investigate the association between HLA class I (-A, -B, and -C), and HLA class II (-DRB1) genes in individuals sensitive to dust mites (*Dermatophagoides farinae, Dermatophagoides pteronyssinus*, or *Blomia tropicalis*) and mite-insensitive controls.
Methods: 396 participants were grouped as mite-sensitive and mite-insensitive according to immediate hypersensitivity as determined by skin-prick tests, and to HLA genotyping by polymerase chain reaction-sequence specific oligonucleotide (PCR-SSO).
Results: After chi-square heterogeneity testing no significant differences were observed in HLA-A, B, and C genes, except for the HLA-DRB1 locus, which, showed a negative association for *DRB1*04*, between mite-sensitive and mite-insensitive individuals. In high resolution, *DRB1*04:11* allele was significantly different from all other results (*P* = 0.0042, OR = 0.26, and 95%CI = 0.09–0.70). The analysis stratified by etiologic agent confirmed these associations.
Conclusion: Our results suggest a possible association between HLA-DRB1 genes and hypersensitivity to dust mites.

1. Introduction

The development of advanced techniques in molecular biology has allowed the study of structural and functional genomics, the genetics of certain populations, and evolutionary genetics, studies that can help to gain a better understanding of the role of each individual gene in the physiology of the immune response. In humans, the immune system, has evolved to protect the host from a universe of pathogens, is composed of a large number of highly polymorphic genes, i.e., the presence of multiple alleles at a locus, being found at frequencies greater than 5% in certain populations, which results in a complex system with important consequences for the pathophysiology of several diseases that affect humans [1–3].

Allergy is one of these diseases. It produces immune responses to environmental antigens, causing tissue inflammation and organ dysfunction. The etiology of atopy involves genetic factors that are still poorly understood. Sensitization occurs when antigen presenting cells (APCs) of predisposed individuals process allergens (proteins) and present the resulting peptides within HLA molecules to the allergen-specific CD4+ T cells. The latter produce cytokines that induce a class switch in B cells to IgE antibodies, which bind to the high affinity FceRI on mast cells and basophils (rich in vasoactive substances). Upon a second contact, the allergen cross-links these IgE antibodies, and the effector cells react immediately to release preformed inflammatory substances within seconds. The ability of these allergens to make individuals become sensitized and respond by producing IgE antibodies varies and is determined by the individual's genetic makeup and by cultural and environmental factors [4,5].

---

* Corresponding author at: Universidade Estadual de Maringá (UEM), Departamento de Ciências Básicas da Saúde (DBS), Laboratório de Imunogenética, Av. Colombo, n° 5790, bloco T20, CEP 87020-900, Maringá, Paraná, Brazil.

E-mail addresses: marcelacclima@hotmail.com (M.C. da Costa Lima Caniatti), sdborelli@uem.br (S.D. Borelli), alfguilherme@uem.br (A.L.F. Guilherme), lttsuneto@uem.br (L.T. Tsuneto).

http://dx.doi.org/10.1016/j.humimm.2016.10.014
0198-8859/

Table 1
Overview of HLA-DRB1 data associated with sensitization to house dust mites.

HLA alleles groups	OR	*P*	Investigation
*DRB1**04*	<1	0.002	Development of a sensitization to house dust mite D. pteronyssinus [22]
	<1	0.010*	The risk of developing asthma in citrus red mite-exposed adults [24]
	>1	0.006	HLA-DR genotypes and immunoglobulin E responses to common major allergens [43]
*DRB1**07*	>1	0.009	Development of a sensitization to house dust mite *D. pteronyssinus* [22]
	>1	0.010*	The risk of developing asthma in citrus red mite-exposed adults [24]
*DRB1**11*	>1	0.020*	The influence of the MHC class I and class II genes in the susceptibility to atopic asthma in a Venezuelan population [44]
*DRB1**13*	>1	0.021	The association between tumor necrosis factor, HLA-DR alleles, and IgE-mediated asthma in Taiwanese adolescents [39]
*DRB1**14*	<1	0.020	Development of a sensitization to house dust mite *D. pteronyssinus* [22]
HLA allele			
*DRB1**08:03:02*	>1	0.009	Association between HLA class II genes alleles and Allergic rhinitis in house dust mites sensitive Chinese subjects [45]
HLA haplotypes			
*DRB1**11:01 DQA1**05:01 DQB1**03:01*	>1	<0.010*	The influence of the MHC class I and class II genes in the susceptibility to atopic asthma in a Venezuelan population [44]
*DRB**01/DRB1**03/ DRB1**11*	>1	<0.010	The relevance of HLA-class II molecules to the regulation of immune response to the mite allergen D. pteronyssinus and to clinical atopic disorders [46]
*DQB**03:03/**05:03, DRB1**02/DRB1**07,* and *DPB**04:02*	<1	< or =0.01	The relevance of HLA-class II molecules to the regulation of immune response to the mite allergen D. pteronyssinus and to clinical atopic disorders [46]

* Corrected *P* value; OR = odds ratio.

Both the prevalence and severity of allergic respiratory diseases have increased over the past 5 decades, represent global health problems for all age groups, particularly among children. This is possibly due to environmental changes and increased exposure to allergens. More than 50,000 species of mite allergens have been described, and house dust mites, such as *Dermatophagoides pteronyssinus* (*D. pteronyssinus*) and *Dermatophagoides farinae* (*D. farinae*), are the most common among the known atopic allergens. These mites have been found in house dust samples worldwide, being more prevalent in warm, humid climates [6,7,4].

The human leukocyte antigen (HLA) system is a complex of several loci in the major histocompatibility complex (MHC) region of chromosome 6 in humans, whose encoded products are found in cell-surface molecules and subdivided into class I and II according to their molecular structure, tissue distribution, and biological function. This system is characterized by a high degree of polymorphism, uneven distribution of allele frequencies in the population, and prevalence of typical alleles in certain populations. HLA molecules are responsible for the presentation of peptides to immunocompetent T cells. In addition to interacting with natural killer cell receptors the HLA molecules are considered to play a key role in the adaptive immune response, since they are involved in the onset, maintenance, protection, or predisposition to certain diseases [8–10].

In a previous study, allelic and genotypic associations in pro-inflammatory ($IL1A^{-889}$ and $IL2^{-330}$), and anti-inflammatory ($IL4^{-590}$, $IL4RA^{+1902}$ and $IL10^{-592}$) cytokine variants were observed in allergic individuals [11]. Considering that HLA molecules are also immune response genes and connect innate and adaptive immune responses, the prior results led us to the current study. In addition, no other study has yet distinguished between the three most frequent allergen sources in tropical regions.

It is worth mentioning that in the southern hemisphere, no database exists for the sensitization to the most important allergen sources, namely the different species of dust mites.

To date, some studies have investigated the relationship between HLA genes and sensitivity to dust mites (Table 1), however, the importance of these associations remains unclear. Considering that the identification of candidate genes in mite-sensitive individuals could reveal mechanisms of interaction between allergens and hosts, the aim of the present study was to conduct a genetic association study to investigate markers of immune response in HLA class I (-A, -B, and -C), and HLA class II (-DRB1) genes in individuals sensitive to dust mites (*D. farinae, D. pteronyssinus*, or *Blomia tropicalis*) compared to mite-insensitive controls.

2. Methods

2.1. Ethical considerations

The study was approved by the Research Ethics Committee of Universidade Estadual de Maringá (protocol No. 412.420/2013) and conducted in accordance with the provisions of the Declaration of Helsinki. All participants provided written informed consent prior to their inclusion in the study. In the case of minors, under 18 years of age, written consent was obtained from their parents/legal guardian.

2.2. Participants, inclusion and exclusion criteria

The inclusion criteria adopted by this cross-sectional study included 343 children (individuals under 14 years of age) and 53 adolescents and educators (individuals over 14 years of age) from 3 public institutions located in the city of Maringá (Paraná, southern Brazil: latitude 23°25′31″S and longitude 51°56′19″W) who voluntarily agreed to participate in the study. Individuals were randomly invited to participate, and 396 agreed to enter the study.

The exclusion criteria included, consanguineous individuals and Asian descent. Whereas to the ethnical group, considering the rejection of subjects of Asian origin, all other participants were considered to be white Brazilians, bearing in mind that, the Brazilian population is heterogeneous as well as highly mixed.

2.3. Allergy testing, and sample collection

Each participant's sensitized status was determined by skin prick testing. At least 1 of the 3 tested mite allergens (*D. farinae, D. pteronyssinus*, and *Blomia tropicalis*) had to be positive. A positive response was defined as presence of erythema ranging from <15 mm (+) to >30 mm (++++). For each individual, a negative and a positive control parameter were tested. Reactions were read and noted by two specialists, 10–15 min after the reagents were applied, according to the manufacturer's instructions (Anthygenus™, Rio de Janeiro, RJ, Brazil). The mite-insensitive group consisted of individuals with no history of allergy and who showed no simultaneous reaction to the 3 allergens, serving as healthy controls.