

## HLA Loci and Respiratory Allergic Diseases

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### ABSTRACT

HLA cell-surface glycoprotein molecules act in the very beginning of the allergic sensitization process, making them natural candidates for research on the genetic susceptibility for respiratory allergies. Thus, along past decades, this topic has been subject to some research and, consequently, several HLA alleles have been implicated in respiratory allergic diseases development. Current editorial introduces, revise, summarize, and comment the major advances in the role of HLA genes for the development of, and protection against, respiratory allergic disease. A general picture is drawn and new challenges on the field are relocated, especially those that might enlighten respiratory allergies aetiology and, thus, contribute in advances for diagnosis and treatment.

**Key words:** HLA; MHC; Susceptibility; Association; Respiratory system; Allergic diseases

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### INTRODUCTION

Respiratory allergic diseases could be defined as allergic conditions with respiratory manifestations affecting upper or lower respiratory tract, or both. It occurs after the exposure of predisposed individuals to certain allergens, resulting in an exaggerated inflammatory response mediated by immunoglobulin E (IgE) antibodies<sup>[1]</sup>. The respiratory symptoms of such immune system overreaction result, mostly, in allergic rhinitis or allergic asthma, or both, and place, presently, a considerable burden on both developed and developing societies, as also on patients and their families<sup>[2]</sup>. In fact, respiratory allergies are the most common allergies, and rhinitis and asthma affects up to 700 million people worldwide, with a dramatic increasing prevalence along the past decades<sup>[3]</sup>. Of particular concern is their prevalence among children, since, in such cases, the prognosis tends to be of a chronic and aggravated disease, making respiratory allergies the most common chronic diseases among adolescents and young adults<sup>[4,5,6]</sup>.

Respiratory allergic diseases have been shown to be interrelated in the so called 'atopic march', beginning with atopic dermatitis and evolving to allergic rhinitis and/or asthma along childhood<sup>[7]</sup>. Indeed, about 66% of children with atopic dermatitis develop symptoms of allergic rhinitis, and 30% became asthmatic<sup>[8]</sup>. Also, more than two thirds of asthmatic patients show allergic rhinitis and, on the other hand, about one third of allergic rhinitis patients are also affected by asthma<sup>[9]</sup>. However, despite all the evidences that join asthma and allergic rhinitis in the concept 'one airway one disease', questions remain on if they are part of the same disease process or if they are distinct entities that have their own specific causes<sup>[10,11]</sup>.

The specific causes that lead to respiratory allergies still are in study but it is evident that it results from a complex interplay between genetic factors and environmental exposure. The heritability of asthma, evaluated through several twin studies, shows to be high, with genetic factors accounting for around two thirds of the susceptibility. Nevertheless, despite the strong evidences of a genetic determination for atopy, there is not clear that specific allergies, such to house dust mite or grass pollen, are strongly determined by

inheritance<sup>[12]</sup>. Thus, despite with conflicting results, several studies identified and evaluated hundreds of candidate-genes for respiratory allergic diseases susceptibility and, among those, several genetic markers were confirmed as been positively associated<sup>[13,14]</sup>.

## THE HLA LOCI

Since the Human Leukocyte Antigen (HLA) region, also known as the human Major Histocompatibility Complex (MHC), harbours a polymorphic set of membrane receptors coding genes that, in the context of the immune system action, distinguish ‘self’ from ‘non-self’, it is not surprising that several alleles and haplotypes of those loci have been associated to a wide series of different types of allergies, namely those with respiratory outcomes<sup>[15,16]</sup>. Located in the short arm of chromosome 6 (6p21.3), the HLA region constitutes an intricate and interrelated cluster of genes along approximately 4 megabases, involving more than 300 *loci*, from which at least 160 are functional genes<sup>[17,18]</sup>. These functional genes are considered the most polymorphic of the human genome and about 40% of them have an important role in the regulation and action of the immune system<sup>[19,20]</sup>. Three main regions have been identified in the human MHC, accordingly to the structure and function of its genes: class I, class II and class III. The most telomeric region of the human MHC hosts the HLA class I genes, which includes 3 high polymorphic, known as classical (HLA-A, HLA-B and HLA-C) and 3 low polymorphic, known as non-classical (HLA-E, HLA-F and HLA-G), besides a dozen of HLA pseudogenes and one HLA non-coding gene<sup>[21]</sup>. On the other hand, HLA class II are located on the most centromeric region of the human MHC, consisting of alpha and beta chain genes, the classical HLA-DPA, -DPB, -DQA, -DQB, -DRA and -DRB, and also the non-classical HLA-DMA, -DMB, -DOA and -DOB, besides some pseudogenes and non-HLA genes<sup>[21]</sup>. Located between class I and class II, the class III region of the MHC has no known HLA like genes but is the most gene-dense region in the human genome<sup>[22]</sup>. The loci that constitute this region are responsible for expressing proteins with an important role on modulating and regulating immune response<sup>[23]</sup>.

Classical HLA class I genes (HLA-A, HLA-B and HLA-C) express cell-surface glycoprotein molecules on almost all nucleated cells, playing an important role in “self” and “non-self” immune recognition. These molecules display at cell surface small protein fragments almost originated in the cytosol. Their interaction with inhibitory or activating receptors from the surface of Natural Killer (NK) or cytotoxic CD8+ T-cells modulates the lytic activity. As a result, when a cell expresses foreign proteins, due to a viral infection, or shows a different expression pattern, due to an oncogenesis process, HLA class I signals those changes through its own binding to the resulting peptides and, after recognition by NK or CD8+ T cells, an immune response is triggered<sup>[24,25,26]</sup>. This same immune mechanism is responsible for allograft rejection when HLA compatibility between donor and recipient is missing<sup>[27]</sup>. Non-classical class I loci (HLA-E, HLA-F and HLA-G) are best known for their participation on the regulation of the innate immunity but they can also play a role in regulating adaptive responses. HLA-E, -F and -G co-express in the placenta trophoblast cells and several studies have shown a poor prognosis associated to their higher expression in different types of malignant tumours, facts that emphasize their role in immune modulation and protection against NK lysis<sup>[28,29]</sup>. In opposition to the ubiquitous expression of classical class I, these non-classical loci tend to be conditional and tissue or organ specific<sup>[30]</sup>. HLA-G is the better studied locus and the most polymorphic among

the non-classical class I group. With 51 alleles found worldwide, HLA-G locus expresses 17 distinct functional proteins and, due to alternative splicing, can assume membrane-bound and soluble isoforms (IMGT/HLA Database, release 3.22.0, 2015-10-10)<sup>[31]</sup>. Its functions are oriented towards immune inhibition and tolerance and one of its most known implications is on the prevention of maternal-foetal rejection<sup>[32]</sup>. Cells from placenta migrate into the maternal uterus and produce both membrane and soluble HLA-G isoforms, which will inhibit maternal immune response against foetal foreign antigens through interaction with inhibitory receptors in maternal leukocytes, establishing an immune privilege<sup>[30]</sup>. This mechanism of inhibition and tolerance mediated by HLA-G has revealed to be involved in tumour escape from the immune system and, in fact, a higher expression has been significantly correlated with poor prognosis in patients with solid tumours<sup>[33,34,35]</sup>.

The alpha and beta chains expressed by the classical class II genes (HLA-DPA, -DPB, -DQA, -DQB, -DRA and -DRB) associate each other non-covalently to compose heterodimer transmembranar molecules on the surface of a restricted set of cells that interact with CD4+ T-helper cells, predominantly antigen-presenting cells (APC) such as macrophages, dendritic cells and B lymphocytes<sup>[36]</sup>. Both alpha and beta chains contribute to form the HLA class II peptide binding groove and peptides presented by it on the cell surface of APC result from internalized and processed exogenous antigens that could derive from cell surface proteins, soluble proteins or proteins from a virus, bacteria or protozoa invaders<sup>[37]</sup>. When CD4+ T-helper cells become activated, after recognizing a foreign peptide presented within the antigen binding groove of a class II molecule, they differentiate and secrete cytokines which influence the proliferation, function and differentiation of other immune cells, including other T cells, B cells and macrophages, triggering an adaptive immune response against foreign elements<sup>[38]</sup>. The non-classical class II proteins, HLA-DM and -DO, lack the ability to bind peptides but both molecules play a critical role in the HLA classical class II ability to functionally bind self and non-self peptides on APC, controlling the very first steps of an immune response<sup>[39]</sup>.

Despite with non-HLA genes, some of the MHC class III loci act as critical mediators of the immune response. Examples of such loci are complement components C2, CFB, C4B and C4A, that code for plasma proteins that act against pathogens and induce inflammatory responses<sup>[40]</sup>, TNF, an important multifunctional proinflammatory agent that triggers a cascade of inflammatory mediators<sup>[41]</sup>, and 3 Heat Shock Protein genes (HSPA1L, HSPA1A and HSPA1B) that act as danger-signalling molecules to the innate immune system, showing a regulatory role, namely on natural killer cell response to cancer<sup>[42,43]</sup>.

## HLA, IMMUNITY, AND RESPIRATORY ALLERGIES

Respiratory allergies, as any other allergies, result from a deregulated action of the immune system that starts with the sensitisation to harmless substances from the environment, in a process that involves both innate and adaptive immunity. HLA cell-surface glycoprotein molecules act in the very beginning of this sensitization process, presenting the allergens to T lymphocytes and triggering an immune response. When the organism contacts for the first time with a foreign substance, namely through inhalation, ingestion or epithelium contact, a sensitization mechanism is started with the APCs, namely Dendritic Cells (DC), internalizing those molecules and presenting them on the cell surface attached to the binding groove of the HLA class II molecules (HLA-DR, HLA-DQ and HLA-DP)<sup>[44]</sup>. Presenting

allergen peptides by DC, or other APC, depends both on the expression of the HLA class II and on the allergen processing through the endocytic pathway<sup>[45]</sup>. HLA class II genes expression is activated by CIITA (MHC II transactivator), a MHC master regulator molecule coded in the chromosome 16, and, after synthesis, is translocated into the endoplasmic reticulum (ER)<sup>[46]</sup>. In the ER, HLA class II  $\alpha$  and  $\beta$  chains are assembled together with an ‘invariant chain’ (Ii), a specialized chaperone that provides a scaffold for the assembly and that blocks the peptide binding groove with a CLIP domain (class II-associated Ii peptide) to avoid premature peptide binding<sup>[45,47,48]</sup>. Later, after transportation across Golgi complex into the endocytic pathway, Ii is partially removed, leaving the CLIP domain in the peptide-binding groove of the HLA molecule<sup>[49]</sup>. Thus, allergens internalized and processed in APC through the endocytic pathway happens to be together with CLIP-HLA class II complexes inside the endosomes, allowing the exchange of CLIP by antigen peptides, a process intermediated by the non-classical HLA class II molecules, HLA-DM and HLA-DO<sup>[50]</sup>. HLA class II molecules loaded with the allergen peptides are transported to the cell membrane of the APC and, after migration in to the lymph node, presented to naïve CD4<sup>+</sup> T lymphocytes in a cell to cell contact involving T-cell receptors (TCR). In the presence of Interleukin-4 (IL-4), naïve T lymphocytes differentiate into T helper type 2 cells (Th2), with subsequent clonal expansion and production of a specific cytokine profile, namely IL-4, IL-5 and IL-13<sup>[51]</sup>. Through cell contact interaction and cytokine stimulation, especially IL-4, Th2 induce B cell to switch from their naïve state, of expressing cell surface Immunoglobulin D (IgD) or IgM, to express IgE antibodies with affinity to the specific antigen (allergen). Yet, this immunoglobulin class switching should only occurs if that same allergen was also internalized by the B cell and exhibited at cell surface in the binding groove of a HLA class II molecule. B cell switched to IgE proliferates through clonal expansion, produce antibodies, and becomes memory cells (as also happens with Th2 cells), leading to sensitization<sup>[52,53]</sup>.

IgE antibodies produced by B lymphocytes in the sensitization phase becomes attached on mast cells (or other cell types as eosinophils) surface to their IgE high-affinity receptor, Fc $\epsilon$  receptor I (Fc $\epsilon$ RI)<sup>[54]</sup>. In a subsequent exposure to the same allergen, the antigens bind to IgE antibodies in the membrane of mast cells and triggers their degranulation, releasing a diverse group of biologically active products, namely histamine and cytokines, that induce an immediate hypersensitivity reaction which, if localized in the airways, could result in reduced airflow and wheezing<sup>[55,56]</sup>. Additionally, allergens processed by APC are presented through HLA class II at cell surface and activate Th2 memory cells, which proliferate and produce cytokines that stimulate B memory cells to proliferate and secrete IgE specific antibodies. Th2 cell cytokines and IgE from B cells activate cells of the innate immune system, namely mast cells that will degranulate in contact with the antigen and maintain the allergy into a late phase<sup>[57,58,59]</sup>.

In opposition to the above described Th2 cell differentiation, that lead to IgE B cell switching and degranulation of mast cells, when a Th1 response is activated no allergic reactions occurs. Th1 polarization also results from MHC class II antigen presentation through APC and seems to be driven by the type of antigen experience and cytokine stimulation<sup>[60]</sup>. In such cases, Th1 cells produce a different profile of cytokines, such as IL-2, IFN- $\gamma$  and TNF- $\beta$ , which will not switch B cells to IgE but, instead, to IgG. A Th1 response, in opposition to Th2 that is humoral, will result in a cell-mediated immunity<sup>[61]</sup>.

Classical MHC class I molecules (HLA-A, HLA-B and HLA-C)

are best known on their ability to present antigens originated from the cytosol, namely associated to infection or tumour escape, but they could also bind to exogenous substances in a process named as ‘cross-presentation’ or ‘cross-priming’, and thus be also implicated in sensitization or, after, in allergic exacerbation through a CD8<sup>+</sup> T cell cytotoxic response<sup>[62,63]</sup>. Despite most peptides presented by classical HLA class I are thought to be derived from the breakdown of cytosolic proteins in the proteasome, and then actively transported into the ER via the transporter associated with antigen processing (TAP) molecular complex, where it is loaded to the peptide binding groove, in ‘cross-presentation’ antigens may follow alternative TAP dependent routes<sup>[64,65,66]</sup>. Despite under investigation, present knowledge suggests that the intake of extracellular antigens to load in APC MHC class I could depend on different factors, such as the type of antigen, the signaling mechanisms and the receptors involved as mediators in endosome internalization<sup>[67]</sup>. Thus, DC cross-present external antigens through MHC class I, that could be an allergen, leading to CD8<sup>+</sup> T cell activation and a cytotoxic response. The CD8<sup>+</sup> T-cell activation and expansion in allergic sensitization and airway inflammation resembles the well-known pattern for viral defense in which a pool of memory CD8<sup>+</sup> T cells persists and could be reactivated after repetitive antigen encounters<sup>[66,68]</sup>.

However, the role of HLA molecules in respiratory allergies is not just about presenting antigens/allergens to T cells through APC. For example, soluble HLA-G (sHLA-G) has immunosuppressive properties and could participate in the mechanisms of allergens immunotolerance through their ability to inhibit T-cell proliferation and induce T and NK CD8<sup>+</sup> cells apoptosis<sup>[69,70]</sup>. Soluble HLA-G inhibits human dendritic cell-triggered allogeneic T-cell proliferation without altering dendritic differentiation and maturation processes<sup>[69]</sup>.

## HLA AND THE RESPIRATORY ALLERGIC DISEASE SUSCEPTIBILITY

Since a wide spectrum of respiratory allergic diseases has been associated with several genetic markers located in the HLA region, we selected, to summarize, analyse and exemplify this topic, those with a better-established relationship. Thus, allergic rhinitis, allergic asthma, aspirin exacerbated respiratory disease, allergic bronchopulmonary aspergillosis, and food allergies with respiratory outcomes were selected to approach and analyse the role of HLA loci in respiratory allergic diseases, the aim of this editorial.

### 1. Allergic rhinitis

Allergic rhinitis (AR) affects the nose and is induced after exposure to allergens in sensitized individuals. As other allergies, it is a IgE-mediated reaction and a symptomatic disorder that, in this case, results in watery rhinorrhoea, sneezing, nasal obstruction and itching. Its two main categories include “intermittent” and “persistent” AR, the former more dependent on the pollen seasonal exposition and the latter to the all year around indoor allergens, such as house dust mites, cockroaches, or fungi<sup>[71]</sup>. AR is increasing all over the world and becoming a burden for the society as well a quality of life loss factor, with important restrictions to daily life. AR is estimated to affect more than 500 million people all over the world, with 60 million only in the United States, a prevalence similar to Europe, ranging from 10% to 20% in adults but much higher in children<sup>[72,73,74]</sup>.

The linkage between AR and HLA markers has long been established<sup>[75]</sup>, specially through alleles belonging to HLA class II loci, such as DRB1\*09: 01, DQB1\*03: 03 and DPB1\*04: 01 in Japanese subjects allergic to house dust mite (HDM)<sup>[76,77,78,79]</sup>. This

linkage between HLA class II and AR has shown to be dependent on the allergen involved in the reaction since, for example, despite DRB1\*01 is strongly associated to the mugwort (*Artemisia vulgaris*) pollen allergen 'Art v 1'<sup>[80]</sup>, when the allergen is the 'Amb a 5' from the short ragweed (*Ambrosia artemisiifolia*) the DRB1\*15 shows the strongest association<sup>[81]</sup>, as well as DRB1\*12: 01 for 'Cry j1' and Cry j2' allergens from the Japanese cedar (*Cryptomeria japonica*)<sup>[79]</sup>. Besides this specificity with the allergen, HLA conferring susceptibility to AR also vary between populations. For example, HLA-DRB1\*08: 03 and HLA-DQB1\*06: 01 are associated with a higher risk of HDM-sensitive allergic rhinitis in Chinese subjects<sup>[82]</sup> but in Japanese the alleles associated are DRB1\*09: 01 and DQB1\*03: 03<sup>[79]</sup>. On the other hand, several HLA class II alleles have been associated to a protective effect against AR, such as DQA1\*02: 01, DQB1\*06: 02, DRB1\*03: 01 and DRB4\*01: 01 for *Artemisia* pollen-induced allergic rhinitis in Chinese population<sup>[83,84]</sup> or DRB1\*04: 11 for HDM induced AR in Brazilians<sup>[85]</sup>.

Most recently, evidences show that soluble HLA-G (sHLA-G) isoforms serum levels, as well as sHLA-A, -B, -C, are significantly increased in AR patients, and that sHLA-G might be considered as a biomarker for assessing AR clinical severity<sup>[86,87,88]</sup>. Moreover, allergen-specific sublingual immunotherapy (SLIT), that aims to achieve clinical tolerance to the causal allergen through oral administration of high-dose allergens by shifting Th2 immune response, reduces sHLA-G and sHLA-A, -B, -C serum levels in patients with AR<sup>[89]</sup>. Presently, the role of HLA-G in AR, and in allergic diseases in general, is not clear but, since it is a tolerance-inducing molecule, the most plausible hypothesis is that it is expressed and secreted by immune cells during the allergic reaction and may represent a reactive attempt to suppress allergic inflammation<sup>[90]</sup>.

## 2. Allergic asthma

Allergic asthma is a chronic inflammatory disease of the airways caused by a complex interaction between genetic susceptibility and environmental factors in which exposure to certain allergens cause intermittent attacks of breathlessness, airway hyper-reactivity, wheezing, and coughing<sup>[91,92]</sup>. An estimate of about 334 million people worldwide are affected with asthma, being the allergic, by far, the most predominant form of the disease, making it a huge burden for the society<sup>[93]</sup>.

As said before, genetic factors are determinant on the development of allergic asthma and HLA class II loci are among the most relevant and consistent. In fact, despite a genetically heterogeneous disease that could be influenced by more than 100 loci located in different chromosomes, such as 2, 5, 9, 15, 17 or 22, HLA-DQ was the first locus to be identified as conferring susceptibility to asthma<sup>[94,95,96]</sup>. Among HLA class II, DQB1 and DRB1 have been showing the strongest associations with asthma<sup>[96,97,98,99]</sup>. Examples of these associations are the DRB1\*01 and DQB1\*05: 01 with susceptibility to *Artemisia vulgaris* allergic asthma in patients from Murcia-Spain<sup>[98]</sup>, the DRB1\*07 with susceptibility to citrus red mite (*Panonychus citri*) sensitive asthma in Koreans and DRB1\*04 conferring protection<sup>[99]</sup>, the DRB1\*13 with susceptibility to mite-sensitive asthma in Taiwanese<sup>[100]</sup> or the haplotype HLA-DRB1\*11: 01-DQA1\*05: 01-DQB1\*03: 01 conferring susceptibility to develop mite-sensitive asthma in Venezuelans<sup>[101]</sup>. However, these associations between HLA class II and asthma vary widely between populations. A study with Iranians shows that DRB1\*12, DQB1\*06: 03 and DQB1\*06: 04 may predispose to childhood allergic asthma and DQB1\*05: 01 and DQB1\*06: 02 to protection<sup>[102]</sup> but in an

Indian pediatric population only DRB1\*03 was implicated in susceptibility<sup>[103]</sup>, a result somehow consistence with Croatian children with atopic asthma that showed positive correlation with DRB1\*01 and DRB1\*03 and negative correlation with DRB1\*16<sup>[104]</sup>. Among Chinese, two studies show different results, one suggesting that DQA1\*01: 04 and DQB1\*02: 01 alleles were implicated in susceptibility, with DQA1\*03: 01 and DQB1\*03: 01 alleles being protective<sup>[105]</sup>, and the other identifying DQA1\*01: 01, DQA1\*06: 01, DQB1\*03: 03 and DQB1\*06: 01 as susceptible alleles to asthma development<sup>[106]</sup>. Other loci from HLA class II region have also been associated to asthma, as HLA-DRB4 with severe persistent asthma<sup>[107]</sup> or HLA-DPA1\*02: 01 and DPB1\*09: 01 with pediatric asthma in Asian populations<sup>[108]</sup>.

Besides class II, HLA class I loci, such as HLA-B\*08 conferring risk in Croatian children<sup>[104]</sup> or HLA-C\*07 as a protective marker in Venezuelans<sup>[101]</sup>, also have been associated to allergic asthma. However, among HLA class I, it has been the non-classical HLA-G who has shown a higher consistency in the association with allergic asthma<sup>[95,109]</sup>. The increased levels of soluble HLA-G (sHLA-G) in the circulating plasma of children with atopic asthma<sup>[110,111]</sup> and in bronchoalveolar lavage from adults<sup>[112]</sup>, or the expression of a specific soluble isoform of HLA-G, the sHLA-G5, in the airway epithelial cells<sup>[110]</sup>, are important evidences of this association. A single nucleotide polymorphism (SNP), the rs1063320 (+3142G>C), present within the 3' untranslated region (UTR) of the HLA-G, has been associated with asthma in children of mothers with asthma, being the +3142C a risk allele and +3142G protective<sup>[113]</sup>. Further studies had shown that the +3142C allele disrupts the targeting of specific microRNAs (miR-152 family) preventing the transcripts to be down-regulated and, as so, leading to a higher HLA-G expression<sup>[114]</sup>. Additionally, adult asthmatic with an asthmatic mother were also shown to have higher levels of sHLA-G in bronchoalveolar lavage fluid when the +3142C allele is present, supporting the idea that the pathogenesis of the disease may be different among offspring depending on the asthmatic status of the mother and that HLA-G play an important role in it<sup>[124]</sup>.

## 3. Aspirin exacerbated respiratory disease

Aspirin exacerbated respiratory disease (AERD), considered a pseudoallergic pathology since it is not IgE-mediated, is characterized by nasal polyposis, asthma and hypersensitivity to medication that inhibits cyclooxygenase-1 enzymes, namely aspirin and other nonsteroidal anti-inflammatory drugs<sup>[116]</sup>. Both upper and lower respiratory reactions occur in AERD, including rhinitis, conjunctivitis, laryngospasm and bronchospasm, and, despite its prevalence is less than 1% in general population, it could represent up to 20% of asthmatics<sup>[116,117]</sup>.

One of the best genetic markers for AERD is HLA-DPB1\*03: 01. Dekker *et al* (1997) found in a study with 59 Polish patients that HLA-DPB1\*03: 01 is associated to risk and DPB1\*04: 01 to protection against the disease<sup>[118]</sup>. Later, Choi *et al* (2004) confirmed the susceptibility of DPB1\*03: 01 in a Korean population and suggests also a possible involvement of DRB1\*09: 01-associated haplotypes<sup>[119]</sup>. Simultaneously, Park *et al* (2004) adds that HLA-DPB1\*03: 01 marker might predict a higher leukotriene receptor antagonist dose to control asthmatic symptoms in AERD patients<sup>[120]</sup>. Most recently, a genome-wide association study in a Korean population confirmed the importance of HLA-DPB1 in the genetic aetiology of AERD and identified in this locus that the SNP rs1042151 (Met105Val) is the most significantly associated with susceptibility to the disease, showing also a gene dose association



with the percent decline of FEV<sub>1</sub> (forced expiratory volume in one second) after an aspirin challenge<sup>[121]</sup>. Soon after, Kim *et al* (2014), also with Korean patients, validated another DPB1 SNP as a genetic marker to predict the AERD phenotype, the rs3128965, which was also associated with the percent decline of FEV<sub>1</sub> after an aspirin challenge and with the requirement for steroid and leukotriene receptor antagonists therapeutic<sup>[122]</sup>. A recent study suggests that HLA-DQB1\*03: 02 and HLA-DRB1\*04, and their related haplotypes, are involved in predisposing patients to AERD, whereas HLA-DQB1\*03: 01 and HLA-DRB1\*11 have a negative association<sup>[123]</sup>. Also, HLA-DQB1\*03: 02 was identified as a genetic marker for favourable response to aspirin desensitization among AERD patients<sup>[124]</sup>.

#### 4. Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) results from allergic reactions to fungus from the *Aspergillus* genus, usually the *A. fumigatus* specie, leading to lung inflammation and causing bronchospasm, coughing, breathing difficulty and airway obstruction<sup>[125]</sup>. Despite uncommon in general population, 2% to 15% of cystic fibrosis patients and up to 6% of asthmatics could be affected with ABPA, being its early diagnose important since it is associated with asthma poorer outcomes<sup>[126,127]</sup>.

The presence of HLA-DRB1\*15: 01 and HLA-DRB1\*15: 03 alleles confer relative high risk of developing ABPA, being the alleles DRB1\*15: 02 and DQB1\*02: 01 protective markers<sup>[128,129,130]</sup>. When considering ABPA patients with cystic fibrosis, as was done in a study with patients recruited in Murcia- Spain, the correlation between HLA-DQB1\*02: 01 allele and its protective effects is maintained as well as DRB1\*15: 01 for risk, together with HLA-DRB1\*11: 04, DRB1\*11: 01, -DRB1\*04 and -DRB1\*07: 01 alleles<sup>[131]</sup>.

#### 5. Food allergies with respiratory outcomes

Food allergy, mediated by IgE antibodies, is an immunological reaction to particular components of a diet and, among other symptoms, could result in respiratory outcomes, such as runny nose, coughing, wheezing, swelling of the throat and breathlessness<sup>[132]</sup>. Based on numerous studies, the prevalence of food allergy could affect around 5% of adults and 8% of children, and is increasing year after year<sup>[133]</sup>. Despite allergies could arise from any kind of food, in more than 85% of cases food allergies result from milk, egg, peanut, tree nuts, shellfish, fish, wheat, sesame seed and soy<sup>[134]</sup>.

Besides environmental factors, and similarly to other allergies, food allergies are also determined by genetics and shows familial aggregation<sup>[135,136]</sup>. Among others, HLA loci have been associate to food allergies, namely those showing respiratory outcomes such as peanut, milk and eggs allergies<sup>[137]</sup>. A genome wide association study (GWAS) developed by Hong *et al* provide evidences that the HLA-DR and -DQ gene region group significant genetic risk for food allergies<sup>[138]</sup>. This study identified and replicated genetic variants significantly associated with peanut, milk, and eggs allergies, in the HLA-DR and -DQ gene region, tagged by rs7192 (a non-synonymous SNP of the HLA-DRA gene) and rs9275596 (intergenic between the HLA-DQB1 and HLA-DQA2 genes). Authors refer that both SNPs are known to significantly affect DNA methylation in several nearby genes, namely HLA-DRB1 and HLA-DQB1, which, in turn, mediate the detected association to food allergy. Previously, peanut allergy risk association with HLA-DRB1\*08 and HLA-DQB1\*04 were reported<sup>[139]</sup>, as well as HLA-DQB1\*06: 03 for risk and DQB1\*02 as a protective factor<sup>[140]</sup>, but others studies show no HLA association<sup>[141]</sup>. A recent study using a bioinformatic approach

evaluated the binding affinities between digested fragments of food allergens and the HLA class II membrane receptors<sup>[142]</sup>. This study found that peptides generated from milk allergens bind to DRB1\*01: 01, DQ7 (DQA1\*05: 01/DQB1\*03: 01) and DQ8 (DQA1\*03: 01/DQB1\*03: 02), but not to DRB1\*03: 01, DRB1\*04: 04, DRB1\*12: 01 and DRB1\*15: 01. The peptides generated from egg allergens bind to DRB1\*01: 01, DQ4 (DQA1\*04: 01/DQB1\*04: 02), DQ7 and DQ8, but not to DRB1\*03: 01, DRB1\*04: 04 and DRB1\*12: 01. Thus, in this study, the alleles DRB1\*01: 01, DQ7 and DQ8 were considered as susceptible to cow's milk allergy and DRB1\*03: 01, DRB1\*04: 04, DRB1\*12: 01 and DRB1\*15: 01 as protective. The alleles DRB1\*01: 01, DQ4, DQ7 and DQ8 are considered as susceptible to egg allergy and DRB1\*03: 01, DRB1\*04: 04 and DRB1\*12: 01 as protective.

## CONCLUSION

Allergies occurs after the exposure of predisposed individuals to certain allergens, resulting in an exaggerated inflammatory response mediated by IgE antibodies, a reaction that could affect upper or lower respiratory tract, or both<sup>[1]</sup>. In fact, allergies with respiratory manifestations are the most common allergies, with rhinitis and asthma affecting up to 700 million people worldwide, with a dramatic increasing prevalence along the past decades<sup>[3]</sup>. The considerable burden placed by respiratory allergies on present society, with particular concern in their prevalence among children, ask us for a higher research effort in order to better understand its aetiology<sup>[2]</sup>. Nevertheless, it is already established that respiratory allergic diseases follow a common pathway, the so called 'atopic march', that starts with atopic dermatitis and could continue across allergic rhinitis into asthma<sup>[7,8]</sup>. Additionally, it is already evident that, despite the important influence of environmental factors, genetics play a major role, making respiratory allergies the result of a complex interplay between genetic factors and environmental exposure<sup>[12]</sup>.

Among the hundreds of candidate-genes that have been evaluated for respiratory allergic diseases susceptibility, and regardless the conflicting results and the need for further studies, HLA loci occupy a central position. Considering its role in the context of the immune system action, particularly in distinguish 'self' from 'non-self', the HLA loci association to respiratory allergic diseases is not surprising<sup>[15,16]</sup>. In fact, HLA cell-surface glycoproteins act in the very beginning of the sensitization process, presenting the allergens to T lymphocytes and triggering an immune response, making these molecules one of the main suspects on the allergies aetiology. Nevertheless, besides the association that has been identified between HLA and respiratory allergic diseases, little is known about the mechanisms that underpin it. Small and poorly defined samples are among the most common research handicaps that have made the enlightenment of the HLA and allergies relationship difficult. Some of these pathologies, despite being included in the same bulk, could be the consequence of different aetiologies, depending on the genetic or the environmental exposition in specific populations. Additionally, has have been demonstrated, HLA association seems to be depend on specific allergens that trigger the respiratory allergy and could vary accordingly to the population genetics. Thus, future research should be able to use well characterized samples, considering each of the different allergens that triggers the specific respiratory allergy in well genetically characterized populations. However, meeting these conditions will make it even more difficult to obtain sufficiently large samples, posing additional challenges on the research development.

As seen, the specific HLA allele implications with protection or

susceptibility for respiratory allergic disease constitute a highly diverse set, varying accordingly with the allergen involved and, for the same disorders, between different human populations. On these HLA and respiratory allergic disease associations two different pictures seems to emerge: a directly implication of the HLA alleles or an association through a close linkage with other loci that may be the direct cause. In this unclear involvement of HLA loci, gene-gene and gene-environment interactions could be present, making even more difficult a comprehensible analysis of the results obtained on the studies. As that, each HLA association study needs to identify, characterize and discriminate better the specific conditions in which the disease appears and develops, since it can make all the difference in the sense of the obtained data.

A new step forward on the HLA association with respiratory allergic disease demands for a much more careful approach in future studies. Besides the above considerations, HLA studies need to be done with DNA high resolution techniques and always assure four digits typing. However, high resolution data should be also analysed in the context of their serologic meaning, especially grouping antigens accordingly to their ability to interact with specific allergens. The need to enlarge the picture of possible mechanisms and pathways involved in the aetiology of the respiratory allergic disease requires the study of new DNA markers along the MHC region with particular emphasis on segments revealing linkage with the already identified genetic markers. Requiring additional efforts on research, given its enormous potential on the enlightenment of the respiratory allergic disease aetiology, is the HLA soluble forms, in particular sHLA-G.

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