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

Review

HLA and asthma phenotypes/endotypes: A review

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ARTICLE INFO

Article history:

Received 31 July 2013

Accepted 23 June 2014

Available online xxxxx

Keywords:

Asthma

HLA

Allergic

Occupational

Aspirin

ABSTRACT

Asthma is a complex chronic inflammatory disease of the airways caused by the interaction of genetic susceptibility with environmental influences. Genome-wide association studies (GWAS) represent the most powerful approach for asthma, that have identified several genes (e.g., IL18R1, IL33, SMAD3, ORMDL3, HLA-DQ and IL2RB loci). HLA super-locus is a genomic region in the chromosomal position 6p21. Since no gene can be considered as an asthma gene, able to reflect the complex etiology and the heterogeneity of the disease the terms 'phenotype' and more recently 'endotype' have been used. This review, according to literature availability, focuses on the relationship between human leukocyte antigens (HLA) region specifically the HLA class II genes and different asthma phenotypes/endotypes, such as allergic asthma/Th2 associated, occupational and aspirin-sensitive asthma. The most common HLA haplotypes in the different asthma phenotypes are HLA-DRB1 in allergic asthma, HLA-DQB1 in occupational asthma and HLA-DPB1 in aspirin-sensitive asthma. However, it is difficult to study the role of class II genes in vivo because of the heterogeneity of human population, the complexity of MHC, and the strong linkage disequilibrium among different class II genes. Despite the variation and the inconsistency of the HLA haplotypes and alleles in different types of asthma, the association between HLA class II genes and asthma has been demonstrated in the majority of studies.

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1. Introduction

Asthma is a complex chronic inflammatory disease of the airways caused by the interaction of genetic susceptibility with environmental influences. Environmental exposures throughout life can modulate the expression of asthma susceptibility genes, making asthma a dynamic disease [1]. The physiology of asthma

involves many different cells, T lymphocytes, eosinophils and mast cells being key cells in the airway inflammatory process and also mediators (cytokines, histamine, leukotrienes) [2]. Airway inflammation and remodelling are critical components of asthma. It is shown that many genes are involved in the pathogenesis of asthma [3,4]. However no gene can be considered as an asthma gene, able to reflect the complex etiology and the heterogeneity of the disease. To describe the heterogeneity in the manifestations of asthma, the term 'phenotype' has been initially used [2], to define subtypes of asthma often focused on observable characteristics and

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classified by clinical or physiological criteria, by exposure to environmental triggers and by defining pathophysiology concerning the type of underlying inflammation. Environmental triggers include allergens, occupational allergens and irritants, exercise, drugs (such as aspirin) [5]. Sufficient clinical and laboratory data need to be collected on each individual for the definition of a specific phenotype. Thus, asthma classification can be based on proposed cause (allergic, nonallergic, and occupational), pathology (eosinophilic, noneosinophilic), severity, and physiological parameters [6]. Recently, the concept of the endotype has emerged in the classification of asthma. This term is used to describe specific asthma subphenotypes that include a unique or distinctive functional or pathophysiological mechanism, such as Th2 associated, early onset allergic asthma, severe late onset eosinophilic, aspirin-sensitive asthma, allergic bronchopulmonary mycosis and non Th2 associated, neutrophilic and obesity-related asthma [7]. The identification of different endotypes combined with the identification of molecular mechanisms and factors responsible for the development of them may contribute to the introduction of novel endotype-specific treatments [7].

A study by Deichmann et al. [8] was the first to associate a specific genetic locus, chromosome 11q13, to asthma. Since then, more than 1000 publications related a variety of polymorphisms in more than 200 candidate genes to asthma phenotypes. There are three major approaches to associate candidate genes with asthma phenotypes: Genome-wide linkage studies, candidate-gene association studies and genome-wide association studies (GWAS) [9]. GWAS represent the most powerful approach for asthma [9–11], to date, several other genetic studies have been reported [12,13]. One of the latest and largest of these approaches was from the GABRIEL consortium applied in 10365 patients which discovered that the IL18R1, IL33, SMAD3 (a gene activated by TGF- β), ORMDL3, HLA-DQ and IL2RB loci were all significantly associated with asthma [14]. Despite the identification of genes associated with asthma by the methods mentioned above, few of them have been replicated extensively. The human leukocyte antigen (HLA) super-locus is a genomic region in the chromosomal position 6p21 that encodes the six classical transplantation HLA genes and at least 132 protein coding genes that encode TNF, LTA, and TAP, many of which have been associated with asthma phenotypes in diverse populations [4] or have important roles in the regulation of the immune system as well as some other fundamental molecular and cellular processes [15]. Genes in this complex are categorized into three basic groups: class I, class II, and class III (Fig. 1).

The first studies concerning the association between HLA region with asthma development were based on class I HLA region [16–18]. The following studies connected class II HLA region with

asthmatic manifestations and were reported by Huang et al. [19] in 1981, Wang et al. [20], and by Caraballo et al. [21] and Hsieh et al. [22], all applied in Chinese population.

To control population admixture, several studies of immunogenetic investigation in atopic diseases and allergic asthma have been applied in several races and nationalities. The majority of published reviews have investigated several regions containing a large number of susceptibility genes in asthma. Nevertheless, reviews focusing on HLA region are scarce and the available reviews focus either on HLA region including several diseases [3], or on a specific asthma phenotype such as occupational asthma [23].

In particular, MHC class II genes on chromosome 6 are responsible for the majority of familial clustering in asthma are highly polymorphic and strongly influence allergen-specific IgE response. The majority of HLA class II genes in diverse populations, are linked to a limited set of class II-DR or -DQ alleles [9]. However, it is difficult to study the role of class II genes *in vivo* because of the heterogeneity of human population, the complexity of MHC, and the strong linkage disequilibrium among different class II genes. Although the phenotypic heterogeneity has been considered as a major limitation in understanding the genetic determinants of asthma, few studies have examined to what extent a better phenotypic resolution leads to identify new genetic determinants. Moffatt et al. [14] previously applied this approach with a single asthma characteristic, age at asthma onset (childhood versus adult onset). Results indicate that HLA-DQ may be fundamental to later-onset disease. Adult-onset asthma is thought to have a minor atopic component [24]. Also Li et al. performed a GWAS on a population of well-characterized patients with severe or difficult-to-treat asthma and identified the RAD50-IL13 region and the HLA DR/DQ region [9]. Very recently a large population-based study on 3001 adult asthmatic patients recruited in the frame of three epidemiological surveys (the European Community Respiratory Health Survey (ECRHS), the Swiss Study on Air Pollution and Lung Disease in Adults (SAPALDIA) and the Epidemiological Study on the Genetics and Environment of Asthma (EGEA) was the first to identify genetic variants associated with refined asthma phenotypes, mainly characterized by disease activity, age of asthma onset and atopic status, by Latent class analysis (LCA) [25]. Associations of genome-wide significance were observed between “active adult-onset nonallergic asthma” and between “inactive/mild nonallergic asthma”. 15 SNPs identified in previous GWAS of asthma have been replicated with at least one asthma phenotype, most of them with the “active allergic asthma” phenotype. Most of the replications were observed for the active allergic asthma phenotype, including SNPs in or near IL1RL1, IL18R1, DPP10, RAD50-IL13, HLA-DQ, IL33, RORA, ORMDL3/GSDMB and IL12RB. This may have occurred because childhood-onset asthma is more prone to association with allergic phenotypes, and has been more intensively investigated in previous asthma GWAS.

It is a fact that the HLA region is the most consistent genomic locus identified for immune diseases. Asthma and autoimmune diseases share extensive immunologic pathways. However, a comparison of GWAS-identified genes between asthma and autoimmune diseases showed that rs2395185 in HLA-DRA was associated with asthma in the SARP/CSGA/CAG, TENOR, and GABRIEL studies [26]. The minor allele T was associated with risk of asthma development. In contrast, the same allele in another study was found to be protective for ulcerative colitis [27]. Furthermore, a GWAS of paediatric asthma in Asian populations identified rs987870 (between HLA-DPA1 and HLA-DPB1) with the opposite direction of allelic effects from autoimmune diseases. According to Li et al. a possible explanation for this difference might be the existence of different antigen triggers between asthma and autoimmune diseases [26].

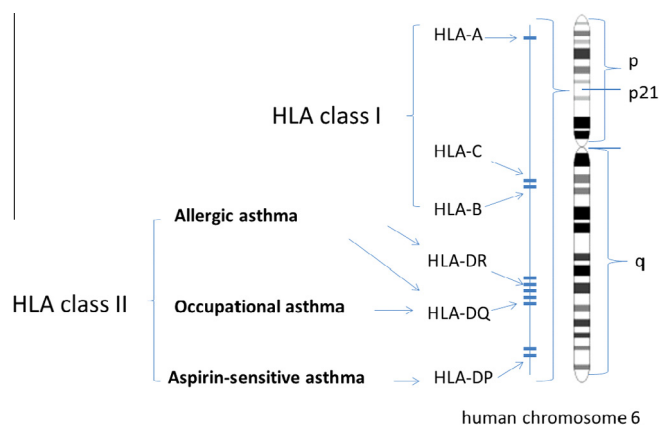


Fig. 1. Map of the human Chromosome 6 including HLA class I and II genes.

HLA genes have also been implicated as a risk factor in asthma related diseases, such as allergic rhinitis (HLA-DQB1, HLA-B [28] and HLA-G [29]), allergic bronchopulmonary aspergillosis (HLA-DRB1) [30], allergic fungal sinusitis and other chronic hypertrophic rhinosinusitis disorders (HLA-DQB1*03) [31] and atopic dermatitis (HLA-B7) [32]. Nevertheless, HLA-DQB1 was associated with protection against allergic bronchopulmonary aspergillosis [30]. Moreover, HLA genes have also been associated with other diseases, such as diabetes, rheumatoid arthritis [3] or psoriasis vulgaris [33].

Moreover, HLA typing could play a role in the use of appropriate therapeutic modalities in allergic asthma and rhinitis, as CD4 T cells recognize a bimolecular complex of the specific epitopes bound to specific HLA class II molecules (HLA restriction) encoded by the three different loci, HLA DR, DP or DQ. Several studies implicated T cell responses as a determinant of the clinical efficacy of allergen Specific Immuno-Therapy. Fleva et al. suggested that HLA typing could possibly play a role in the selection of atopic patients candidates for grass pollen immunotherapy, by predicting a favourable outcome [34]. Furthermore, it has been reported that CD86, HLA-DR, and TLR4 might be useful parameters for monitoring mite allergen specific immunotherapy [35]. Treatment of patients with allergic asthma using low doses of peptides containing T cell epitopes from Fel d 1, the major cat allergen, reduces allergic sensitization and improves surrogate markers of disease [36]. Peptide immunotherapy for HLA-DR molecules has also been used for cat and grass pollen allergy [37–39]. The epitope complexity must be taken into account in the design of a general strategy for identification and characterization of T cell epitopes in allergens [40]. Schulten et al. made a large scale of airborne allergens, for each allergen all available sequences were collected and total of 87 antigenic regions were recognized [40].

In the present review, according to literature availability, we focus on the relationship between HLA region and certain asthma phenotypes/endotypes, such as allergic/Th2 associated asthma, occupational and aspirin-sensitive asthma.

2. Allergic/Th2 associated asthma

Allergy is defined as a T helper 2 (Th2) driven hypersensitivity disorder of the immune system to normally harmless substances in the environment [41]. Asthma can be triggered by an elevated IgE in response to a specific allergen. Implicated sources can be indoor allergens (house dust mites, cockroach, fungi, moulds, animal danders) and selected outdoor allergens (trees, weeds, and grass pollens, fungal spores) and also air pollutants-ozone, nitrogen oxides, sulphur dioxide diesel exhaust particles [42,43]. The involvement and interaction between genetic and environmental factors in asthma phenotypes/endotypes is unquestionable and is manifested either as early onset allergic asthma in childhood and adolescence or as late onset eosinophilic adult asthma. Besides, several studies have associated the risk of asthma development with early life sensitization [44,45]. Several reports have demonstrated that the HLA region associated to asthma and allergy is the DQ and/or DR loci (Table 1).

Before the 90s, HLA typings were done by using commercially available HLA immunoplates (Behring, West Germany) [19,20], whereas in most recent studies HLA typing was detected by polymerase-chain reaction amplification and hybridization with sequence specific oligonucleotide probes method (PCR-SSOP) [46]. Initially the studies investigating the HLA region focused on HLA class I genes showed association with asthma development [18–20,47,48] or not [16,49,50]. However, one recent report, which included HLA class I genes, conducted in Chicago on European des-

cent and Dutch families, was the only study to support HLA-G (HLA class I) as a novel asthma and bronchial hyperresponsiveness susceptibility gene [51]. These families are unique in that the affected parent had phenotypic characteristics measured at the age of current measurements in offspring [52].

The following years, studies results favored the association of HLA class II genes with asthma phenotypes such as HLA-DQ, HLA-DR and HLA-DP. HLA-DQ was the first asthma-susceptibility locus to be identified, and extended haplotypes encompassing HLA-DQ and HLA-DR have been studied for their effects on specific allergen sensitization [53]. The GABRIEL (A Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community) Consortium conducted a previous, comparatively small GWAS, which showed that multiple markers on chromosome 17q21 were strongly and reproducibly associated with childhood-onset asthma [54]. Moffat et al. in another study report results of a GWAS conducted with a sample of 10,365 persons, 10 times the size of that used in their first-generation study, both on childhood-onset asthma and on later-onset asthma [14]. One recently published study by Lasky-Su et al. described results from a genome-wide association study on asthma performed in a large asthmatic population of 3855 subjects [55]. Their findings replicated the HLA-DQA1 region in the pathogenesis of asthma.

Several studies have been addressed to Chinese population. Outdoor, indoor and occupational triggers are important risk factors for asthma onset in China [56–58]. Chinese studies were one of the initial to include HLA class I genes such as a report in Shenyang area, North-east China [20]. They concluded that HLA-B61 (HLA class I) was associated with bronchial asthma. Furthermore, Huang et al. studied a Chinese population sample and concluded that individuals carrying HLA-B5 had a higher probability to develop asthma and those carrying HLA-B17 were less likely to become asthmatics in their childhood [19]. Furthermore, Gao et al. [59,60] also demonstrated that the alleles HLA-DQA1*01:04 and HLA-DQB1*02:01 were correlated with susceptibility among Northern of Han nationality in China [59] and that HLA-DRB alleles, DR6(13) and DR52 were significantly implicated among Beijing Chinese [60]. Wang et al. concluded that HLA-DRB1*15:01/15:02 allele [61] was associated with asthma in the patients among the Hans in Shanxi province. Furthermore, Guo et al. also proposed that HLA-DQA1*01:01, DQA1*06:01 and HLA-DQB1*03:03, DQB1*06:01 might be the susceptible alleles of asthma in Chinese [62]. These reports in Chinese population support that mostly the HLA-DQ and HLA-DR allele are correlated with the susceptibility to asthma. However, some studies dispute the association between asthma and HLA class II genes (either alleles or haplotypes) in Chinese population. Among them, Li et al. found no significant difference in the HLA-DQ and DR loci between asthmatic patients and controls in southern Chinese people [63].

In addition, many studies focus on sensitivity to isolated allergens such as house dust mite which is the most common and studied allergen [64–66]. A genetic study between allergic asthma and the HLA system suggested the existence of an HLA-linked recessive gene controlling the IgE immune responsiveness to mite allergens and conferring susceptibility to allergic asthma [67]. A study that concluded the association between HLA-DR haplotype and mite-sensitive asthma was reported by Lara-Marquez et al. in a Venezuela population [68]. They suggested that HLA-DRB1*11:01, DQA1*05:01, DQB1*03:01 haplotype was associated with atopic asthma, conferring susceptibility to develop mite-sensitive asthma to both atopics, and to non-atopic controls carrying this haplotype. On the contrary, another finding of the same study concerned HLA class I genes. They concluded that the allele HLA-C7 might have a protective role for developing atopic asthma in the

Table 1
Studies on HLA genes in allergic asthma.

Authors [Ref nr]	Implicated allergens/substances	HLA (haplotype, allele) susceptibility to asthma	HLA-(haplotype, allele) Protection against the disease-controls	Population-country studied	Nr of pts
Brostoff et al. [17]	Intrinsic asthma	HLA-W6	–	Caucasian	26
Huang et al. [19]	Not defined	HLA-B5	HLA-B17	Chinese	99
				Asia	
Wang et al. [20]	Not defined	HLA-B61	–	Chinese	93
				Asia	
Caraballo et al. [21]	Mites	HLA- DPB1*04:01	–	Mulatto	43
				Colombia	
Movahedi et al. [46]	Dust, dander, cockroach, food additives, cigarette, cocoa, weeds, grass, mites, strawberry, tree	HLA-DRB1, HLA-DQA1, HLA-DQB1	–	Iran	112
Ostergaard et al. [47]	Not defined	HLA-A1, B8	–	Caucasian	57
Flaherty et al. [50]	Moulds	No association	–	Caucasian	100
Nicolae et al. [51]	Not defined	HLA-G	–	European descent and Dutch families	867
Lasky-Su et al. [55]	Not defined	HLA-DQA1		Caucasian	3855
Gao et al. [59]	Not defined	HLA-DQA1*01:04 HLA-DQB1*02:01	HLA-DQA1*03:01, HLA-DQB1*03:01	Hans-China	125
				Asia	
Gao et al. [60]	House dust mite	HLA-DRB, DR6(13), DR52	–	Beijing	50
				Chinese	
				Asia	
Wang et al. [61]	Not defined	HLA-DRB1*15:01/15:02	–	Hans-China	138
				Asian	
Guo et al. [62]	Mites	HLA-DQA1*01:01, HLA-DQA1*06:01, HLA-DQB1*03:03, HLA-DQB1*06:01	–	Chinese	98
				Asia	
Li et al. [63]	Mites, pollen, cat, dog, moulds	No association	–	Chinese	73
				Asia	
Lara-Marquez et al. [68]	Mites	HLA-DRB1*11:01, HLA-DQA1*05:01, HLA-DQB1*03:01	HLA-C7	Venezuela	71
Aron et al. [69]	Not defined	HLA-DRB1*04	–	France	14
Moffatt et al. [70]	Not defined	No association	–	Aboriginal Australians	234
Hizawa et al. [71]	Mites	HLA-D and non-HLA loci	–	USA	299
Cho et al. [73]	Mites	HLA-DRB1, HLA-DR7	HLA-DR4	Caucasian	91
Howell et al. [74]	Mites, pollen, dog	HLA-DRB1*15	HLA-DRB1*08	Asthmatic family pedigrees	176
Moffat et al. [75]	Mites	No association	–	Australia	1004
Torio et al. [77]	Mugwort pollen	HLA-DRB1*01, HLA-DQB1*05:01	–	Spain	123
Woszczek et al. [78]	Grass pollen	HLA-DRB1*02, B5*	–	Poland	82
Young et al. [81]	Mites, grass pollen, moulds	No association	–	UK	431
Torio et al. [82]	Not defined	No association	–	Spain	189
Kauppinen et al. [83]	Cow allergen Bos d 2	HLA-DRB1*01:01, HLA-DRB1*04:04, HLA-DQB1*03:02, HLA-DQB1*05:01	HLA-DRB1*03:01, HLA-DQB1*02:01	Caucasian	40
Juhn et al. [84,85]	Not defined	HLA DRB1*03	–	USA	340
Hanchard et al. [87]	Not defined	HLA DRB1*03	–	USA	383
Noguchi et al. [88]	Mites	HLA-DPA*02:01 HLA-DPB1*09:01	–	Asia	1653
Ivković-Jureković et al. [89]	Mites, grass pollen, ragweed	HLA-DRB1*01, HLA-DRB1*03	–	Croatia	143
Parapanissiou et al. [90]	Mites	HLA-DRB1*04, HLA-DQA1*03:01	–	Greece	60
Munthe-Kaas et al. [91]	Birch	HLA-DQB1*06:03, HLA-DRB1*13	–	Norwegian	959
	Mugwort	HLA-DQB1*06:09, HLA-DRB1*13, HLA-DQB1 *05:01, HLA-DRB1*01	–		
Shreffler et al. [92]	Peanut	No association	–	USA	73
Knutsen et al. [93]	Moulds	–	HLA-DQB1*03	USA	186

population studied. HLA-DRB1*04 alleles were also suggested from Aron et al. for atopic asthmatics in France, presenting skin test sensitivity to one or more of common allergens including *Dermatophagoides pteronyssinus*, cat, grass mix, tree pollen mix, *Alternaria*, and also elevated serum total and specific IgE concentrations [69]. A recent GWAS of asthma by Li et al., supported also the involvement of the DRB1/DQA1 locus in asthma, and reported also no significant evidence for the involvement of class I or III alleles [9]. In this report, they detected atopy by measuring total serum IgE levels in the population studied. However, HLA-DRB1 alleles did not predict the presence of asthma, in Aboriginal Australians [70].

Mite sensitization has been reported in many studies in Asia and concluded the involvement of HLA region in allergic asthma. In one of the few studies concerning HLA-DP, Caraballo et al. reported that DPB1*04:01 was significantly decreased in asthmatic patients who were allergic to at least two mites (*D. pteronyssinus*, *Dermatophagoides farinae*) in Mulatto population (an admixture population of European and African ancestries) [21]. Besides, Hiza-wa et al. despite their findings on HLA-D region associated with the expression of *D. pteronyssinus*-specific IgE responsiveness in Caucasian population, they suggested then that there was also a strong influence of non-HLA loci [71,72]. In the study by Cho et al. it was shown that HLA-DRB1 and HLA-DR7 were associated with the risk of developing asthma. In addition, they concluded that HLA-DR7 might increase, and DR4 decrease, the risk of developing asthma in citrus red mite (CRM)-exposed adults [73]. Howell et al. investigated the association between HLA region and a variety of major allergens in 176 individuals from 20 asthmatic family pedigrees [74]. They concluded that storage mites were the dominant allergens and that HLA-DRB1*08 was negatively associated with asthma and atopy, while HLA-DRB1*15 was positively associated with asthma. In order to control population admixture, Moffat et al. investigated an Australian population and this was one of the first studies that showed association between HLA-DRB1 and house dust mite allergens but failed to associate this locus with either asthma or eosinophilia [24]. However in another previously published survey in an Australian population sample, the same authors had shown association between tumour necrosis factor/HLA-DR haplotypes [75]. In another report addressed to Taiwanese adolescents sensitized to *D. farinae*, the HLA-DR13(+)/LTalphaN-coI*1 haplotype was associated with the higher risk of developing clinical asthma [76].

Besides mites, sensitization to pollens plays also a significant role in asthma phenotypes. In the population of Spain, Torio et al. was the first to conclude that the HLA-DRB1*01-DQB1*05:01 genotype was strongly associated with a positive response to *Artemisia vulgaris* [77]. In another study, Woszczek et al. compared patients suffering only from rhinitis and sensitized to grass-pollen allergy, with asthmatic patients sensitized to the same allergen and found a significant association between HLA-DRB1*02, B5* haplotype and asthma phenotype [78]. In the study by Blumenthal et al. HLA-DR2, (HLA-B7, SC31, DR2), and (HLA-B8, SC01, DR3) haplotypes were shown to distinguish subjects with asthma from those with rhinitis only in ragweed pollen allergy [79]. On the contrary, recently Dzurilla et al. reported no association between bronchial asthma induced by pollen allergens and HLA-DRB1, -DQB1 alleles in the Slovak population of 109 patients [80]. However some reports concluded that class II HLA restriction is insufficient to account for individual differences in reactivity to common allergens [81,82].

Another study suggested that the HLA class II alleles DRB1*01:01, DRB1*04:04, DQB1*03:02, and DQB1*05:01, and the haplotypes that include them, were associated with sensitization to the major cow dander allergen Bos d 2, whereas HLA-DRB1*03:01 and DQB1*02:01 were dissociated with it [83].

3. Childhood/Th2 associated early onset allergic asthma

Juhn et al. have published several results on childhood asthma concerning the influences of family history of asthma or atopy on the development of asthma. The patients included were recruited from a previous study concerning the relationship between HLA type and measles vaccine responses [84]. No specific information on sensitization to allergens in the patient group was evident. After concluding that the HLA DRB1*03 allele was associated with asthma in a retrospective cohort of 383 children [84], they extended their haplotype analysis in the same group by associating HLA Class II genes with the severity of asthma in children [85]. In another report applying the same study group, they concluded that HLA type appeared to influence the progression of asthma from initial symptoms to disease [86]. Finally, more recently, the same group of authors, in order to investigate the possibility that their first association [84] might be confounded by an unrecognized ancestral haplotype exhibiting strong linkage disequilibrium between HLA DRB1*03 and other HLA alleles, they repeated their previous association study (the same group of children) using haplotypes inferred between DRB1*03 (and adjacent class II alleles) and class I HLA alleles [87]. They concluded once again that HLA DRB1*03 appeared to be an independent asthma susceptibility locus. In a Chinese population based study, Hsieh et al. [22] showed association of HLA-DQw2 allele with childhood asthma. Noguchi et al. performed the first GWAS in Asian paediatric population and found that HLA-DPA*02:01/DPB1*09:01 was strongly associated with paediatric asthma [88].

In the most recent study by Ivković-Jureković et al. in a group of 143 Croatian children with atopic asthma, sensitized to common inhalant allergens, such as *D. pteronyssinus* (Der p), Der p + *Dactylis glomerata* (Dact g) or *Ambrosia elatior* (Amb a), concluded that HLA-DRB1*01, and HLA-DRB1*03 genotype increased the risk for atopic asthma and high serum IgE [89].

Parapanissiou et al. was the first Hellenic study, suggesting that HLA-DRB1*04 and HLA-DQA1*03:01 were possibly important factors in the development of atopic asthma in Greek children sensitized to mites [90].

In Iranian children with allergic asthma, diagnosed by Skin prick tests (SPT) including a variety of common allergens (such as dust, dander, cockroach, food additives, cigarette, cocoa, weeds, grass, mite, strawberry and trees), Movahedi et al. suggested that that HLA-DRB1, DQA1 & DQB1 alleles and haplotypes might be implicated in susceptibility to allergy and asthma and serum IgE production [46].

Munthe-Kaas et al. by investigating subgroups of asthma of specific allergies in Norwegian children, they associated birch sensitization with DQB1 0603-DRB1 13 and mugwort or *A. vulgaris* sensitization with DQB1 0609-DRB1 13 and DQB1 0501-DRB1 01 [91], findings which had also been supported by Torio et al. earlier, concerning *A. vulgaris* association for Spanish population [77]. However, a study on children with peanut allergy failed to demonstrate an association between the HLA class II alleles and asthma [92]. Concerning mould sensitivity, Knutsen et al. suggested that HLA-DQB1*03 might provide protection from development of *Alternaria*-sensitive severe asthma [93,94].

4. Occupational asthma

Occupational exposure is also a significant factor for asthma and includes around 9–15% of asthma in adults of working age [95]. Though there is a huge list of substances implicated in the development of occupational asthma, data concerning HLA region have been evaluated only in few of them. These substances include highly reactive small molecules, irritants that may cause an

Table 2
Studies on HLA genes in occupational asthma.

Authors [Ref nr]	Implicated allergens/ substances	HLA (haplotype, allele) susceptibility to asthma	HLA-(haplotype, allele) Protection against the disease-controls	Population-country studied	Nr of pts
Mapp et al. [98]	Diisocyanate	HLA-DQA1*01:04 HLA-DQB1*05:03	HLA-DQA1*01:01 HLA-DQB1*05:01	Italy	67
Kim et al. [99]	Diisocyanate	HLA-DRB1*15 HLA-DPB1*05	–	Korea	55
Choi et al. [100]	Diisocyanate	HLA DRB1*15:01 HLA-DQB1*06:02 HLA-DPB1*05:01	–	Korea	84
Balboni et al. [104]	Diisocyanate	HLA-DQB1*05:03	HLA-DQB1*05:01	Italy	30
Rihs et al. [106]	Diisocyanate	No association		Germany	32
Beghé et al. [108]	Diisocyanate	No association		Italy	142
Horne et al. [109]	Cedar	HLA DQB1*06:03 HLA-DQB1*03:02		Canada	56

alteration in airway responsiveness, known immunogens such as platinum salts and complex plant and animal biological products that stimulate the production of IgE [83,96]. Exposure intensity is an important determinant of sensitization and asthma caused by respiratory sensitizers. HLA class II alleles contribute to individual susceptibility to low-molecular-weight chemicals. [97]. In particular, isocyanates which are compounds of low molecular weight are a primary cause of occupational asthma in industrialized countries. Several studies have supported the involvement of HLA region in the pathogenesis of diisocyanate (TDI) induced asthma. As only a small proportion of subjects exposed to diisocyanates develop occupational asthma, this fact might imply an individual predisposition [98]. To identify the TDI-induced asthma in patients, diisocyanate-specific inhalation challenge tests were conducted in all studies.

Studies based on Korean population showed that the HLA haplotype DRB1*15-DPB1*05 could be a susceptibility gene marker for the development of TDI-induced asthma among the exposed workers [99,100] (Table 2). Mapp et al. showed in their studies that the frequencies of DQA1*01:04 and DQB1*05:03 were significantly increased in asthmatics compared with asymptomatic exposed subjects, while DQA1*01:01 and DQB1*05:01 were significantly increased in asymptomatic exposed subjects [98,101–103]. However, no significant difference was found in the distribution of DRB1 alleles between asthmatics and controls.

Balboni et al. was in agreement with the hypothesis of Mapp et al. considering HLA-DQB1*05:03 and suggested that residue 57 of HLA-DQB1 is a potentially critical location [104]. A study of Bignon et al. has also favored for allele DQB1*05:03 and allelic combination DQB1*02:01/03:01 in association with susceptibility to asthma [105]. Conversely, allele DQB1*05:01 and the DQA1*01:01-DQB1*05:01-DR1 haplotype was suggested as protective against the disease. Other groups of studies were unable to demonstrate the influence of HLA Class II Alleles in Isocyanate-Induced Asthma, based on a German population [106] and on diisocyanate-exposed workers [107]. Beghé et al. also failed to demonstrate that HLA class II alleles were significantly associated with the phenotype of TDI-induced asthma in a European study [108].

Few data exist on other causes of occupational asthma such as platinum or red cedar. A group of scientists investigated platinum refinery workers, suggesting that the relative risk was associated with HLA phenotype and was greater at lower levels of exposure [23]. Furthermore, Horne et al. by investigating occupational asthma due to western red cedar, demonstrated that DRB1 and DQB1 HLA class II alleles were 'protective' against western red cedar asthma [109]. In conclusion, the possibility of early diagnosis of occupational asthma must be improved by future studies that could evaluate the association of HLA-region in the development of occupational asthma.

The investigation of genetic susceptibilities in the workplace might determine environmentally responsive genes, identify susceptible subpopulations or provide valuable input in setting occupational exposure limits [110]. HLA-DRB1*15:01-DQB1*06:02-DPB1*05:01 haplotype might be used as a genetic marker for TDI occupational asthma in Koreans via enhanced specific IgE sensitization in exposed subjects [111]. Studies should be focused on developing early diagnostic biomarkers by using a comprehensive approach based on the pathogenic mechanisms of isocyanate-induced occupational asthma. However, social and ethical implications of a genetic screening at the workplace should be taken into consideration.

5. Aspirin-sensitive asthma

The prevalence of aspirin sensitivity in the general population ranges from 0.6% to 2.5%, and is increased in asthmatics [112]. According to Specjalski et al. Aspirin-sensitive asthma (ASA) affects 10–20% of adults with asthma. This distinct clinical syndrome, is characterized by intolerance to ASA, bronchial asthma, and chronic rhinosinusitis with nasal polyposis [113]. Recently, Wenzel et al. suggested aspirin exacerbated disease as an endotype or even subendotype of adult eosinophilic group (severe asthma, later onset asthma) in whom sensitivity to non-steroidal anti-inflammatory drugs has been identified [5].

The diagnosis of this disorder is based only on provocation challenges with aspirin or NSAIDs as no in vitro test can be applied [113]. Pathophysiologically, increased cysteinyl leukotriene production and increased expression of leukotriene C4 synthase has been associated to ASA [114]. In addition, cysteinyl leukotriene receptor antagonists and leukotriene C4 synthase inhibitors have a beneficial effect on ASA symptoms [115].

The first reports which investigated the associations of HLA polymorphisms with ASA were reported on Caucasian population [116–118] (Table 3). One of the first studies was based on HLA class I typing and concluded the association of HLA-A1/B8 with severe polyp disease and asthma, which might imply that abnormalities of immune response are likely to be associated with the pathogenesis of both conditions [119].

Other studies showed association between aspirin-sensitive asthma and the HLA-region and were reported by Mullarkey et al., who found a significant increase in HLA-DQw2 in ASA-sensitive asthmatics, representing the involvement of HLA region in ASA [116]. However, Lympant et al. were unable to show significant association between aspirin sensitivity and HLA-DQw2. Nevertheless, they observed a significant decrease in the incidence of DPB1*04:01 in both aspirin-sensitive and aspirin-insensitive asthmatic subjects in the populations studied [117]. Furthermore, Dekker et al. [118] in a polish study reported that the

Table 3

Studies on HLA genes in aspirin sensitive asthma.

Authors [Ref nr]	Implicated allergens/ substances	HLA (haplotype, allele) susceptibility to asthma	HLA-(haplotype, allele) Protection against the disease-controls	Population-Country studied	Nr of pts
Mullarkey et al. [116]	Aspirin	HLA-DQw2	–	Caucasian	26
Dekker et al. [118]	Aspirin	No association	–	Poland	59
Moloney et al. [119]	Aspirin	HLA-AI/B8	–	Caucasian	29
Choi et al. [120]	Aspirin	HLA-DPB1*03:01	–	Korea	149
Park et al. [122]	Aspirin	HLA-DPB1	–	Korea	975
Kim et al. [123]	Aspirin	HLA-DRA	–	Korea	467

DPB1*03:01 frequency was increased in ASA patients, while DPB1*04:01 in ASA subjects was decreased when compared with normal controls. However, no significant HLA-DRB1 associations with ASA were found. The first study to strongly support HLA-DPB1*03:01 allele as an independent risk factor for the ASA development in an Asian population was reported by Choi et al. who also suggested that HLA-DRB1*09:01 haplotypes could be possibly involved in ASA [120].

In conclusion, in the two different ethnic populations reported, Caucasian and Asian population, a consistency of HLA-DPB1*03:01 as a positive risk factor was suggested, implying that genes controlling ASA susceptibility are closely related to the HLA-DPB1 locus. Moreover, Kim et al. investigated the association of TNF- α genetic polymorphism with HLA DPB1*03:01 in ASA and concluded that TNF- α promoter polymorphism might significantly increase susceptibility to ASA by gene-to-gene interaction with HLA DPB1*03:01 [121]. A recent GWAS applied in Korean asthmatics, revealed also that the HLA-DPB1 gene polymorphism might be the most susceptible genetic factor for the risk of ASA and confirmed the importance of HLA-DPB1 in the genetic etiology of ASA [122]. Finally, Kim et al. suggested that HLA-DRA polymorphisms might contribute to nasal polyposis susceptibility, one of the clinical manifestations of patients with ASA [123]. However, in another study HLA-DR typing of aspirin sensitive asthmatics showed no association with ASA [124]. Concerning contribution of HLA typing to ASA endotype, Palike et al. proposed that a potential genetic biomarker could be HLA-DPB1*03:01 [125], whereas Park et al. suggested that the same HLA locus might predict the requirement for leukotriene receptor antagonist treatment [126].

It is a fact that further studies with a larger sample size need to be performed for better understanding the association of these haplotypes with ASA and future research should focus on identification of biomarkers for a comprehensive diagnostic approach.

6. Conclusion

Despite the variation and the inconsistency of the HLA haplotypes and alleles in different types of asthma the association between HLA class II genes and asthma has been demonstrated in the majority of studies presented. This inconsistency may derive from the fact that potential risk factors are not adequately controlled in different study groups. Other issues are the often small sample size, the heterogeneity of human populations and of course the complexity of MHC. As population-based cohorts with simple asthma phenotypes/endotypes represent a valuable and largely untapped resource for genetic studies of asthma, more sophisticated analytical approaches are needed to study the expression of all genes combined with different exposure conditions for understanding this complex response, to unravel the nature and overall importance of gene–environment and gene–gene interactions in the development of asthma and allergic phenotypes/endotypes, disease progression and severity, and response to therapy.

7. Future perspectives

Although phenotyping was first defined by clinical characteristics as a result of the interaction of the patient's genes with the environment, large-scale studies are currently focused on molecularly understanding these phenotypes and more specifically endotypes to achieve more targeted and personalized approaches to asthma therapy. It is a fact that despite the effectiveness and safety of the current treatment of asthma including inhaled corticosteroids and long-acting inhaled $\beta(2)$ -agonists, a number of patients is still poorly controlled. Recently, on-going studies include the use of Th2 cell antagonists, humanized antibodies against IgE, interleukin 5, and interleukin 13, small interfering oligonucleotides, microRNAs, kinase inhibitors, and combination therapies [127]. However, except for kinase inhibitors which might have a major clinical impact, most of these new treatments target a single mediator or receptor, through the analysis of biomarkers and might be most effective in particular asthma phenotypes or endotypes. As current literature attempts to stratify patients by endotype, it is a challenge whether MHC typing could play important role in the future on therapeutic strategies in asthma as a biomarker. Several studies implicate T cell responses as a determinant of the clinical efficacy of allergen Specific Immuno-Therapy. As previously mentioned, CD4 T cells recognize a bimolecular complex of the specific epitopes bound to specific HLA class II molecules HLA DR, DP or DQ. Each of these loci is extremely polymorphic. The exact molecular structures (epitopes) recognized by T cells specific for common allergens have not been thoroughly mapped as the number of allergen epitopes is extremely large. This complexity must be taken into account in the design of a general strategy for identification and characterization of T cell epitopes in allergens [40]. Large panels of synthetic peptides were tested for binding to the various HLA class II molecules [128]. Peptide immunotherapy demonstrated an induction of functional allergen-specific regulatory T cells [129]. Treatment with selected epitopes from a single allergen resulted in suppression of responses to other (“linked”) epitopes within the same molecule. This phenomenon was induced after peptide immunotherapy in human asthmatic subjects and in a novel HLA-DR1 transgenic mouse model of asthma [36]. Peptide immunotherapy with CD4 T cell epitopes has been used extensively in mouse models to prevent and ameliorate antigen-specific inflammatory responses and is the subject of current clinical trials in allergy and autoimmunity [130]. It is a fact that HLA class II transgenic mice provide an excellent model for studying the genetic and molecular basis of allergic response and has been used as a tool in several reports [131][132]. Rajagopalan et al. demonstrated in a transgenic mouse model that HLA-DRB1*03:01 played an important role in mounting a Th2-predominant immune response to house dust mite and Th2-type inflammation in the lung [132]. The experiments on transgenic mice can contribute to overcome the heterogeneity of human population, the complexity of MHC, and the strong linkage

disequilibrium among different class II genes in studying the role of class II genes in vivo.

Additional studies on molecular medicine will probably shed more light in identifying reliable biomarkers concerning HLA region, to target phenotypes/endotypes with appropriate existing and novel specific therapies.

References

- [1] Arruda LK, Sole D, Baena-Cagnani CE, Naspitz CK. Risk factors for asthma and atopy. *Curr Opin Allergy Clin Immunol* 2005;5:153–9.
- [2] Kroegel C. Global initiative for asthma (GINA) guidelines: 15 years of application. *Exp Rev Clin Immunol* 2009;5:239–49.
- [3] Shiina T, Hosomichi K, Inoko H, Kulski JK. The HLA genomic loci map: expression, interaction, diversity and disease. *J Hum Genet* 2009;54:15–39.
- [4] Shiina T, Inoko H, Kulski JK. An update of the HLA genomic region, locus information and disease associations: 2004. *Tissue Antigens* 2004;64:631–49.
- [5] Wenzel S. Severe asthma: from characteristics to phenotypes to endotypes. *Clin Exp Allergy* 2012;42:650–8.
- [6] Green RH, Brightling CE, Bradding P. The reclassification of asthma based on subphenotypes. *Curr Opin Allergy Clin Immunol* 2007;7:43–50.
- [7] Lotvall J, Akdis CA, Bacharier LB, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011;127:355–60.
- [8] Deichmann KA, Starke B, Schlenker S, et al. Linkage and association studies of atopy and the chromosome 11q13 region. *J Med Genet* 1999;36:379–82.
- [9] Li X, Howard TD, Zheng SL, et al. Genome-wide association study of asthma identifies RAD50-IL13 and HLA-DR/DQ regions. *J Allergy Clin Immunol* 2010;125(328–35):e11.
- [10] Ramasamy A, Kuokkanen M, Vedantam S, et al. Genome-wide association studies of asthma in population-based cohorts confirm known and suggested loci and identify an additional association near HLA. *PLoS One* 2012;7:e44008.
- [11] Tamari M, Tanaka S, Hirota T. Genome-wide association studies of allergic diseases. *Allergol Int* 2013;62:21–8.
- [12] Song GG, Lee YH. Pathway analysis of genome-wide association study on asthma. *Hum Immunol* 2012.
- [13] A genome-wide search for asthma susceptibility loci in ethnically diverse populations. The collaborative study on the genetics of asthma (CSGA). *Nat Genet* 1997;15:389–92.
- [14] Moffatt MF, Gut IG, Demenais F, et al. A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med* 2010;363:1211–21.
- [15] Choo SY. The HLA system: genetics, immunology, clinical testing, and clinical implications. *Yonsei Med J* 2007;48:11–23.
- [16] Bruce CA, Bias WB, Norman PS, et al. Studies of HLA antigen frequencies, IgE levels, and specific allergic sensitivities in patients having ragweed hayfever, with and without asthma. *Clin Exp Immunol* 1976;25:67–72.
- [17] Brostoff J, Mowbray JF, Kapoor A, et al. 80% of patients with intrinsic asthma are homozygous for HLA W6. Is intrinsic asthma a recessive disease? *Lancet* 1976;2:872–3.
- [18] Morris MJ, Vaughan H, Lane DJ, Morris PJ. HLA in asthma. *Monogr Allergy* 1977;11:30–4.
- [19] Huang LS, Hsieh KH, Liu SY. HLA and childhood asthma (author's transl). *Zhonghua Min Guo Wei Sheng Wu Ji Mian Yi Xue Za Zhi* 1981;14:102–6.
- [20] Wang WX, Yang SZ, Chui XW, Zhang HL. Association of HLA-Bw61 with asthma in the Chinese. *Tissue Antigens* 1988;32:215–7.
- [21] Caraballo L, Marrugo J, Jimenez S, et al. Frequency of DPB1*0401 is significantly decreased in patients with allergic asthma in a mulatto population. *Hum Immunol* 1991;32:157–61.
- [22] Hsieh KH, Shieh CC, Hsieh RP, Liu WJ. Association of HLA-DQw2 with Chinese childhood asthma. *Tissue Antigens* 1991;38:181–2.
- [23] Taylor AN. Role of human leukocyte antigen phenotype and exposure in development of occupational asthma. *Curr Opin Allergy Clin Immunol* 2001;1:157–61.
- [24] Moffatt MF, Schou C, Faux JA, et al. Association between quantitative traits underlying asthma and the HLA-DRB1 locus in a family-based population sample. *Eur J Hum Genet* 2001;9:341–6.
- [25] Siroux V, Gonzalez JR, Bouzigon E, et al. Genetic heterogeneity of asthma phenotypes identified by a clustering approach. *Eur Respir J* 2014;43:439–52.
- [26] Li X, Ampleford EJ, Howard TD, et al. Genome-wide association studies of asthma indicate opposite immunopathogenesis direction from autoimmune diseases. *J Allergy Clin Immunol* 2012;130(861–8):e7.
- [27] Silverberg MS, Cho JH, Rioux JD, et al. Ulcerative colitis-risk loci on chromosomes 1p36 and 12q15 found by genome-wide association study. *Nat Genet* 2009;41:216–20.
- [28] Bonnelykke K, Matheson MC, Pers TH, et al. Meta-analysis of genome-wide association studies identifies ten loci influencing allergic sensitization. *Nat Genet* 2013;45:902–6.
- [29] White SR. Human leukocyte antigen-G: expression and function in airway allergic disease. *Clin Exp Allergy* 2012;42:208–17.
- [30] Muro M, Mondejar-Lopez P, Moya-Quiles MR, et al. HLA-DRB1 and HLA-DQB1 genes on susceptibility to and protection from allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. *Microbiol Immunol* 2013;57:193–7.
- [31] Schubert MS, Hutcheson PS, Graff RJ, et al. HLA-DQB1*03 in allergic fungal sinusitis and other chronic hypertrophic rhinosinusitis disorders. *J Allergy Clin Immunol* 2004;114:1376–83.
- [32] Mathias RA, Weinberg A, Boguniewicz M, et al. Atopic dermatitis complicated by eczema herpeticum is associated with HLA B7 and reduced interferon-gamma-producing CD8+ T cells. *Br J Dermatol* 2013;169:700–3.
- [33] Shawkatova I, Javor J, Parnicka Z, et al. HLA-C, DRB1 and DQB1 alleles involved in genetic predisposition to psoriasis vulgaris in the Slovak population. *Folia Microbiol* 2013;58:319–24.
- [34] Fleva A, Daniilidis M, Sidiropoulos J, et al. Can HLA typing predict the outcome of grass pollen immunotherapy? *Exp Clin Immunogenet* 2001;18:13–23.
- [35] Wang CM, Chuang JJ. Effect of mite allergen immunotherapy on the altered phenotype of dendritic cells in allergic asthmatic children. *Ann Allergy Asthma Immunol* 2013;110:107–12.
- [36] Campbell JD, Buckland KF, McMillan SJ, et al. Peptide immunotherapy in allergic asthma generates IL-10-dependent immunological tolerance associated with linked epitope suppression. *J Exp Med* 2009;206:1535–47.
- [37] Worm M, Lee HH, Kleine-Tebbe J, et al. Development and preliminary clinical evaluation of a peptide immunotherapy vaccine for cat allergy. *J Allergy Clin Immunol* 2011;127(89–97):e1–14.
- [38] Etto T, de Boer C, Prickett S, et al. Unique and cross-reactive T cell epitope peptides of the major Bahia grass pollen allergen, Pas n 1. *Int Arch Allergy Immunol* 2012;159:355–66.
- [39] Till SJ, Raynsford EJ, Reynolds CJ, et al. Peptide-induced immune regulation by a promiscuous and immunodominant CD4T-cell epitope of Timothy grass pollen: a role of Cbl-b and Itch in regulation. *Thorax* 2013.
- [40] Schulten V, Oseroff C, Alam R, et al. The identification of potentially pathogenic and therapeutic epitopes from common human allergens. *Ann Allergy Asthma Immunol* 2013;110:7–10.
- [41] Holt PG, Macaubas C, Stumbles PA, Sly PD. The role of allergy in the development of asthma. *Nature* 1999;402:B12–7.
- [42] Gilmour MI, Jaakkola MS, London SJ, et al. How exposure to environmental tobacco smoke, outdoor air pollutants, and increased pollen burdens influences the incidence of asthma. *Environ Health Perspect* 2006;114:627–33.
- [43] Bush RK. Indoor allergens, environmental avoidance, and allergic respiratory disease. *Allergy Asthma Proc* 2008;29:575–9.
- [44] Illi S, von Mutius E, Lau S, et al. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet* 2006;368:763–70.
- [45] Sporik R, Squillace SP, Ingram JM, et al. Mite, cat, and cockroach exposure, allergen sensitisation, and asthma in children: a case-control study of three schools. *Thorax* 1999;54:675–80.
- [46] Movahedi M, Moin M, Gharagozloo M, et al. Association of HLA class II alleles with childhood asthma and Total IgE levels. *Iran J Allergy Asthma Immunol* 2008;7:215–20.
- [47] Ostergaard PA, Eriksen J. Association between HLA-A1, B8 in children with extrinsic asthma and IgA deficiency. *Eur J Pediatr* 1979;131:263–70.
- [48] Morris MJ, Faux JA, Ting A, et al. HLA-A, B and C and HLA-DR antigens in intrinsic and allergic asthma. *Clin Allergy* 1980;10:173–9.
- [49] Turton CW, Morris L, Buckingham JA, et al. Histocompatibility antigens in asthma: population and family studies. *Thorax* 1979;34:670–6.
- [50] Flaherty DK, Geller M, Surfus JE, et al. HLA antigen frequencies and natural history in Alternaria-sensitive and perennial nonallergic asthmatics. *J Allergy Clin Immunol* 1980;66:408–16.
- [51] Nicolae D, Cox NJ, Lester LA, et al. Fine mapping and positional candidate studies identify HLA-G as an asthma susceptibility gene on chromosome 6p21. *Am J Hum Genet* 2005;76:349–57.
- [52] Rich SS. Results of genetic studies in man. *Clin Exp Allergy* 1995;95–6.
- [53] Marsh DG, Meyers DA, Bias WB. The epidemiology and genetics of atopic allergy. *N Engl J Med* 1981;305:1551–9.
- [54] Moffatt MF, Kabesch M, Liang L, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature* 2007;448:470–3.
- [55] Lasky-Su J, Himes BE, Raby BA, et al. HLA-DQ strikes again: Genome-wide association study further confirms HLA-DQ in the diagnosis of asthma among adults. *Clin Exp Allergy* 2012;42:1724–33.
- [56] Chung KF, Zhang J, Zhong N. Outdoor air pollution and respiratory health in Asia. *Respirology* 2011;16:1023–6.
- [57] Krstev S, Ji BT, Shu XO, et al. Occupation and adult-onset asthma among Chinese women in a population-based cohort. *Am J Ind Med* 2007;50:265–73.
- [58] Yue W, Pan XC, Ding J. Risk factors for allergic asthma in a case-control study among adults. *Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi* 2004;25:706–9.
- [59] Gao J, Lin YQiu C, et al. Relationship between HLA-DQA1, -DQB1 genes polymorphism and susceptibility to bronchial asthma among Northern Hans. *Zhonghua Yi Xue Za Zhi* 2002;82:379–83.
- [60] Gao J, Lin Y, Qiu C [HLA-DRB1 alleles polymorphism in susceptibility to asthma in Beijing Chinese]. *Zhonghua Yi Xue Za Zhi* 1998;78:591–4.
- [61] Wang C, Peng ZLi J, et al. Comparative study of HLA-DRB1 allele in patients with chronic bronchitis and bronchial asthma. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 1999;16:371–3.
- [62] Guo X, Ni P, Li L. Association between asthma and the polymorphism of HLA-DQ genes. *Zhonghua Jie He He Hu Xi Za Zhi* 2001;24:139–41.

- [63] Li PK, Lai CK, Poon AS, et al. Lack of association between HLA-DQ and -DR genotypes and asthma in southern Chinese patients. *Clin Exp Allergy* 1995;25:323–31.
- [64] Custovic A, Taggart SC, Francis HC, et al. Exposure to house dust mite allergens and the clinical activity of asthma. *J Allergy Clin Immunol* 1996;98:64–72.
- [65] Ohshima Y, Yamada A, Hiraoka M, et al. Early sensitization to house dust mite is a major risk factor for subsequent development of bronchial asthma in Japanese infants with atopic dermatitis: results of a 4-year followup study. *Ann Allergy Asthma Immunol* 2002;89:265–70.
- [66] Tovey ER, Almqvist C, Li Q, et al. Nonlinear relationship of mite allergen exposure to mite sensitization and asthma in a birth cohort. *J Allergy Clin Immunol* 2008;122:114–8 [e1–5].
- [67] Caraballo LR, Hernandez M. HLA haplotype segregation in families with allergic asthma. *Tissue Antigens* 1990;35:182–6.
- [68] Lara-Marquez ML, Yunis JJ, Layrisse Z, et al. Immunogenetics of atopic asthma: association of DRB1*1101 DQA1*0501 DQB1*0301 haplotype with *Dermatophagoides* spp.-sensitive asthma in a sample of the Venezuelan population. *Clin Exp Allergy* 1999;29:60–71.
- [69] Aron Y, Swierczewski E, Lockhart A. HLA class II haplotype in atopic asthmatic and non-atopic control subjects. *Clin Exp Allergy* 1995;25(Suppl. 2):65–7 [discussion 95–6].
- [70] Moffatt MF, Faux JA, Lester S, et al. Atopy, respiratory function and HLA-DR in Aboriginal Australians. *Hum Mol Genet* 2003;12:625–30.
- [71] Hizawa N, Collins G, Rafnar T, et al. Linkage analysis of *Dermatophagoides pteronyssinus*-specific IgE responsiveness with polymorphic markers on chromosome 6p21 (HLA-D region) in Caucasian families by the transmission/disequilibrium test. Collaborative Study on the Genetics of Asthma (CSGA). *J Allergy Clin Immunol* 1998;102:443–8.
- [72] Hizawa N, Freidhoff LR, Chiu YF, et al. Genetic regulation of *Dermatophagoides pteronyssinus*-specific IgE responsiveness: a genome-wide multipoint linkage analysis in families recruited through 2 asthmatic sibs. Collaborative Study on the Genetics of Asthma (CSGA). *J Allergy Clin Immunol* 1998;102:436–42.
- [73] Cho SH, Kim YK, Oh HB, et al. Association of HLA-DRB1(*07 and DRB1(*04 to citrus red mite (*Panonychus citri*) and house dust mite sensitive asthma. *Clin Exp Allergy* 2000;30:1568–75.
- [74] Howell WM, Strandberg P, Warner JA, Warner JO. HLA class II genotype, HLA-DR B cell surface expression and allergen specific IgE production in atopic and non-atopic members of asthmatic family pedigrees. *Clin Exp Allergy* 1999;29(Suppl. 4):35–8.
- [75] Moffatt MF, James A, Ryan G, et al. Extended tumour necrosis factor/HLA-DR haplotypes and asthma in an Australian population sample. *Thorax* 1999;54:757–61.
- [76] Lin YC, Lu CC, Su HJ, et al. The association between tumor necrosis factor, HLA-DR alleles, and IgE-mediated asthma in Taiwanese adolescents. *Allergy* 2002;57:831–4.
- [77] Torio A, Sanchez-Guerrero I, Muro M, et al. HLA class II genotypic frequencies in atopic asthma: association of DRB1*01-DQB1*0501 genotype with *Artemisia vulgaris* allergic asthma. *Hum Immunol* 2003;64:811–5.
- [78] Woszczek G, Kowalski ML, Borowiec M. Association of asthma and total IgE levels with human leukocyte antigen-DR in patients with grass allergy. *Eur Respir J* 2002;20:79–85.
- [79] Blumenthal M, Marcus-Bagley D, Awdeh Z, et al. HLA-DR2, [HLA-B7, SC31, DR2], and [HLA-B8, SC01, DR3] haplotypes distinguish subjects with asthma from those with rhinitis only in ragweed pollen allergy. *J Immunol* 1992;148:411–6.
- [80] Dzurilla M, Vrlík M, Homolova M, Buc M. No association between bronchial asthma and HLA-DRB1, -DQB1 alleles in the Slovak population. *Bratisl Lek Listy* 2013;114:93–5.
- [81] Young RP, Dekker JW, Wordsworth BP, et al. HLA-DR and HLA-DP genotypes and immunoglobulin E responses to common major allergens. *Clin Exp Allergy* 1994;24:431–9.
- [82] Torio A, Sanchez-Guerrero I, Muro M, et al. Analysis of the phenotypic distribution of HLA class I and class II in atopic and non-atopic asthma patients. *Eur J Immunogenet* 2000;27:81–5.
- [83] Kauppinen A, Perasaari J, Taivainen A, et al. Association of HLA class II alleles with sensitization to cow dander Bos d 2, an important occupational allergen. *Immunobiology* 2012;217:8–12.
- [84] Juhn YJ, Kita H, Lee LA, et al. Childhood asthma and human leukocyte antigen type. *Tissue Antigens* 2007;69:38–46.
- [85] Juhn YJ, Kita H, Bagniewski SM, et al. Severity of childhood asthma and human leukocyte antigens type. *J Asthma* 2007;44:163–8.
- [86] Martyn MB, Molis W, Jacobson RM, et al. Human leukocyte antigen type and progression from onset of symptoms to development of asthma. *Allergy Asthma Proc* 2010;31:120–5.
- [87] Hanchard NA, Jacobson RM, Poland GA, Juhn YJ. An assessment of the association between childhood asthma and HLA DRB1*03 using extended haplotype analysis. *Tissue Antigens* 2010;76:491–4.
- [88] Noguchi E, Sakamoto H, Hirota T, et al. Genome-wide association study identifies HLA-DP as a susceptibility gene for pediatric asthma in Asian populations. *PLoS Genet* 2011;7:e1002170.
- [89] Ivkovic-Jurekovic I, Zunec R, Balog V, Grubic Z. The distribution of HLA alleles among children with atopic asthma in Croatia. *Coll Antropol* 2011;35:1243–9.
- [90] Parapanissiou E, Papastavrou T, Deligiannidis A, et al. HLA antigens in Greek children with allergic bronchial asthma. *Tissue Antigens* 2005;65:481–4.
- [91] Munthe-Kaas MC, Carlsen KL, Carlsen KH, et al. HLA Dr-Dq haplotypes and the TNFA-308 polymorphism: associations with asthma and allergy. *Allergy* 2007;62:991–8.
- [92] Shreffler WG, Charlop-Powers Z, Sicherer SH. Lack of association of HLA class II alleles with peanut allergy. *Ann Allergy Asthma Immunol* 2006;96:865–9.
- [93] Knutsen AP, Vijay HM, Kumar V, et al. Mold-sensitivity in children with moderate-severe asthma is associated with HLA-DR and HLA-DQ. *Allergy* 2010;65:1367–75.
- [94] Knutsen AP, Vijay HM, Kariuki B, et al. Association of IL-4RA single nucleotide polymorphisms, HLA-DR and HLA-DQ in children with Alternaria-sensitive moderate-severe asthma. *Clin Mol Allergy* 2010;8:5.
- [95] Mapp CE, Boschetto P, Maestrelli P, Fabbri LM. Occupational asthma. *Am J Respir Crit Care Med* 2005;172:280–305.
- [96] Malo JL, Lemiere C, Gauthrin D, Labrecque M. Occupational asthma. *Curr Opin Pulm Med* 2004;10:57–61.
- [97] Taylor AJ. HLA phenotype and exposure in development of occupational asthma. *Ann Allergy Asthma Immunol* 2003;90:24–7.
- [98] Mapp CE, Beghe B, Balboni A, et al. Association between HLA genes and susceptibility to toluene diisocyanate-induced asthma. *Clin Exp Allergy* 2000;30:651–6.
- [99] Kim SH, Oh HB, Lee KW, et al. HLA DRB1*15-DPB1*05 haplotype: a susceptible gene marker for isocyanate-induced occupational asthma? *Allergy* 2006;61:891–4.
- [100] Choi JH, Lee KW, Kim CW, et al. The HLA DRB1*1501-DQB1*0602-DPB1*0501 haplotype is a risk factor for toluene diisocyanate-induced occupational asthma. *Int Arch Allergy Immunol* 2009;150:156–63.
- [101] Mapp CE. Occupational asthma: interactions between genetic factors and adverse environment? *Med Lav* 1994;85:187–92.
- [102] Fabbri LM, Mapp CE, Balboni A, Baricordi R. HLA class II molecules and asthma induced by toluene diisocyanate. *Int Arch Allergy Immunol* 1995;107:400–1.
- [103] Mapp CE, Balboni A, Baricordi R, Fabbri LM. Human leukocyte antigen associations in occupational asthma induced by isocyanates. *Am J Respir Crit Care Med* 1997;156:S139–43.
- [104] Balboni A, Baricordi OR, Fabbri LM, et al. Association between toluene diisocyanate-induced asthma and DQB1 markers: a possible role for aspartic acid at position 57. *Eur Respir J* 1996;9:207–10.
- [105] Bignon JS, Aron Y, Ju LY, et al. HLA class II alleles in isocyanate-induced asthma. *Am J Respir Crit Care Med* 1994;149:71–5.
- [106] Rihs HP, Barbalho-Krols T, Huber H, Baur X. No evidence for the influence of HLA class II in alleles in isocyanate-induced asthma. *Am J Ind Med* 1997;32:522–7.
- [107] Bernstein JA, Munson J, Lummus ZL, et al. T-cell receptor V beta gene segment expression in diisocyanate-induced occupational asthma. *J Allergy Clin Immunol* 1997;99:245–50.
- [108] Beghe B, Padoan M, Moss CT, et al. Lack of association of HLA class I genes and TNF alpha-308 polymorphism in toluene diisocyanate-induced asthma. *Allergy* 2004;59:61–4.
- [109] Horne C, Quintana PJ, Keown PA, et al. Distribution of DRB1 and DQB1 HLA class II alleles in occupational asthma due to western red cedar. *Eur Respir J* 2000;15:911–4.
- [110] Christiani DC, Mehta AJ, Yu CL. Genetic susceptibility to occupational exposures. *Occup Environ Med* 2008;65:430–6 [quiz 6, 397].
- [111] Palikhe NS, Kim JH, Park HS. Biomarkers predicting isocyanate-induced asthma. *Allergy Asthma Immunol Res* 2011;3:21–6.
- [112] Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *Int J Epidemiol* 1999;28:717–22.
- [113] Specjalski K, Chelminska M. Pathogenesis of aspirin-induced asthma. *Pol Arch Med Wewn* 2006;115:265–70.
- [114] Cowburn AS, Sladek K, Soja J, et al. Overexpression of leukotriene C4 synthase in bronchial biopsies from patients with aspirin-intolerant asthma. *J Clin Invest* 1998;101:834–46.
- [115] Dahlen B, Nizankowska E, Szczeklik A, et al. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am J Respir Crit Care Med* 1998;157:1187–94.
- [116] Mullarkey MF, Thomas PS, Hansen JA, et al. Association of aspirin-sensitive asthma with HLA-DQw2. *Am Rev Respir Dis* 1986;133:261–3.
- [117] Lympay PA, Welsh KI, Christie PE, et al. An analysis with sequence-specific oligonucleotide probes of the association between aspirin-induced asthma and antigens of the HLA system. *J Allergy Clin Immunol* 1993;92:114–23.
- [118] Dekker JW, Nizankowska E, Schmitz-Schumann M, et al. Aspirin-induced asthma and HLA-DRB1 and HLA-DPB1 genotypes. *Clin Exp Allergy* 1997;27:574–7.
- [119] Moloney JR, Oliver RT. HLA antigens, nasal polyps and asthma. *Clin Otolaryngol Allied Sci* 1980;5:183–9.
- [120] Choi JH, Lee KW, Oh HB, et al. HLA association in aspirin-intolerant asthma: DPB1*0301 as a strong marker in a Korean population. *J Allergy Clin Immunol* 2004;113:562–4.
- [121] Kim SH, Ye YM, Lee SK, et al. Association of TNF-alpha genetic polymorphism with HLA DPB1*0301. *Clin Exp Allergy* 2006;36:1247–53.
- [122] Park BL, Kim JW, Cheong HS, et al. Extended genetic effects of ADH cluster genes on the risk of alcohol dependence: from GWAS to replication. *Hum Genet* 2013;132:657–68.

- [123] Kim JH, Park BL, Cheong HS, et al. HLA-DRA polymorphisms associated with risk of nasal polyposis in asthmatic patients. *Am J Rhinol Allergy* 2012;26:12–7.
- [124] Jones DH, May AG, Condemi JJ. HLA DR typing of aspirin sensitive asthmatics. *Ann Allergy* 1984;52:87–9.
- [125] Palikhe NS, Kim JH, Park HS. Update on recent advances in the management of aspirin exacerbated respiratory disease. *Yonsei Med J* 2009;50:744–50.
- [126] Park HS, Kim SH, Sampson AP, et al. The HLA-DPB1*0301 marker might predict the requirement for leukotriene receptor antagonist in patients with aspirin-intolerant asthma. *J Allergy Clin Immunol* 2004;114:688–9.
- [127] Hansbro PM, Scott GV, Essilfie AT, et al. Th2 cytokine antagonists: potential treatments for severe asthma. *Expert Opin Investig Drugs* 2013;22:49–69.
- [128] Wang P, Sidney J, Kim Y, et al. Peptide binding predictions for HLA DR, DP and DQ molecules. *BMC Bioinform* 2010;11:568.
- [129] Verhoef A, Alexander C, Kay AB, Larche M. T cell epitope immunotherapy induces a CD4+ T cell population with regulatory activity. *PLoS Med* 2005;2:e78.
- [130] Larche M, Wraith DC. Peptide-based therapeutic vaccines for allergic and autoimmune diseases. *Nat Med* 2005;11:S69–76.
- [131] Papouchado BG, Chapoval SP, Marietta EV, et al. HLA-DQ/human CD4-restricted immune response to cockroach allergens in transgenic mice. *Tissue Antigens* 2000;55:303–11.
- [132] Rajagopalan G, Tilahun AY, Iijima K, et al. HLA-DR polymorphism modulates response to house dust mites in a transgenic mouse model of airway inflammation. *Tissue Antigens* 2011;77:589–92.