

10 Mite Allergens

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INTRODUCTION

From the early 1960s, considerable literature has been published concerning the taxonomy, biology, immunochemistry, and control of mites implicated in allergic reactions. Numerous species have been described as the source of allergens capable of sensitizing and inducing allergic symptoms in sensitized and genetically predisposed individuals. Allergic diseases triggered by mite allergens include allergic rhinoconjunctivitis, asthma, atopic dermatitis, and other skin diseases. The most studied species, because of their abundance and allergenic importance, belong to the family Pyroglyphidae, especially *Dermatophagoides pteronyssinus*, *D. farinae*, and *Euroglyphus maynei*. These mites are called house-dust mites. House-dust mites are commonly present in human dwellings and are especially abundant in mattresses, sofas, carpets, and blankets. Other species, such as *D. microceras*, *D. siboney*, and *Gymnoglyphus longior*, and other genera, such as *Hirstia* and *Malayoglyphus*, are also considered allergenic, although their study is limited.

Numerous mite allergens have been purified, sequenced, and cloned. An important group of mites, referred to as "storage mites," comprises mainly members of the Acaridae and Glycyphagidae families that live in stored food and grains. All mite species present in the home environment and capable of inducing IgE-mediated sensitization are currently called "domestic mites" (1). Approximately 150 storage mite species are known (2); approximately 20 can be considered to be important from an economic and sanitary perspective. The most studied species are *Blomia tropicalis*, because of its abundance in tropical and subtropical regions of the world (3), and *Lepidoglyphus destructor*, because of its frequent presence in barns. Storage mite species can be present in kitchen floor dust, cupboards, and pantries. In humid homes, storage mites can also be found in mattress dust. They can be an important plague with economical consequences and cause occupational respiratory allergies in farmers and other occupationally exposed individuals. The most important genera are *Lepidoglyphus* (family Glycyphagidae), *Glycyphagus* (family Glycyphagidae), *Acarus* (family Acaridae), *Tyrophagus* (family Acaridae), *Aleuroglyphus* (family Acaridae), *Suidasia* (family Suidasidae), *Chortoglyphus* (family Chortoglyphidae), and *Cheyletus* (family Cheyletidae).

ALLERGENS FROM HOUSE-DUST MITES

The main source of allergens in house dust in the United States are the mite species *D. pteronyssinus*, *D. farinae*, *E. maynei*, and *B. tropicalis* (4). Most ecological studies in temperate climates have demonstrated that *D. pteronyssinus* (originally known as the European house-dust mite) and *D. farinae* (American house-dust mite) are the predominant house-dust mites worldwide. In tropical and subtropical areas of the world, *B. tropicalis* occurs with a very high frequency and, in some regions, it is present at a similar rate as *D. pteronyssinus* (5).

Mite allergens are capable of inducing an IgE-mediated immune response. These allergens can be extracted and isolated by conventional biochemical methods, molecular

cloning, or by using proteomic approaches. Mite allergens are present in mite bodies, secreted, and excreted. Fecal particles contain a great proportion of mite allergen (6). Mite allergens can be detected in many areas of the home, including beds, carpets, upholstered furniture, and clothing. Leather-covered couches, wood furniture, and bare floors contain fewer mites than the above-mentioned locations. Beds are the ideal habitat for mites, since they provide the ideal temperature, food and moisture for their proliferation, and allergens they produce accumulate deep inside old mattresses and pillows. They can also be detected airborne. Studies using volumetric samples equipped with sizing devices have shown that mite allergens remain airborne for a short period of time. Allergenic activity has been detected in particles smaller than 1 μm and in particles larger than 10 μm . Mite allergens settle more rapidly than cat allergens, which remain airborne for longer periods of time and can be detected in air samples collected in homes under disturbed and undisturbed conditions. Mite fecal pellets may occasionally enter the lung and cause inflammation and bronchoconstriction. Fergusson and Brodie (7) demonstrated the presence of Der p 1 in bronchial alveolar lavage fluids of asthmatic children after an overnight exposure to 13.4 and 27.3 μg of Der p 1 in carpets and mattresses, respectively. Exposure to 2 μg of Der p 1 and/or Der f 1/g of dust is considered a risk factor for sensitization; exposure to 10 $\mu\text{g}/\text{g}$ of dust is considered a major risk factor for sensitization and asthma in genetically predisposed individuals. Allergen levels in excess of 10 $\mu\text{g}/\text{g}$ of dust have been identified in many parts of the world, and there seems to be no difference between mite allergens levels in homes of mite-allergic asthmatic and nonallergic control individuals (1).

CHARACTERIZED HOUSE-DUST MITE ALLERGENS

Most of the isolated allergens have been placed in groups on the basis of their chronological characterization and/or homology with previously purified *Dermatophagoides* spp. allergens (Table 1). Purified allergens are named according to the first three letters of the genus, the first letter of the species and a number indicating the group in which they are placed. Thus, the first identified allergen of *D. pteronyssinus* was named Der p 1 and belongs to group 1.

Table 1 Biological Function, Molecular Weight and Prevalence of Specific IgE Binding of Several Mite Allergens

Group	Biological function	Molecular weight (kDa)	Mite species	% IgE binding
1	Cystein protease	25	Bt, Dp, Df, Dm, Em	80–100
2	Cholesterol-binding proteins	14	Bt, Dp, Df, Ds, Em, Ld, Tp, Gd, As	80–100
3	Tripsina	25 to 30	Bt, Dp, Df, Ds, Em	16–100
4	α -Amylase	57	Bt, Dp, Dm, Em	40–46
5	Unknown	15	Bt, Dp, Ld	50–70
6	Chymotrypsin	25	Bt, Dp, Df	40
7	Unknown	25,31,29,26	Dp, Df, Ld	50
8	Glutathion-S-transferase	26	Dp	40
9	Collagenolytic serin protease	30	Dp	90
10	Tropomyosin	37	Bt, Dp, Df, Ld	50–95
11	Paramyosin	96,92,98	Bt, Dp, Df	80
12	Unknown	14	Bt	50
13	Fatty acid-binding proteins	15	Bt, Df, Ld, Tp	10–23
14	Vitellogenin	117	Df, Dp, Em	90
15	Chitinase	62.5,98,105	Df	70
16	Gelsolin	55	Df	35
17	Calcium-binding proteins	33	Df	35
18	Chitinase	60	Df	60
19	Antimicrobial peptide	7	Bt	10
20	Argininquinase		Dp	
21	Unknown	13.2	Dp, Bt	
22	Unknown		Dp	

Abbreviations: As, *Acarus siro*; Bt, *B. Tropicalis*; Df, *Dermatophagoides farinae*; Dm, *Dermatophagoides microceras*; Dp, *Dermatophagoides pteronyssinus*; Em, *Euroglyphus mayne*; Gd, *Glycyphagus domesticus*; Ld, *L. Destructor*; Tp, *T. Putrescentiae*.

Source: <http://www.allergen.org/Allergen.aspx>.

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Group 1: Der p 1 and Der f 1, and group 2 (Der p 2 and Der f 2) are considered major allergens on the basis of the frequency of patients sensitized, amount of specific IgE, and content in mite extract. Der p 1 is a glycoprotein with sequence homology and thiol protease functions similar to the enzymes papain, actinidin, bromelain and cathepsins B and H (8). Der p 1 and Der f 1 are synthesized as proenzymes and removal of the propiece is necessary to unmask their proteolytic activity. A study suggests that group 1 mite allergens are a new subgroup among C1 family cysteine peptidases, and that the rapid inactivation of Der p 1 prodomain is a newly identified mechanism that may contribute to the potency of this allergen (9). Several mechanisms have been demonstrated to be involved in the hyperresponsiveness and airway inflammation associated with this allergen; Der p 1 upregulates the IgE synthesis by cleaving the low-affinity IgE receptor (CD23) from the surface of human B-cell lymphocytes (10). Der p 1 cleaves the α subunit of the IL-2 receptor (IL-2R or CD25) from the surface of human peripheral blood T cells and, as a result, these cells show markedly diminished proliferation and interferon γ secretion, which consequently shifts the immune response toward Th2 cells. The cysteine protease activity of Der p 1 seems to selectively enhance the IgE response, and the proteolytic activity of Der p 1 conditions T cells to produce more IL-4 and less IFN-gamma (11,12). The enzymatic activity for Der p 1, and other mite allergens, may also contribute to their immunogenicity by increasing mucosal permeability. The peptidase activity creates conditions that favor delivery of any allergen to antigen-presenting cells by a process that involves cleavage of tight junctions that regulate paracellular permeability (13). Studies using A549 epithelial cells demonstrate that Der p 1 produces both damage and activation of airway epithelial cells. Der p 1 activates the release of cytokines from this cell line in a protease-activated receptor (PAR)-independent manner, in agreement with another study, which shows that Der p 3, but not Der p 1, activates the PAR2 signaling cascade (14). Conflicting reports have emerged in the literature regarding Der p 1 and PAR activation (15,16). A functional PAR2 has been demonstrated on A549 cells by a specific PAR2 agonists, which induces the production of IL-6 and IL-8. However, the mouse fibroblasts expressing the human PAR1, PAR2, or PAR4 demonstrate that Der p 1 does not affect intracellular calcium mobilization in these cells, providing evidence against a PAR-mediated mechanism. Der p 1 and Der f 1 cleave the lung surfactant protein A (SP-A) and the lung surfactant protein D (SP-D), lung collectins, which have protective roles in allergy, in a time- and concentration-dependent manner at multiple sites. Cleavage of these collectins abrogates their lectin activity and lectin-associated functions such as bacterial agglutination and allergen binding. The cleavage and consequent inactivation of SP-A and SP-D may be a novel mechanism to account for the potent allergenicity of Der p 1 and Der f 1 (17). Work in mice suggests that the cysteine protease activity of Der p 1 crucially contributes to in vivo immune responses, including the production of not only IgE but also IgGs. In this study, intranasal administration of proteolytically active Der p 1 to sensitized mice leads to enhanced inflammatory cellular infiltration of the lungs and systemic production of IgE, in comparison to inactive Der p 1, which has no effect (18).

Eur m 1 is an important allergen of *E. mainey* and has an amino acid (aa) sequence homology of approximately 85% with Der p 1 and Der f 1 (19). Der s 1, a major allergen of *D. siboney*, purified using cross-reacting monoclonal antibodies directed against group 1 allergen from *Dermatophagoides* spp., has an 89% frequency of specific IgE binding (20).

Because of its high prevalence in house dust, and worldwide distribution, the group 1 allergen is used as a standard to estimate environmental exposure to *Dermatophagoides* spp. in the indoor environment.

Group 2: Der p 2 and Der f 2 are heat- and pH-stable proteins of 14 kDa (21,22). These allergens have 88% sequence similarity. In their native stage and, expressed as a fusion protein, both have an 83% frequency of specific IgE recognition (23). The aa sequences of Der p 2 and Lep d 2 have 28% and 26.4% similarity, respectively, with the human epididymis 1 (HE1) gene product. These proteins seem to arise from secretions of the male mite reproductive tract (24). Der p 2 and Der f 2 show a significant degree of sequence polymorphism. The polymorphic residues are also found in regions containing T-cell epitopes (25). Crystallographic studies suggest that Der p 2 is a lipid-binding protein (26). The existence of Eur m 2 in *E. maynei* has also been demonstrated (27).

The aa sequence of Der f 2 is homologous to other group 2 allergens from different mite species and the Niemann-Pick type C2 disease protein (NPC2/ HE1) with cholesterol-binding activity. The structural relationship between Der f 2 and the myeloid differentiation type 2

molecule (MD2), which associates with Toll-like receptor 4 on the cell surface and is part of the mammalian innate immune system involved in the recognition of lipopolysaccharide from gram-negative bacteria, was indicated by sequence homology search at <http://expasy.org/tools/blast> (28).

In Central Europe, more than 95% of mite-allergic patients are sensitized to Der p 1 and Der p 2. Diagnostic tests containing these allergens plus the highly cross-reactive allergen, Der p 10, may improve the diagnostic selection of patients for immunotherapy with *D. pteronyssinus* extracts (29). Suzuki M et al. demonstrated that the conformation of Der f 2 was critical in the determination of Th1/Th2 shift on the basis of physicochemical and immunological analyses (30). This study suggests that the rigidly folded and singly dispersed structure is required for the generation of Th2 type cells by the allergen, while conformational variant protein leads to Th1 skewing, irrespective of the same aa sequence.

Groups 3 and 4: Group 3 has a trypsin-like serine protease activity and 50% sequence similarity with other serine proteases, including chymotrypsin (31). The sequence of Der p 3 has 81% sequence identity with Der f 3 and both have a 41% sequence identity with bovine trypsin. A frequency of IgE binding between 51% and 90% for Der p 3 and between 42% and 70% for Der f 3 has been described (32). Der p 4 is an enzyme similar to carbonic anhydrases, which shows significant homology with mammalian α -amylase (33). It is recognized as an allergen by 25% to 46% of mite-allergic individuals.

Group 5: Der p 5 is a 15 kDa allergen, which has an estimated IgE binding prevalence of 50% (34). Studies with epithelial cells demonstrate that Der p 5 also induces the secretion of IL-6 and IL-8, even to a higher extent than Der p 1. This effect of Der p 5 is dose-dependent, not blocked by protease inhibitors, and is specific.

Groups 6 and 7: Der p 6 is a chymotrypsin-like serine protease, which shows a 40% to 60% frequency of IgE binding. It has 37% similarity with Der p 3 (35). Der p 7 and Der f 7 have 86% of similarity in aa sequences. Recombinant Der f 7 reacts with 46% of sera from asthmatic children (36). The allergenicity of r Der p 7 is demonstrated by direct specific IgE binding and skin testing; about 50% of mite-allergic individuals analyzed are sensitized to this allergen (37).

Groups 8 and 9: Der p 8 is a 26 kDa allergen with strong homology with rat and mouse glutathione-S-transferase (GST). Approximately 40% of mite-allergic subjects tested with recombinant Der p 8 bind specific IgE to this allergen (38). At least eight isoforms of native Der p 8 were detected by two-dimensional gel and immunoblot analyses. Sera from Taiwanese asthmatics show 96% and 84% IgE reactivity to native Der p 8 and recombinant Der p 8, respectively. Native Der p 8 shows 75% and 65% IgE reactivity with sera from Malaysia and Singapore, respectively. Native Der p 8 exists in multiple isoforms and inclusion of these isoforms for diagnostic and therapeutic purposes may be necessary. The presence of cross-reactive IgE between Der p 8 and GST in *Periplaneta americana* cockroach suggests that GST in mites and cockroach may be considered a pan-allergen (39).

Der p 9 is a 24 kDa protein, as indicated by mass spectroscopy, with collagenolytic serine protease activity and a frequency of IgE reactivity higher than 80% (40).

Groups 10 and 11: These groups are comprised of tropomyosin and paramyosin, respectively. They are involved in muscle contraction in invertebrates and are present in low concentrations in mite extracts. The invertebrate tropomyosins are allergenic in man with high IgE cross-reactivity and therefore, have been referred to as pan-allergens. Der f 10 is a 32 kDa allergen with significant homology with tropomyosins from different species (41). Der p 10 may be involved in the cross-reactivity process between mites, shrimp, and insects in shrimp-allergic patients (42,43). Allergic cross-reactivity has been reported between Der p 10 and Blo t 10. Although Blo t 10 and Der p 10 are highly conserved and significantly cross-reactive, unique IgE epitopes do exist (44).

Der f 11 has 34% to 60% sequence identity with other known paramyosins (45); 62% of mite-sensitive asthmatic patients react when skin tested with recombinant Der f 11 and 50% have a positive specific IgE determination to Der f 11 (46). rDer p 11 has a frequency of specific IgE binding in the sera of allergic patients of 60%, suggesting that Der p 11 is also an important allergen (47). The aa sequence of Der p 11 shares over 89% identity with aa sequence of Der f 11 and Blo t 11 (48).

Group 12: Group 12 has only been described by cDNA cloning from *B. tropicalis* Blo t 12 having a mature sequence of 14 kDa, which binds specific IgE with a 50% frequency and does

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not show homology with other known proteins (49). The aa sequence of Blo t 12 had no significant homology with known proteins. However, a limited homology with the C-terminal region of the putative chitinase allergen from *D. farinae* was observed. Recombinant Blo t 12 has been expressed in both *Escherichia coli* and *Pichia pastoris* expression systems (50). An isoform of Blo t 12 was isolated by molecular cloning and showed 14.4% specific IgE reactivity in the sera of allergic subjects from Singapore (51).

The IgE reactivity of this isoform has been tested in Colombian mite-allergic patients and shows 23.4% and 17% reactivity by ELISA and skin prick tests (SPT), respectively (52).

Groups 13 and 14: The group 13 allergen belongs to the family of fatty acid-binding proteins (FABPs) and has been cloned and characterized from a number of mites of clinical importance (53). Der f 13 shares a medium to high sequence homology with human FABPs, with the closest one being human brain FABP, having 39.1% aa identity and 58.6% similarity. A solution structure study reveals that Der f 13 adopts the typical β barrel fold of FABPs, which is very similar to that of other human FABPs (54). ELISA inhibition assays with monoclonal antibody specific for Blo t 13 suggest that the homologous allergen Der s 13 is also present in *D. sibirica* (55).

Eleven percent of patients with asthma in Colombia show IgE reactivity to Blo t 13. In the mite-allergic population from Cuba, the frequency of IgE reactivity to this allergen is 53% (56). Blo t 13 has approximately 35.3% sequence identity with FABPs of human, bovine, mouse, and rat (57). Tyr p 13 was isolated from a cDNA library of the mite *Tyrophagus putrescentiae*, showing 62.3% of identity in the aa sequence with Blo t 13. The recombinant allergen showed 6.4% of reactivity in allergic individuals from Korea (58). In the sheep scab mite, *Psoroptes ovis*, a genomic sequence encoding for a FABP with 55% similarity with Blo t 13 has been identified (59).

Group 14 is an apolipoprotein-like lipid transport protein, isolated by molecular cloning from *Dermatophagoides* spp. (60,61).

Group 15: Der f 15 is homologous to insect chitinases. It is a major allergen recognized by dogs and cats and by the sera of approximately 70% of mite-allergic humans (62). McCall et al. isolated a pair of natural Der f 15 proteins with apparent molecular weight masses of 98 and 109 kDa. The proteins were heavily O-glycosylated leading to the discrepancy between the calculated (61.2 kDa) and apparent molecular mass. It was concluded that the 98 and 109 kDa proteins reflected glycosylation variants of the same protein.

Two variants of Der p 15 have been isolated, encoding mature proteins of 58.8 and 61.4 kDa. Their aa sequences had 90% identity with Der f 15. Der p 15-specific IgE was detected in 70% of a panel of 27 human allergic sera (63). They are, therefore, potentially important allergens for humans as well as dogs.

Groups 16 and 17: Der f 16 polypeptide sequence has similarity to gelsolin, a Ca^{2+} - and polyphosphoinositide 4,5-bisphosphate (PIP2)-regulated actin filament severing and capping protein. In allergic individuals, IgE reactivity by skin and serological tests are between 62% and 50%, respectively (64). Der f 17 is a calcium-binding protein, which binds IgE in 35% of the sera from mite-allergic patients (65).

Group 18: Der f 18 is a 60,000 kDa molecular weight chitinase, which is a strong allergen for dogs and also reacts with 60% of mite-allergic humans (66). The cDNA for Der p 18 encodes a mature protein of 49.2 kDa with 88% sequence identity to Der f 18. Specific IgE to this allergen has been reported in 63% of a panel of 27 human allergic sera (67).

Groups 19 and 20: The allergen list from International Union of Immunological Societies Allergen Nomenclature Sub-Committee (<http://www.allergen.org/Allergen/>, updated 09/Jan/2008) shows that recombinant Blo t 19, under the biochemical name of antimicrobial peptide homologue, binds IgE in 10% of mite-allergic subjects. Der p 20 and Der f 20 are mite arginine kinase. Its sequence is highly conserved amongst invertebrates, showing 80% identity to crustaceans and 75% to insects compared with 45% for mammalian enzymes (68). Recombinant Der p 20 tested in allergic children showed a prevalence of specific IgE reactivity between 44.2% and 12.2%, with IgE levels lower than those obtained for Der p 1, Der 2, Der p 3, Der p 4, Der p 5, Der p 6, and Der p 7 (69).

Group 21: A novel allergen from *B. tropicalis*, Blo t 21, has been described. It is a 129-aa protein with an alpha-helical secondary structure and localizes to midgut and hindgut contents of *B. tropicalis*, as well as fecal particles. The gene encoding this novel antigen could be a duplicate (paralogous gene) of the Blo t 5 gene in the *B. tropicalis* genome. Blo t 21 shares 41%

and 39% aa identity with Der p 21 (UniProtKD/TrEMBL Q2L7C5) and Blo t 5, respectively. Blo t 21 shares some primary and secondary structural similarities with Blo t 5. However, there seems to be little cross-reactivity between these allergens. Positive responses to Blo t 21 were shown in 93% by means of ELISA and 95% by means of skin prick testing when assayed in 43 adult patients with allergic rhinitis (70).

Group 22: A sequence of 155 aa and 16,896 Da has been registered in GenBank (<http://www.ncbi.nlm.nih.gov>) and termed Der f 22.

ALLERGENS FROM STORAGE MITES

Several storage mite allergens have been purified, cloned, and sequenced (71). Some of these allergens can be considered as pan-allergens. The allergenicity of *B. tropicalis*, *L. destructor*, *Glycyphagus domesticus*, *T. putrescentiae*, *Acarus siro*, *Aleuroglyphus ovatus*, *Suidasia medanensis*, and *Thyreophagus entomophagus* has been demonstrated. Table 2 shows a list of the main families and species of storage mite that have been described as allergenic (72). Several allergens from these species have been purified, sequenced, and cloned. Some of these allergens have shown sequence homology and biological function similar to those previously described in *Dermatophagoides* spp. The main allergens described in storage mites include FABP, tropomyosin, and paramyosin homologues, apolipophorine-like proteins, alfa-tubulines, and other, such as group 2, 5, and 7 allergens. The allergenicity of other species such as *A. farris*, *Austroglyphus malaysiensis*, *B. kulagini*, *B. tjibodas*, *Cheyletus eruditus*, *Chortoglyphus arcuatus*, *Gohieria fusca*, *Th. entomophagus* and *T. longior* has been investigated (Table 2).

Allergens from *Blomia tropicalis*

Several allergens of *B. tropicalis* are cloned and sequenced (73–80). Allergen sequence identity between *B. tropicalis* and *D. pteronyssinus* or *D. farinae* mite allergens ranges from moderate (30–45%) to high (50–70%) and to highly conserved (80–95%).

B. tropicalis allergens show variable degrees of sequence homology with purified allergens of *D. pteronyssinus*, such as Blo t 5, a homologue of Der p 5; Blo t 13, with homology to FABPs; Blo t 11, a homologue of paramyosin; Blo t 10, a homologue of tropomyosin and Der p 10; Blo t 3, a trypsin-like protease; Blo t 4, homologous to Der p 4 (amylase); and Blo t 1, homologous to Der p 1, a cysteine protease. Blo t 1, with an estimated molecular weight of

Table 2 Main Families and Species of Storage Mite That Have Been Described as Allergenic

Family	Species
Glycyphagidae	<i>Glycyphagus domesticus</i>
	<i>G. privatus</i>
	<i>Gohieria fusca</i>
	<i>Lepidoglyphus destructor</i>
Echimyopodidae	<i>Blomia tropicalis</i>
	<i>B. kulagini</i>
	<i>B. tjibodas</i>
Chortoglyphidae	<i>Chortoglyphus arcuatus</i>
Ebertiidae	<i>Suidasia medanensis</i>
Acaridae	<i>Tyrophagus putrescentiae</i>
	<i>T. longior</i>
	<i>Acarus siro</i>
	<i>A. farris</i>
	<i>Thyreophagus entomophagus</i>
	<i>Aleuroglyphus ovatus</i>
Cheyletidae	<i>Cheyletus eruditus</i>
	<i>Ch. tenuipilis</i>
	<i>Ch. malaccensis</i>

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26 kDa, is an important allergen. Recombinant Blo t 1 reacted positively with IgE in 90% and 65% of sera from asthmatic children and adults from Singapore, respectively. Furthermore, there is a low correlation between IgE reactivity to Blo t 1 and Der p 1 (81).

Several studies have focused on the in vitro cross-reactivity of purified Blo t 5 and Der p 5 (82,83) and Blo t 10 and Der p 10 (tropomyosin). Most group 5 studies demonstrate low to moderate cross-reactivity at the molecular level. Yi et al. demonstrated that Blo t 10 and Der p 10 are highly conserved molecules, sharing 95% aa identity, and that they are cross-reactive allergens, although unique IgE epitopes do exist (84). Blo t 5 is recognized by 60% to 70% of *B. tropicalis*-sensitive patients, especially those residing in tropical areas (75,85).

Unlike *D. pteronyssinus*, where the group 1 and 2 allergens are the major allergens, the group 5 allergen of the *B. tropicalis*, Blo t 5, is the dominant major allergen (86). The recombinant Blo t 5 shows up to 70% of IgE reactivity in sensitized asthmatic patients, whereas the homologous Der p 5 reacts with 40% to 50% of sera from mite-allergic asthmatic individuals (87). Despite the sequence homology between the group 5 allergens, the IgE cross-reactivity of the major allergen Blo t 5 and the minor allergen Der p 5 is surprisingly low (88). The three-dimensional structure of Blo t 5 is a triple-helical bundle fold not described previously in other identified major allergens (89). Therefore, the molecular function of group 5 allergen remains unknown.

In vivo studies using inhalation tests to investigate the clinical significance of sensitivity to *B. tropicalis* and its cross-reactivity with *D. pteronyssinus* are scarce. Stanaland et al. (90) demonstrated that 83% of *B. tropicalis*-sensitive patients in Florida had a positive nasal challenge with a *B. tropicalis* extract. Therefore, a positive skin test to *B. tropicalis* is a good indicator of possible allergic symptoms after inhalation of *B. tropicalis* allergens. Other studies in Brazil and Singapore have demonstrated the allergenicity of *B. tropicalis*, in vivo, also using nasal challenges (91,92). In Brazil, a group of *D. pteronyssinus*- and *B. tropicalis*-sensitive patients was evaluated; 90% of the patients had a positive nasal challenge to *D. pteronyssinus* and 60% to *B. tropicalis*. The study conducted in Singapore included 20 adults with persistent allergic rhinitis, five of whom had a history of asthma. Significant increases in subjective and objective nasal symptoms, together with a significant increase of tryptase and LTC4 concentrations in nasal secretion, were found in all patients after each challenge with *B. tropicalis*. A study conducted by García Robaina et al. (93) demonstrated that patients who are sensitized to two mite species (*D. pteronyssinus* and *B. tropicalis*) may only react to one of them. This had been previously suggested for even more closely related species such as *D. pteronyssinus* and *D. farinae* (94). In some cases, it may, therefore, be necessary to conduct challenge tests to better define the relevant allergen from a clinical point of view and to start the appropriate specific immunotherapy treatment. The study by García Robaina et al. confirms previous in vivo and in vitro cross-reactivity observations using whole extracts as well as purified allergens. It suggests that although there is some in vitro and in vivo allergenic cross-reactivity between *B. tropicalis* and *D. pteronyssinus*, clinical symptoms induced by the inhalation of *B. tropicalis* and *D. pteronyssinus* allergens seem to be species specific, although some patients may react to common allergens.

Standardized extracts of *B. tropicalis* are only available in some European and Asian countries, in Cuba and in some African and South American countries. However, *B. tropicalis* extracts are only available under experimental conditions in the United States and many other countries throughout the world. There is a definitive need to use standardized extracts of *B. tropicalis* in countries with tropical, subtropical, and temperate climates of the world where *Blomia* species are endemic. Because of its wide distribution, the high rate of sensitization in many countries and the specificity of the allergic reactions, the inclusion of *B. tropicalis* for the diagnosis and treatment of specific IgE-mediated allergic reactions to this mite is warranted. A list of the main *B. tropicalis* allergens is shown in Table 3.

Allergens from *Lepidoglyphus destructor*

The most important storage mite species by distribution and abundance, excluding *B. tropicalis*, is *L. destructor*. At least 20 allergenic proteins have been identified in the extract of *L. destructor* (95). The major allergen, Lep d 2, formerly named Lep d 1, is a protein of 141 aa and molecular weight of 14 to 18 kDa by SDS-PAGE (96). It is present in the digestive tract of the mite (97). Lep d 2 has been cloned, sequenced, and expressed as a recombinant protein (rLep d 2) (98).

Table 3 Described Allergens in *B. tropicalis*

Allergens	Dp/Df allergens	Identity (identical residues/total residues)	MW (kDa)	Molecular function	IgE reactivity	
					Bt	Dp/Df
Blo t 1	Der p 1	32% (108/333)	26	cysteine protease	62–90%	80%
Blo t 2 ^b	Der p 2	39% (57/146)	14	unknown	ND	80%
Blo t 3	Der p 3	49% (131/266)	25	trypsin	50–57%	16–100%
Blo t 4 ^a	Der p 4	65% (335/515)	56	alpha amylase	<15%	40%
Blo t 5	Der p 5	42% (56/134)	14	unknown	43–92%	50–70%
Blo t 6 ^b	Der p 6	58% (164/281)	25	chymotrypsin	<10%	40%
Blo t 10	Der p 10	95% (270/284)	33	tropomyosin	29%	50–95%
Blo t 11	Der f 11	89% (781/875)	110	paramyosin	12–52%	80%
Blo t 12	ND	ND	14	unknown	50%	ND
Blo t 13	Der f 13	80% (105/131)	15	Fatty acid-binding protein	11%	ND
Blo t 19	ND	ND	7.2	antimicrobial peptide	3%	ND

^a<http://www.ncbi.nlm.nih.gov>.^b<http://www.allergen.org>.

Source: Adapted from Ref. 87

Abbreviations: MW, molecular weight; ND, not determined; Bt, *B. tropicalis*; Dp, *Dermatophagoides pteronyssinus*; Df, *Dermatophagoides farinae*.

This allergen possesses high IgE reactivity in vitro (99) and in vivo (100). Lep d 2 presents a high degree of polymorphism, with two distinct isoforms, Lep d 2.01 and Lep d 2.02. Lep d 2.02 has two variants and Lep d 2.01, three, two of which (Lep d 2.0101a and Lep d 2.0101b) have identical aa sequences. The rest of variants differ only in a few aa. The frequency of these variants may differ between wild and cultured mites (101).

Lep d 5 has been partially cloned and expressed. This partial clone of 110 aa and a molecular mass of 12.5 kDa is recognized by 9% of the sera from patients sensitized to *L. destructor* (102). Two isoforms have been sequenced, Lep d 5.02 with 171 aa and 19.5 kDa and Lep d 5.04, with 169 aa and 19.3 kDa. The allergen Lep d 7 has been sequenced and cloned; the calculated molecular mass is 22 kDa, without N-glycosylation sites. The recombinant protein rLep d 7 was recognized by 62% of the sera of *L. destructor*-positive subjects. The biochemical function of the group 7 mite allergens is unknown, and Lep d 7 does not show significant homologies to proteins other than to the group 7 mite allergens (102).

An allergenic protein homologous to tropomyosin Lep d 10 was identified as an allergen from a phage display cDNA library. The molecule of 284 aa is formed by two polypeptide chains. The sequence exhibits a prominent seven-residue periodicity. The IgE-binding frequencies of the recombinant Lep d 10 is estimated at 13% among subjects with IgE reactivity to mites and/or crustaceans (103).

The allergen Lep d 13 is sequenced and cloned. Its length is 131 aa with a calculated molecular weight mass of 14.6 kDa. It is involved in the intracellular transport of lipids, belonging to the family of FABP. The recombinant protein rLep d 13 is recognized by approximately 13% of the sera of *L. destructor* sensitized patients (102).

Other allergens have been sequenced, including the proteases Lep d 3 UniProtKB/Swiss-Prot (<http://www.expasy.uniprot.org>) (Q1M2L7), a GST Lep d 8 (Q1M2L6) and Lep d 12 (Q1M2L5) (104). An α -tubulin was identified as a putative allergen from a phage display *L. destructor* cDNA library. The IgE-binding frequency to the recombinant allergen is 12% among subjects with IgE reactivity to mites and/or crustaceans (103).

Allergens from *Glycyphagus domesticus*

G. domesticus is a phylogenetically closely related species with *L. destructor*. A 15 kDa allergen, belonging to group 2, and termed Gly d 2, is cloned and expressed as a recombinant protein. Gly d 2 shows a high degree of homology with Lep d 2. Three isoforms of Gly d 2 have been isolated; 16 out of 17 sera of sensitized patients recognize this recombinant protein (105). Other proteins homologous to group 3 (Q1M2M8), 5 (Q1M2M7), 7 (Q1M2M5), 8 (Q1M2M4), 10 (Q1M2L8) and 13 (Q1M2M3) are sequenced for this mite species (104).

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Allergens from *Tyrophagus putrescentiae*

T. putrescentiae is one of the most important pest mite species on stored products. The presence of at least 14 allergens has been demonstrated in this mite species by means of crossed radioimmunoelectrophoresis (106). The major allergen is a 16 kDa protein recognized by 80% of sera from sensitized patients (107). This allergen, Tyr p 2, is cloned (108), sequenced, and expressed as a recombinant protein (rTyr p 2). This recombinant protein has demonstrated high IgE reactivity in vitro (99) and in vivo (100). Another allergen, Tyr p 13, homologous to FABPs, has also been identified, sequenced, and cloned. The recombinant allergen was detected by 6.4% of sensitized patients. An α -tubulin has been identified as a putative allergen from a phage display cDNA library of *T. putrescentiae*. The IgE-binding frequency of the recombinant allergen was 29.3% among subjects with IgE reactivity to mites and/or crustaceans (109). Tyr p 10 also has been cloned and shows 64% to 94% shared aa identity with other allergenic tropomyosins. This recombinant allergen is recognized by 12.5% of sera from sensitized patients (110).

Allergens from *Acarus siro*

A. siro belongs to the Acaridae family. A protein of 15 kDa with homology to other FABPs was identified, isolated, cloned, sequenced, and expressed as a recombinant protein. This allergen, Aca s 13, is recognized by 23% of the sera of patients sensitized to this mite (111).

Allergens from *Aleuroglyphus ovatus* and *Chortoglyphus arcuatus*

Numerous IgE-binding bands have been described with layer isoelectric focusing immunoblots in extracts of the brown-legged mite, *A. ovatus*. This species exhibits minimal to moderate cross-reactivity with house-dust mites (112,113). The most frequently detected allergens in the tropical mite, *S. medianensis*, have molecular weights of 21, 24.5, 30, 31, 47, and 50 kDa. Sui m 2, with a molecular weight of 15 kDa (Q2TUH5), has been described (104). There is a moderate degree of cross-reactivity among *S. medianensis*, *B. tropicalis*, and *D. farinae* (114). Anaphylaxis, after the ingestion of flour contaminated with *S. medianensis* has been reported (115). The mite species *Th. entomophagus* also has been implicated in cases of anaphylaxis after the ingestion of contaminated flour (116).

Several bands are recognized in extracts of *C. arcuatus* by specific IgE of sensitized patients. The most predominant bands have between 14 and 25 kDa, between 30 and 45 kDa, and between 46 and 65 kDa. There is minimal cross-reactivity between this mite species and *D. pteronyssinus* and moderate cross-reactivity with other storage mites (117). A tropomyosin allergen, Cho a 10, has been cloned and sequenced from a *C. arcuatus* expression library. The homology between Cho a 10 and Der p 10 is 94% and between Cho a 10 and Lep d 10, 95% (118). *Ch. eruditus* is a predator mite species frequently identified in house dust, especially in rural environments, where it feeds on storage mites. The existence of numerous allergens by immunoblotting (119) has been identified with a prominent band at approximately 16 kDa. There is a variable degree of cross-reactivity of this mite with the other domestic mites.

ALLERGENS OF MITES PRESENT IN AGRICULTURAL SETTINGS AND OF PARASITIC IMPORTANCE

The spider mites are main pests of fruit and horticultural crops and are common sensitizing allergens that are related to the prevalence of allergic diseases (120). Epidemiologic studies have also demonstrated high rates of sensitization in the surrounding population, which is not occupationally exposed to orchard trees (121). Major allergens with 10, 14, 19, 29, 67 and 75 kDa have been described by immunoblotting extracts of the two-spotted spider mite, *Tetranychus urticae* (122). Three allergens have been identified in *Panonychus ulmi*, the apple spider mite, with molecular weights of 33, 41, and 51 kDa. Specific IgE-binding against *Tet. urticae* and *Panonychus ulmi* was partially inhibited by extracts of *D. pteronyssinus* and *T. putrescentiae* (123). In the case of the citrus spider mite, *P. citri*, two allergens of 24 and 35 kDa have been identified. The N-terminal aa sequences of these major allergens of the spider mites are not homologous with any characterized allergens (124).

Allergens of mites used as biological control agents against spider mites and other pests, such as the Phytoseiidae, *Phytoseiulus persimilis* and *Amblyseius cucumeris*, or the

Table 4 Other Mite Families and Species of Allergenic Mites, Excluding House Dust and Storage Mites

Family	Parasites of Plants
Tetranychidae	<i>Tetranychus urticae</i> <i>Panonychus ulmi</i> <i>P. citri</i>
Tydeidae	<i>Pronematus davisi</i> Predator mites
Phytoseiidae	<i>Amblyseius cucumeris</i> <i>Phytoseiulus persimilis</i>
Hypoaspidae	<i>Hypoaspis miles</i>
Hemisarcoptidae	<i>Hemisarcoptes cooremani</i> Parasites of animals
Varroidae	<i>Varroa</i> spp.
Sarcoptidae	<i>Sarcoptes scabiei</i>
Analgiidae	<i>Diplaegidia columbae</i>
Ixodidae	<i>Ixodes pacificus</i> <i>I. holocyclus</i> <i>I. ricinus</i> <i>Rhipicephalus</i> spp.
Argasidae	<i>Argas reflexus</i>

Dermanyssidae, *Hypoaspis miles*, have been described (125,126). These predator mites have species specific as well as common antigens that are cross-reactive with *D. pteronyssinus* (127).

Several parasitic mite species are in frequent contact with humans and domestic animals. The itch mite, *Sarcoptes scabiei*, causes skin lesions and IgE-mediated sensitization in parasitized individuals (128–130). Allergens homologous to serine proteases (group 3) (131), GST (group 8) (132), paramyosin (group 11) (133) and apolipoprotein (134) have been identified. Ticks (Ixodida) belonging to the families Ixodidae and Argasidae have several proteins in their saliva that can induce IgE-mediated reactions after biting. Several cases of anaphylaxis after tick bites are reported (135). The allergenic composition of these mites has been analyzed, and an important allergen of *Argas reflexus*, the European pigeon tick, has been cloned (136). Arg r 1 is a protein belonging to the lipocalin family (137). In the case of the paralysis tick, *Ixodes holocyclus*, an allergen of 28 kDa from the salivary gland has been identified (138). Other allergenic proteins with molecular masses of 51, 38, 35 kDa from *I. pacificus*, *I. ricinus*, *Haemaphysalis punctata* and *Rhipicephalus* spp. have been described (139–142).

Other parasitic mites that have been involved in allergic reactions in humans are the bee parasite, *Varroa jacobsoni*, with an allergenic protein of 13 kDa (143) and the feather mite of domestic birds, *Diplaegidia columbae*, with 20 IgE-binding components ranging from 22 to 200 kDa (144). Two allergens from *Hemisarcoptes cooremani*, a predator of scale insects, of 16 kDa and 19 kDa have been described (145). Other mite families and species of allergenic mites, excluding house dust and storage mites, are shown in Table 4 (72).

CROSS-REACTIVITY OF MITE ALLERGENS

Cross-reactivity is a common feature among mite allergens, especially in those from taxonomically related species. The fact that mite-allergic individuals may be sensitized by various species could be due, in part, to cross-reactivity. Originally, cross-reactivity was studied using whole extracts and radioallergosorbent test (RAST) inhibition techniques. More recently, purified native or recombinant allergens, epitope mapping, and T-cell proliferation techniques have been used (146). Small peptides, with eight to 15 aa, are responsible for specific IgE binding and, to a large extent, of cross-reactivity between different allergens. It is evident that cross-reactivity studies to a great extent depend on the serum pool used and if the patients are mono- or poly-sensitized to different mite allergens.

The allergenic cross-reactivity between *L. destructor* and *B. tropicalis* was initially demonstrated by specific IgE inhibition studies using whole allergen extracts. Puerta et al. (147) demonstrated a greater degree of cross-reactivity between *B. tropicalis* and *L. destructor* than

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between *B. tropicalis* and *Dermatophagoides* spp. The participation of group 2 in the cross-reactivity between these two species has been suggested (95). The sequence identity between Lep d 2 y and Gly d 2 is high (79%), but only 40 % in Tyr p 2 and Der p 2 (105). However, the cross-reactivity among group 2 allergens from storage mites, *L. destructor*, *T. putrescentiae*, and *G. domesticus*, is high, whereas there is only limited cross-inhibition between Der p 2 and the non-pyroglyphid mite allergens (105). This lack of cross-reactivity between Der p 2 and the group 2 of storage mites is a result of the multiple aa substitutions across the surface (148). Other studies have shown limited cross-reactivity between *D. pteronyssinus*, *L. destructor*, and *T. putrescentiae* (149,150), but others have reported a greater cross-reactivity between *Dermatophagoides* spp. and *T. putrescentiae* (151). A low degree of cross-reactivity between *D. pteronyssinus* and *A. siro* and *T. putrescentiae* was described in one study, whereas cross-reactivity between *L. destructor* and *A. siro* was high (152).

Individuals allergic to the *Dermatophagoides* spp. may experience allergic symptoms after the consumption of crustacean and mollusks (153). Der f 10 and Der p 10 proteins with homology to tropomyosin from various animals are involved in the cross-reactivity among *Dermatophagoides* spp., mollusks, and crustaceans. The cross-reactive tropomyosin present in mites, chironomids, mosquitoes, cockroaches, shrimps (42), oysters (154), crabs (155), lobsters (156), and squids (157) could be responsible for cross-reactivity among different arthropods. Immunochemical studies demonstrate that allergens from snails, crustaceans, cockroaches, and chironomids cross-react with house-dust mite allergens. However, house-dust mites are usually the primary source of sensitizing allergens. The nematode, *Anisakis simplex*, a common fish parasite, can act as a hidden food allergen, inducing IgE-mediated reactions. Allergic cross-reactivity between this nematode and the domestic mites, *A. siro*, *L. destructor*, *T. putrescentiae*, and *D. pteronyssinus*, have been reported, in which tropomyosin seems to be involved. The clinical relevance of this cross-reactivity needs to be further investigated (158).

The feather mite, *Dip. columbae*, is a major source of clinically relevant allergens for pigeon breeders. The results of RAST inhibition experiments suggest that this feather mite cross-reacts with *D. pteronyssinus* (144). Arlian et al. (159) demonstrated that antigens of the parasitic mite, *Sar. scabiei*, cross-react with antigens of *D. pteronyssinus*. Proteins with homology to different groups of mite allergens have been identified by molecular cloning in the parasitic mites, *Sar. scabiei* (133) and *P. ovis* (160).

ENZYMATIC ACTIVITY IN MITE EXTRACTS

Important airborne allergens may possess hydrolytic enzymatic activities, such as proteases, glycosidases, and ribonucleases. Several of these enzymes are important allergens, including cysteine and serine proteases and glycosidases (amylase) in mites and molds and ribonucleases in grass and tree pollens and molds. Allergenic mite extracts have enzymes capable of degrading a wide range of substances, including other proteins and allergens and could have negative effects on the efficacy and stability of therapeutic vaccines. House-dust mite allergen extracts contain more than 20 IgE-binding molecules (161-163). Some of them with enzymatic activity included groups 1, 3, 4, 6, 8, 9, and 15 (164,165). Other mite species, such as *G. domesticus* (166), *A. farris* (167), *T. putrescentiae* (168), *B. tropicalis* (169,170), *P. cuniculi* (171), and *A. ovatus* (172) also contain allergens with enzymatic activity. Serine proteases (trypsin and chymotrypsin) seem to be more abundant in fecal than in whole body extracts (173,174). Enzyme allergens are widely present in other allergen sources, such as honey-bee venom (175), imported fire ant (176), vespids (177), and *Candida albicans* (178-180).

Comparative studies have been conducted to analyze the presence of enzymes in mite bodies and spent media. It seems that serine proteases (trypsin and chymotrypsin) are more abundant in fecal than in whole body extracts (181,182). The presence of proteolytic activity in feces extracts is of great clinical importance, since fecal pellets are more likely to become airborne and inhaled, thus reaching the respiratory mucosa. This enzymatic activity seems to play an important role in the allergenicity of certain mites, since it can facilitate the access of the allergen to the immune system and has an adjuvant proallergic role influencing its immunogenicity (183). The enzymatic activity is present in body and mainly in fecal extracts suggesting their role in digestion. The presence or absence of certain digestive enzymes may reflect the trophic specialization, showing different "enzyme patterns" among house-dust and storage mites.

The protease activity of allergens may induce a range of inflammatory effects modulating the adaptive immune system by cleavage of CD23 and CD25, including induction of vascular permeability, edema, activation of neural reflexes leading to bronchoconstriction and stimulation of gland secretion and cough (184,185). Der p 1 additionally may effect the innate defense mechanisms of the lung by inactivating the elastase inhibitors. Der p 1 may also increase the susceptibility to infection of patients with allergic inflammation (186). Der p 1 can damage bronchial epithelium, increasing their permeability and detaching cells in vitro. The resulting breach of the epithelial barrier may increase exposure to antigen-presenting cells and increase the likelihood that IgE will be raised against proteins in mite fecal pellets. Allergens, such as Der p 3 and Der p 9, with serine protease activity, may also induce a nonallergic inflammatory response in the airways through the release of proinflammatory cytokines from the bronchial epithelium (187).

Patients with mite sensitization and allergic asthma often react to a variety of allergens present in mite bodies, feces, and secretions (188,189). The proteolytic activity of mite allergens may play a proallergic role, influencing their immunogenicity by enabling allergens to breach the integrity of the airway epithelial barrier. As a consequence, allergic inflammatory responses are promoted. Furthermore, by disrupting epithelial tight junctions, the enzymatic activity facilitates the transport of allergen across the epithelium (190).

An influence on the innate mechanism of defense has also been described. The proteolytic activity of mite feces interacts with pulmonary elastase, inactivating a human elastase inhibitor in vivo and ex vivo. Because these elastase inhibitors have antimicrobial, as well as antielastase activity, the inactivation of these innate components of the lung defense system by proteolytic enzymes present in mite feces may increase the susceptibility of patients with allergic inflammation to infection and, therefore, produce a possible exacerbation of allergic respiratory diseases (191). Following exposure of the bronchial mucosa to house-dust mite fecal pellete, the mite proteases can access the lung interstitium and promote Th2 responses.

Chronic exposure to mites is an important risk factor for the development of sensitization, allergic respiratory diseases, and chronic inflammation of the lungs (192). While this relationship was primarily established for *Dermatophagoides* spp., other mite species are also the source of potent enzymes (193).

GENETICS OF IGE RESPONSES TO MITE ALLERGENS

High total IgE and specific IgE immune response to mite allergens are known risk factors for asthma and other allergic diseases. There is evidence that IgE synthesis, which involves a great number of metabolic pathways, is under genetic control. Several candidate genes influencing this process are identified. Some of them are also associated with asthma, probably because atopy is a main feature of this disease. The field of immunogenetics of IgE responses has been mainly supported by the late Dr. David Marsh's work on the association of ragweed allergens and the human major histocompatibility complex (HLA) alleles. Since then, a variety of work has been done in this field. Today most data showing genetic influence (linkage or association) on mite-specific IgE responses are related to HLA. In 1990, Caraballo et al., using affected sib pair analysis, showed that IgE hyperresponsiveness to *D. farinae* in patients with allergic asthma was linked to HLA (194). Eight years later, a genome-wide search found strong evidence of linkage between the specific IgE responsiveness to *D. pteronyssinus* and chromosomes 6p21 (HLA-D region), 2q21-q23, 8p23-p21, 13q32-q34, and 5q23-q33 in Caucasians families (195). The role of HLA on the IgE response to this mite was further analyzed by the same authors, evaluating the IgE responses to several allergen components of *D. pteronyssinus* extract (196). Linkage studies involving HLA loci and mite IgE responses have been replicated in other populations (197,198).

Associations between HLA class II genes and IgE hyperresponsiveness to mite allergens have been positive and negative, involving different alleles and loci, and often showing no replication among different studies. This could be explained by the large number of mite allergenic epitopes, the variable level of exposure to each epitope, the ability of each HLA class II allele to present more than one peptide, and the participation of genes from other chromosome regions. In a case-control study, the frequency of allele HLA-DPB1*0401 was remarkably decreased in patients with IgE hyperresponsiveness to mite allergens, suggesting

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B1*0401 was
s, suggesting

that it could be suppressing this phenotype in the nonallergic population (199). This apparent protective role of DPB1 locus has been also observed in an Asian population where DPB1*0201 was negatively associated with the IgE responsiveness to Der p 1 (200).

Using BtM, a short allergen peptide of Blo t 5, it was found that IgE hyper-responsiveness of asthmatic patients was positively associated with HLA-DRB1*03 (*0301 plus *0302) and negatively associated with HLA-DQB1*0601 (201). A positive association between HLA-DRB1*03 and IgE responsiveness to Der p 2 was also found in a study involving a large group of subjects from 76 nuclear and 7 extended families (202). These findings suggest that the group of alleles conforming DRB1*03 may be involved in controlling specific IgE to particular mite allergens, although the role of other HLA alleles also has been documented (203–205).

As suggested by genome-wide linkage searches, associations between mite IgE responsiveness and non-HLA genes have been found, including interleukin-18 (IL18) (206), leukotriene C4 synthase (LTC4S) (207), nitric oxide synthase 1 (NOS1) (208), and dendritic cell-associated nuclear protein 1 (DCNP1) (209), all of them participating in any of the multiple steps of IgE synthesis. For example, there is evidence that cysteinyl leukotrienes can enhance IgE and IgG production in human B cells and a LTC4S knockout mouse has markedly reduced antigen-induced Th2 pulmonary inflammation. Therefore, the finding of Acevedo et al., describing an association between the A-444C polymorphism of LTC4S and low IgE response to *D. pteronyssinus*, supports a role of this gene in the regulation of human IgE responses to mite allergens (207).

The genetics of nitric oxide synthase 1 function in asthma pathogenesis has been investigated for several years and polymorphisms in the NOS1 gene have been associated with asthma and total IgE levels. Nitric oxide, a mediator of innate immunity, also influences the adaptative response in both mouse and humans by exerting a regulatory role in Th1/Th2 generation, and it could contribute to asthma pathogenesis by selective down regulation of the Th1 response or promoting the Th2 response. The results of another investigation extend this hypothesis to mite-specific IgE response in asthmatics patients living in the tropics. Allele 16 of the cytosine adenine (CA) dinucleotide repeat polymorphism in exon 29 of NOS1 was found associated with low levels of specific IgE to *D. pteronyssinus* and *B. tropicalis*, suggesting that nitric oxide synthase 1 and nitric oxide could act through different ways in asthma pathogenesis, one of them by controlling specific IgE response (208).

Because dendritic cells can influence polarization of T cells, the specific IgE response against mite allergens could be regulated by polymorphisms in non-HLA genes related with the mechanisms of allergen recognition and processing. Kim et al. found a single nucleotide polymorphism (SNP) in the promoter region (C-1289T) of the DCNP1 gene; allele T was associated with low levels of specific IgE against Der p 1 in asthmatic patients, while other SNP in the 3'UTR (C1718T) was more frequent in patients with high levels of specific IgE. Dendritic cell-associated nucleoprotein 1 expression seems to be regulated in a differentiation stage-dependent manner. Functional analyses indicates that the promoter allele T would affect the gene expression level by altering DNA-protein interaction, and it was postulated that the genetic polymorphism of DCNP1 may influence production of specific IgE by altering DC functions in the mite allergen presenting and/or processing (209).

Although the mechanisms of HLA influence on specific humoral immune response are partially elucidated, further investigation is needed to understand the role of genes in other chromosomal regions regulating IgE response and conferring susceptibility to allergic disorders. Advances in genomics and molecular biology of allergens will improve the ability to dissect the genetics of specific IgE response, especially because the latter can now be investigated at the epitope level, and genome-wide scans for association studies are available.

SALIENT POINTS

- Numerous mite species are the source of allergens capable of sensitizing and inducing allergic symptoms in sensitized and genetically predisposed individuals. Allergic diseases triggered by mite allergens include allergic rhinoconjunctivitis, asthma, atopic dermatitis, and other skin diseases.

- The main source of allergens in house dust worldwide are the house-dust mite species, *D. pteronyssinus*, *D. farinae*, *E. maynei*, and the storage mites, *B. tropicalis*, *L. destructor*, and *T. putrescentiae*.
- Several storage mite allergens have been purified, cloned, and sequenced. Some of these allergens can be considered as pan-allergens.
- The immune response to mite allergens is very complex, exhibiting marked geographical and racial differences. Human-specific IgE binds to several allergens in variable degrees of frequency and intensity. However, in *Dermatophagoides* spp., group 1 and 2 seem to be the most important.
- The main allergens described in storage mites include FABPs, tropomyosin, and paramyosin homologues, apolipophorine-like proteins, alfa-tubulines and others, such as group 2, 5, and 7 allergens.
- The spider mites are main pests of fruit and horticultural crops and are common sensitizing allergens that are related to the prevalence of allergic diseases.
- Allergens from several parasitic mite species, which are in frequent contact with humans and domestic animals, have been isolated and characterized.
- Cross-reactivity has been traditionally studied using whole extracts and RAST-inhibition techniques. Currently, purified native or recombinant allergens, epitope mapping, and T-cell proliferation techniques are being used. Because of cross-reactivity, individuals allergic to the *Dermatophagoides* spp. may experience allergic symptoms after the consumption of crustacean and mollusks.
- Mite allergen extracts contain enzymes capable of degrading a wide range of substances, including other proteins and allergens, and could have negative effects on the efficacy and stability of therapeutic extracts. Most mite allergens are potent enzymes.
- Advances in genomics and molecular biology of mite allergens will improve the ability to dissect the genetics of specific IgE response, especially since investigation at the epitope level and genome-wide scans for association studies are available.

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INTRODUCTION

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