

House dust mite allergy: The importance of house dust mite allergens for diagnosis and immunotherapy

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ABSTRACT

House dust mite (HDM) allergy belongs to the most important allergies and affects approximately 65–130 million people worldwide. Additionally, untreated HDM allergy may lead to the development of severe disease manifestations such as atopic dermatitis or asthma. Diagnosis and immunotherapy of HDM allergic patients are well established but are often hampered by the use of mite extracts that are of bad quality and lack important allergens. The use of individual allergens seems to be a promising alternative to natural allergen extracts, since they represent well-defined components that can easily be produced and quantified. However, a thorough characterization of the individual allergens is required to determine their clinical relevance and to identify those allergens that are required for correct diagnosis of HDM allergy and for successful immunotherapy. This review gives an update on the individual HDM allergens and their benefits for diagnosis and immunotherapy of HDM allergic patients.

1. Introduction

House dust mites (HDMs), one of the most prevalent indoor allergen sources, have been reported to be associated with allergic diseases including perennial allergic rhinitis, allergic asthma and atopic dermatitis (Platts-Mills et al., 2009; Sanchez-Borges et al., 2017). HDMs can be found almost worldwide and it is estimated that HDM allergy affects 1–2 % of the global population, in total approximately 65–130 million people (Calderon et al., 2015). Diagnosis of HDM allergy includes the anamnesis of a patient, skin prick testing/provocation test and/or the measurement of allergen-specific IgE antibodies. Allergen-specific immunotherapy is applied to improve allergic symptoms and to avoid the development of more severe symptoms, like asthma. However, both diagnosis and immunotherapy are still mainly performed with HDM extracts, which contain a mixture of allergenic and non-allergenic components. Up to date, 40 groups of HDM allergens were identified and registered in the WHO/IUIS Allergen Nomenclature Sub-Committee, but HDM extracts used for diagnosis and

immunotherapy are only standardized for *Dermatophagoides pteronyssinus* (Dp) allergens, Der p 1 and/or Der p 2. Therefore, some important HDM allergens are missing or only present in tiny amounts in most of the extracts and because of this, some HDM allergic patients cannot be diagnosed with those extracts (Casset et al., 2012). Additionally, HDM-allergic patients with IgE sensitizations to allergens other than Der p 1 and Der p 2 benefit less from immunotherapy with HDM extracts containing only those allergens than patients with exclusive IgE reactivity to Der p 1 and/or Der p 2 (Chen et al., 2019; Rodriguez-Dominguez et al., 2020). Therefore, the use of individual purified allergens or recombinant allergens for diagnosis and immunotherapy may be considered as alternative for mite extracts, but it requires a thorough characterization of the different HDM allergens.

This review will discuss different HDM species, mechanisms of HDM allergy, HDM epidemiology and will mainly focus on the description of the individual HDM allergens with emphasis on the clinically relevant allergens that are important for diagnosis and allergen specific immunotherapy of HDM allergic patients.

Abbreviations: APCs, antigen-presenting cells; *B. tropicalis*, *Blomia tropicalis*; Der p, *Dermatophagoides pteronyssinus* allergen; *D. pteronyssinus*, *Dermatophagoides pteronyssinus*; Der f, *Dermatophagoides farinae* allergen; *D. farinae*, *Dermatophagoides farinae*; *D. microceras*, *Dermatophagoides microceras*; *E. maynei*, *Euroglyphus maynei*; HDM, house dust mite; ILC2s, type 2 innate lymphoid cells; JAMs, junction adhesion molecules; PARs, protease-activated receptors; SCIT, subcutaneous immunotherapy; SPT, skin prick test; TCR, T-cell receptor; TSLP, thymic stromal lymphopoietin; ZO-1, zona occludens-1.

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1.1. Classification of HDMs

The major allergenic HDMs are *Dermatophagoides pteronyssinus* (*D. pteronyssinus*), *Dermatophagoides farinae* (*D. farinae*), and *Euroglyphus maynei* (*E. maynei*) belonging to the phylum arthropoda, in the class Arachnida, subclass Acari and the suborder Astigmata (Fig. 1). Within the suborder Astigmata, they belong to the family Pyroglyphidae. Although *Blomia tropicalis* (*B. tropicalis*) is in the same class, order and suborder as *Dermatophagoides* species, they belong to the family Echympodidae and are categorized as a storage mite (Miller, 2019). Nevertheless, *B. tropicalis* mites are mainly found in houses in tropical and subtropical areas and are thus commonly regarded as HDMs (Arlian et al., 1993). Among the HDM species, *D. pteronyssinus* and *D. farinae* represent the most important allergen sources for allergic patients globally, whereas *B. tropicalis* requires a very humid and hot climate and is thus restricted to tropical and subtropical areas (Yi et al., 1999). This review article will mainly focus on the allergens of the HDM species, *D. pteronyssinus*, the major HDM species in Central Europe. The allergens of *D. pteronyssinus* are cross-reactive to the homologous allergens from *D. farinae*, but only low cross-reactivity was found between allergens from these two sources and the homologous allergens from *B. tropicalis* (Kim et al., 2015; Thomas et al., 2003).

1.2. HDM allergy

HDM allergy is an IgE-mediated type I hypersensitivity reaction to dust mite allergens from mite faecal pellets and/or from mite bodies. HDMs can cause inflammation in the respiratory system or skin including allergic rhinitis, asthma and atopic dermatitis. When mite faecal pellets and/or mite bodies are inhaled, mite allergens come into contact with the airway epithelium. The airway epithelium is a continuous layer that covers the surface of the respiratory tract and consists of epithelial cells connected by adherens and tight junctions (Crystal et al., 2008).

Tight junctions are the main regulators of epithelial permeability, which are composed of the transmembrane proteins zona occludens-1 (ZO-1), occludin, claudins and junction adhesion molecules (JAMs) (Hartsock and Nelson, 2008). The cleavage of junction proteins, ZO-1, occludin, claudin and E-cadherin in lung epithelial cells by HDM allergens with protease activity was reported (Wan et al., 1999; Post et al., 2012), which facilitates transepithelial allergen delivery. Thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 are known to be produced by epithelial cells in the lungs, being the first line of defense against infections and stimulators in the airway epithelium (Gauvreau et al., 2023). Naive CD4 + T cells residing in the tissue are activated by T cell

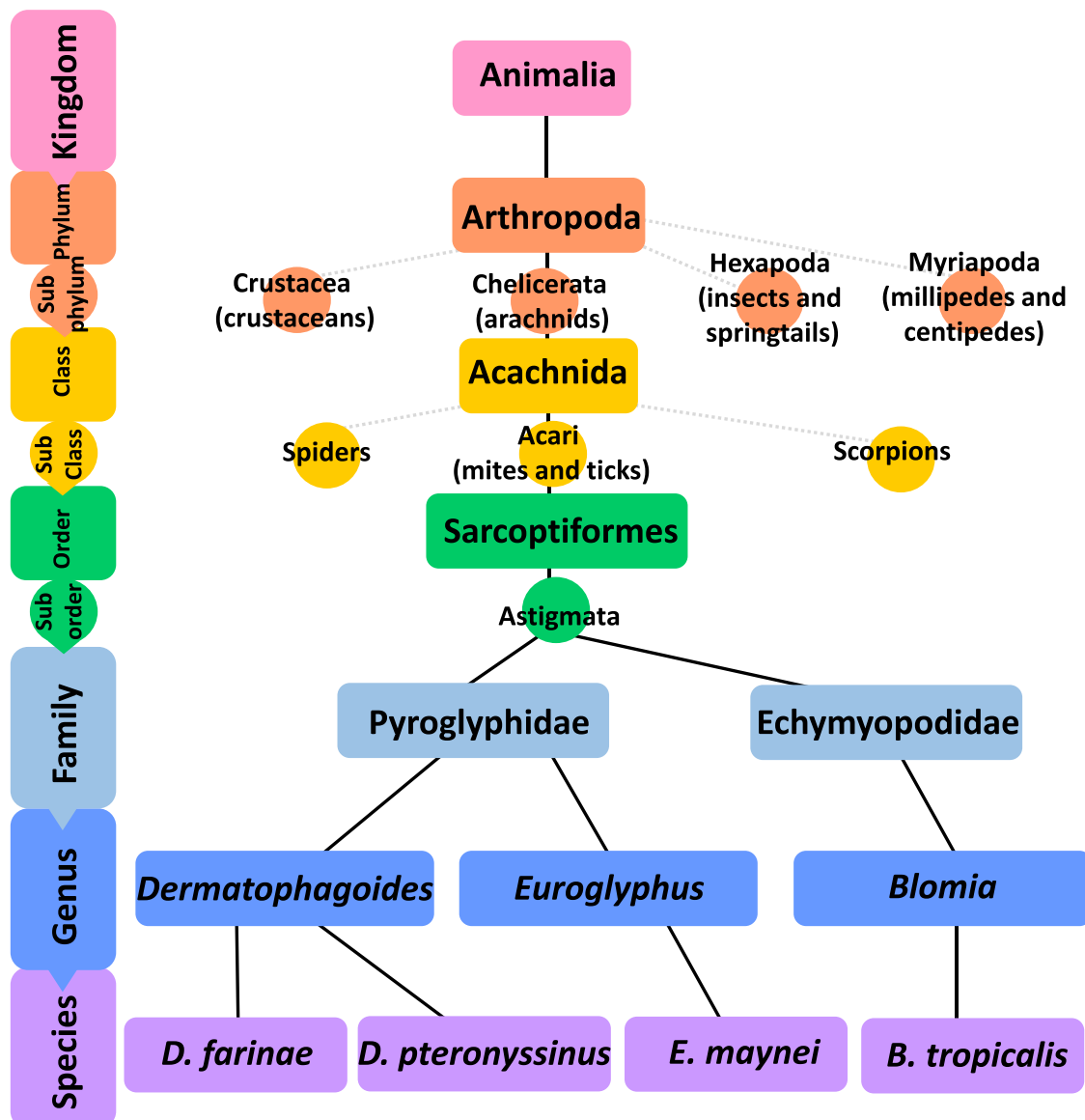


Fig. 1. Classification of mites. The taxonomy of mite species with relevance for allergic patients is shown.

epitopes of allergens presented by antigen-presenting cells (APCs), mainly dendritic cells (DCs). In the presence of T-cell receptor (TCR) stimulation, TSLP signaling in naive CD4 T cells promotes Th2 differentiation and proliferation by inducing IL-4 gene transcription (Omori and Ziegler, 2007; Ryu et al., 2013). Besides IL-4, TSLP as well as IL-25, and IL-33 induce Th2 cytokines secreted by various types of cells such as Th2 cells, and/or type 2 innate lymphoid cells (ILC2s) (Lambrecht and Hammad, 2014; Nakae et al., 2013; van Rijk et al., 2016). Certain HDM allergens activate receptors such as Toll-like receptors (TLRs) (Kirtland et al., 2020) and protease-activated receptors (PARs) (Nadeem et al., 2019) in the airways to generate leukocyte infiltration, amplifying the response to allergens (Post et al., 2010). Th2 cytokines, such as IL-4, IL-5 and IL-13, are involved in regulating the Th2 immune response to allergens, the IgE production or the allergen-induced inflammation. B cells play a key role in the development of HDM allergy through the production of mite allergen-specific IgE antibodies. Secreted HDM allergen-specific IgE antibodies bind onto FcεRI receptors on effector cells such as mast cells and basophils residing in the tissue and blood. When the IgE antibodies bound on effector cells encounter the same HDM allergen, effector cell degranulation by cross-linking of IgE antibodies takes place. Histamine, cytokines/chemokines and lipid mediators are released from the cells and induce inflammation. Sustained inflammation responses are maintained by continuous exposure to HDM allergens, causing airway remodelling with increased smooth muscle mass, subepithelial fibrosis, epithelial desquamation and goblet cell hyperplasia in the lung tissues of asthmatic patients (Bergeron et al., 2010).

Sensitization to HDMs can also result in atopic dermatitis (Gonzalez-Perez et al., 2021). The impaired epidermal barrier in atopic dermatitis patients leads to increased epidermal permeability of the skin, allowing airborne proteins, microbes or other ingredients penetrating into the epidermis (De Benedetto et al., 2011). HDM allergens can interact with local immune cells to initiate Th2 immune responses. HDM allergen-specific IgE antibodies can be detected in atopic dermatitis patients and HDM allergens can exacerbate eczema (Hallai and Gawkrödger, 2009).

2. Epidemiology

2.1. Geographic distribution

Depending on the climate with the relative humidity and temperature, different regions have different distributions of HDM species (D'souza et al., 2021; Fassio and Guagnini, 2018). HDMs are found in all continents except for the Arctic and Antarctic, due to the extremely low temperatures in those areas. Besides, an extremely low relative humidity at high altitudes restricts the growth of HDMs, because they can only grow and survive at a relative humidity exceeding 50 % (Arlian, 1992). However, a relative humidity above 70 % is ideal for the growth of HDMs (Arlian, 1992) and a higher relative humidity leads to higher concentrations of dust mites and mite allergens in the dust of homes. The ideal temperature for the growth of HDMs lies between 18 and 24 °C. A map from 2018 from Filippo Fassio and Fabio Guagnini (Fassio and Guagnini, 2018) which was revised from Wayne Thomas (Thomas, 2010) shows the geographical distribution of *Dermatophagoides* species worldwide. The HDM species *D. pteronyssinus* and *D. farinae* are relatively tolerable to different climate conditions and can survive in the cold Scandinavian countries as well as in rather dry countries such as Israel, Iran and Saudi Arabia. Nevertheless, the ideal climate for HDMs is that of subtropical and tropical countries, where *D. pteronyssinus*, *D. farinae* and *B. tropicalis* co-inhabit most of the homes. Whereas *B. tropicalis* cannot be found in temperate climates, it is the predominant HDM species in tropical countries and is strongly associated with allergic diseases (Chan et al., 2008). In Colombia (Zakzuk et al., 2013), Brazil (Carvalho et al., 2013), Singapore (Kidon et al., 2011), south of China (Zhou et al., 2018), and Malaysia (Amini et al., 2016), HDM-sensitized

patients show a high IgE-binding prevalence to *B. tropicalis* allergens.

2.2. Importance of individual HDM allergens

D. pteronyssinus and *D. farinae* represent the most important allergen sources for HDM allergic patients globally. IgE antibodies from HDM-allergic patients show broad cross-reactivity between *D. pteronyssinus* and *D. farinae* allergens (Der p and Der f), which is caused by the high sequence and structural similarities between homologous Der p and Der f allergens (Thomas, 2015). Up to date, 40 HDM allergen groups have been identified and several of them have been produced as recombinant proteins and characterized (Table 1). Der p 1 and Der p 2 have long been considered as the two major HDM allergens and 80–85 % of *D. pteronyssinus*-sensitized subjects have IgE antibodies to at least one of these two allergens (Muddaluru et al., 2021; Mueller et al., 2016). In 2013, Weghofer, et al. identified Der p 23 as a new major *D. pteronyssinus* allergen. Seventy-four percent of 347 *D. pteronyssinus*-allergic patients from Austria, France and Italy, showed IgE-reactivity to Der p 23 (Weghofer et al., 2013) and several later studies confirmed Der p 23 as a major HDM allergen with IgE-binding frequencies of 70–86 % and high clinical relevance (Jimenez-Feijoo et al., 2020; Romero-Sanchez et al., 2022). Beside the high prevalence of Der p 23 sensitization, it was found that 2–8 % of the patients were mono-sensitized to Der p 23 (Becker et al., 2016; Limao et al., 2021; Lopez-Rodriguez et al., 2022; Muddaluru et al., 2021; Rodinkova et al., 2022), indicating the importance of Der p 23 to be included in the panel of HDM allergens for component-specific diagnosis and immunotherapy.

Der p 5, Der p 7 and Der p 21 bind IgE antibodies from 30 % to 40 % of HDM-sensitized subjects and are classified as mid-tier HDM allergens with high allergenic activity (Thomas, 2018). IgE-binding prevalence data for Der p 4 vary considerably between different studies. In some studies, Der p 4 was recognized by IgE antibodies from 20 % to 30 % of HDM-allergic patients (Muddaluru et al., 2021; Posa et al., 2017; Potapova et al., 2022), whereas in other studies, Der p 4 was only recognized by less than 10 % of HDM allergic patients (Zidarn et al., 2019; Rodriguez-Dominguez et al., 2020). The discrepancy might be explained by cross-reactivity of Der p 4-specific IgE antibodies, but it is supposed that Der p 4 is not clinically relevant for HDM allergic patients (Walton et al., 2015). Other HDM allergens are categorized as minor allergens that react with less than 10 % of sera from HDM-sensitized subjects and/or are of low clinical relevance. Some of those allergens are important for certain disease manifestations (e.g., Der p 11 for atopic dermatitis patients (Banerjee et al., 2015), Der p 20 and Der p 37 for asthma patients (Huang et al., 2022; Sarzsinszky et al., 2021) or are recognized in certain populations by more patients, due to cross-reactivity to other allergen sources (e.g., Der p 10 in seafood allergic patients) (Papia et al., 2021). However, recent studies showed that six HDM allergens, the major allergens Der p 1, Der p 2 and Der p 23, as well as the mid-tier allergens Der p 5, Der p 7 and Der p 21 represent the clinically relevant HDM allergens, which are sufficient to diagnose 98–99 % of HDM allergic patients (Huang et al., 2018) and are needed for allergen-specific immunotherapy. Table 2 shows an overview of component-specific diagnosis studies with different HDM allergens from Europe, Asia and USA, which indicated that in all continents the sensitization patterns were similar, with the six HDM allergens, Der p 1, Der p 2, Der p 5, Der p 7, Der p 21, and Der p 23, as the most important allergens for HDM allergic patients worldwide.

3. Clinically relevant HDM allergens

3.1. Der p 1

Der p 1 was the first HDM allergen molecule identified and the first one that was cloned in 1988 (Chua et al., 1988). It has a molecular weight of 24 kDa and binds IgE antibodies from around 80–100 % of HDM-sensitized subjects, thus representing a major HDM allergen. Der p

Table 1
House dust mite allergens (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*).

Allergen (group)	<i>D. pteronyssinus</i>	<i>D. farinae</i>	Biological function	MW (kDa)	IgE reactivity	Allergenic activity	Clinical relevance	References
1	Der p 1	Der f 1	Cysteine protease	25	80–100	Major allergen	IgE levels to Der p 1 were significantly higher in asthmatic children than in children without asthma	Resch, Y. et al., 2015. J. Allergy Clin. Immunol. 136, 1083–1091. Chua, K.Y. et al., 1988. J. Exp. Med. 167, 175–182. Dilworth, R.J. et al., 1991. Clin. Exp. Allergy 21, 25–32.
2	Der p 2	Der f 2	ML domain lipid binding protein	14	80–100	Major allergen	IgE levels to Der p 2 were significantly higher in asthmatic children than in children without asthma	Resch, Y. et al., 2015. J. Allergy Clin. Immunol. 136, 1083–1091. Chua, K.Y. et al., 1990. Int. Arch. Allergy Appl. Immunol. 91, 124–129. Ichikawa, S. et al., 2005. J. Biochem. 137, 255–263.
3	Der p 3	Der f 3	Trypsin	Der p 3: 31 Der f 3: 29	7–97	Minor allergen	Not yet reported	Smith, W.A. et al., 1994. Clin. Exp. Allergy 24, 220–228.
4	Der p 4	Der f 4	Alpha-amylase	56	0–30	Mid-tier allergen	High titer IgE anti-alpha amylase binding antibodies associated with scabies infection or previous exposure	Hales, B.J. et al., 2007. Clin. Exp. Allergy 37, 1357–1363.
5	Der p 5	Der f 5	Unknown	14	30–40	Mid-tier allergen	IgE levels to Der p 5 were significantly higher in asthmatic children than in children without asthma	SanchezMonge, R. et al., 1996. Allergy 51, 176–180. Resch, Y. et al., 2015. J. Allergy Clin. Immunol. 136, 1083–1091. Weghofer, M. et al., 2008. Int. Arch. Allergy Immunol. 147, 101–109.
6	Der p 6	Der f 6	Chymotrypsin	25	41–65	Minor allergen	Not yet reported	Bennett, B.J. et al., 1996. Clin. Exp. Allergy 26, 1150–1154.
7	Der p 7	Der f 7	Bactericidal permeability-increasing like protein	Der p 7: 26, 30 and 31 Der f 7: 30–31	40	Mid-tier allergen	Not yet reported	Shen, H.D. et al., 1995. Clin. Exp. Allergy 25, 416–422.
8	Der p 8	Der f 8	Glutathione S-transferase	Der p 8: 27 Der f 8: 32	4–96	Minor allergen	Not yet reported	O'Neill, G.M. et al., 1994. Biochim. Biophys. Acta. 1219, 521–528.
9	Der p 9	-	Serine protease	29	92	Minor allergen	Not yet reported	King, C. et al., 1996. J. Allergy Clin. Immunol. 98, 739–747.
10	Der p 10	Der f 10	Tropomyosin	Der p 10: 36 Der f 10: 37	2–81	Minor allergen	Not yet reported	Fernandes, J. et al., 2003. Clin. Exp. Allergy 33, 956–961.
11	Der p 11	Der f 11	Paramyosin	Der p 11: 103 Der f 11: 98	7–82	Minor allergen	A serological marker allergen for HDM-associated atopic dermatitis	Witteman, A.M. et al., 1994 Int. Arch. Allergy Immunol. 105, 56–61. Banerjee, S. et al. (2015). J. Invest. Dermatol. 135, 102–109.
13	Der p 13	Der f 13	Fatty-acid binding protein	15	6	Minor allergen	Not yet reported	Satitsuksanoa, P. et al., 2016. Allergy 71, 1425–1434.
14	Der p 14	Der f 14	Apolipoprotein	177	2–84	Minor allergen	Not yet reported	Epton, M.J. et al., 2001. Int. Arch. Allergy Immunol. 124, 57–60.
15	Der p 15	Der f 15	Chitinase-like protein	Der p 15: 58.8/61.4 Der f 15: 98/109	8–70	Minor allergen	Not yet reported	O'Neil, S.E. et al., 2006. Clin. Exp. Allergy 36, 831–839.
16	-	Der f 16	Gelsolin/villin	53	47	Minor allergen	Not yet reported	Kawamoto, S. et al., 2002. FEBS Lett. 516, 234–238.
17	-	Der f 17	Calcium binding protein	53	35	Minor allergen	Not yet reported	Tategaki, A. et al., 2000. ACI International. suppl. 1, 74–76.
18	Der p 18	Der f 18	Chitin-binding protein	Der p 18: 49.2 Der f 18: 60	38–63	Minor allergen	Not yet reported	O'Neil, S.E. et al., 2006. Clin. Exp. Allergy 36, 831–839.
20	Der p 20	Der f 20	Arginine kinase	40	7–44	Minor allergen	IgE sensitization to Der p 20 is associated with HDM-associated asthma and is associated with active scabies infection	Sarzinszky, E. et al., 2021. Allergy Asthma Immunol. Res. 13, 154–163. Binder, M. et al., 2001. J. Immunol. 167, 5470–5477.

(continued on next page)

Table 1 (continued)

Allergen (group)	<i>D. pteronyssinus</i>	<i>D. farinae</i>	Biological function	MW (kDa)	IgE reactivity	Allergenic activity	Clinical relevance	References
21	Der p 21	Der f 21	Unknown	14	30	Mid-tier allergen	Not yet reported	Weghofer, M. et al., 2008. Allergy 63, 758–767. Kim, C.R. et al., 2015. Mol. Med. Rep. 12, 5467–5474. Reginald, K. et al., 2018. Sci. Rep. 8, 11743.
22	-	Der f 22	Unknown	14.7	Not yet reported	Minor allergen	Not yet reported	
23	Der p 23	Der f 23	Peritrophin-like protein	8	70–86	Major allergen	IgE levels to Der p 23 were significantly higher in asthmatic children than in children without asthma	
24	Der p 24	Der f 24	Ubiquinol-cytochrome c reductase binding protein	13	11	Minor allergen	Not yet reported	Resch, Y. et al., 2015. J. Allergy Clin. Immunol. 136, 1083–1091. Weghofer, M. et al., 2013. J. Immunol. 190, 3059–3067. Cai, Z.L. et al., 2019. Clin. Transl. Allergy 9, 28.
25	Der p 25	Der f 25	Triosephosphate isomerase	Der p 25: 27 Der f 25: 34	54	Minor allergen	Not yet reported	
26	Der p 26	Der f 26	Myosin light chain	Der p 26: 14.1 Der f 26: 18	62	Minor allergen	Not yet reported	
27	-	Der f 27	Serpin	48	42.1	Minor allergen	Not yet reported	An, S. et al., 2013. Mol. Cell Proteomics 12, 1818–1828. Liu, X.Y. et al., 2018. J. Allergy Clin. Immunol. 141, 2268–2271. An, S. et al., 2013. Mol. Cell Proteomics 12, 1818–1828. Liu, X.Y. et al., 2018. J. Allergy Clin. Immunol. 141, 2268–2271.
28	Der p 28	Der f 28	Heat shock protein 70	Der p 28: 45 Der f 28: 70	39	Minor allergen	Not yet reported	
29	Der p 29	Der f 29	Cyclophilin	Der p 29: 27.7 Der f 29: 15	85	Minor allergen	Not yet reported	
30	Der p 30	Der f 30	Ferritin	Der p 30: 12.1 Der f 30: 15	63	Minor allergen	Not yet reported	An, S. et al., 2013. Mol. Cell Proteomics 12, 1818–1828. Liu, X.Y. et al., 2018. J. Allergy Clin. Immunol. 141, 2268–2271. An, S. et al., 2013. Mol. Cell Proteomics 12, 1818–1828. Liu, X.Y. et al., 2018. J. Allergy Clin. Immunol. 141, 2268–2271.
31	Der p 31	Der f 31	Cofilin	Der p 31: 16.8 Der f 31: 15	32.5–34.6	Minor allergen	Not yet reported	
32	Der p 32	Der f 32	Inorganic pyrophosphatase	Der p 32: 45 Der f 32: 35	46	Minor allergen	Not yet reported	
33	Der p 33	Der f 33	Alpha-tubulin	Der p 33: 44.2 Der f 33: 52	65	Minor allergen	Not yet reported	Liu, X.Y. et al., 2018. J. Allergy Clin. Immunol. 141, 2268–2271. ElRamlawy, K.G. et al., 2016. J. Biol. Chem. 291, 21607–21615. Fujimura, T. et al., 2017. Allergy 72, 1728–1736.
34	-	Der f 34	Enamine/imine deaminase	16	62.5	Minor allergen	Not yet reported	
35	-	Der f 35	Unknown	14.4	51	Minor allergen	Not yet reported	
36	Der p 36	Der f 36	Unknown	23	42	Minor allergen	Not yet reported	Bordas-Le Floch, V. et al., 2017. PLoS One 12, e0185830. Huang, H.J. et al., 2022. J. Allergy Clin. Immunol. 149, 1031–1043. Kim, G. et al., 2021. Int. J. Mol. Sci. 22, 8440
37	Der p 37	Der f 37	Peritrophin-A domain containing protein	Der p 37: 30 Der f 37: 29	28	Minor allergen	IgE sensitization to Der p 37 is associated with allergic asthma	
38	Der p 38	Der f 38	Bacteriolytic enzyme	15	26.7–45	Minor allergen	Not yet reported	
39	Der p 39	Der f 39	Troponin C	18	5.7–9.2	Minor allergen	Not yet reported	WHO/IUIS Allergen Nomenclature Sub-Committee. Allergen nomenclature. WHO/IUIS Allergen Nomenclature Sub-Committee. Allergen nomenclature.
40	Der p 40	Der f 40	Thioredoxin like protein	12	8–10	Minor allergen	Not yet reported	

Table 2
IgE-binding frequency of HDM allergens.

Region	Subjects tested	Allergens tested	IgE sensitization patterns	Methods	References
Japan	120 HDM-allergic patients (12–64 years)	Der p 1, Der p 2, Der p 23	Der p 1 (94.2 %), Der p 2 (97.5 %) and Der p 23 (71.7 %)	Der p 1 and Der p 2 (ImmunoCAP ISAC)Der p 23 (ImmunoCAP)	Hasegawa, A. , Utsumi, D., Lund, K., Okano, M., Ohashi-Doi, K., Okubo, K., 2022. Correlation between sensitization to house dust mite major allergens, age, and symptoms in Japanese house dust mite allergic subjects. <i>Int. Immunopharmacol.</i> 107, 108640
231 centers in 13 countries: Belgium, Bulgaria, Canada, Czech Republic, France, Germany, Israel, Italy, Poland, Russian Federation, Slovakia, Spain, and the United States.	1607 HDM-allergic patients	Der p 1, Der p 2, Der p 4, Der p 5, Der p 7, Der p 11, Der p 14, Der p 15, Der p 18, Der p 20, Der p 21, Der p 23 and Der p 37	Der p 1 (83 %), Der p 2 (92 %), Der p 4 (17 %), Der p 5 (33 %), Der p 7 (23 %), Der p 11 (0 %), Der p 14 (1 %), Der p 15 (7 %), Der p 18 (5 %), Der p 20 (2 %), Der p 21 (28 %), Der p 23 (82 %), Der p 37 (19 %)	ImmunoCAP Immuno Solid-phase Allergen Chip (ISAC) technology	Potapova, E. , Bordas-Le Floch, V., Schlederer, T., Vrtala, S., Huang, H.J., Canonica, G.W., Valenta, R., Matricardi, P.M., Mascarell, L., 2022. Molecular reactivity profiling upon immunotherapy with a 300 IR sublingual house dust mite tablet reveals marked humoral changes towards major allergens. <i>Allergy</i> 77, 3084–3095.
Spain, A Coruña	50 HDM-allergic patients	Der p 1, Der p 2, Der p 5, Der p 7, Der p 10, Der p 11, Der p 20, Der p 21, Der p 23, Blo t 5, Blo t 10, Blo t 21, Lep d 2, Tyr p 2	Der p 1: 66 %; Der p 2: 78 %; Der p 5: 44 %; Der p 7: 36 %; Der p 10: 4 %; Der p 11: 0 %; Der p 20: 10 %; Der p 21: 40 %; Der p 23: 86 %; Blo t 5: 29 %; Blo t 10: 11.8 %; Blo t 21: 17.6 %; Lep d 2: 75.7 %; Tyr p 2: 48.6 %;	ALEX ²	Lopez-Rodriguez, R. , Rial, M.J., Esteban-Gorgojo, I., Perez, B.V., Lopez-Araujo, G.A., Perez-Quintero, O., Carballas, C., Parra, A., Pineda, F., 2022. Serodominance profile in a dust mite complex region. <i>Int. Arch. Allergy Immunol.</i> 183, 843–851.
Ukraine	10651 subjects (57.86 % children under the age of 18 % and 42.14 % adults) showing allergic disease in the anamnesis (allergic rhinitis, atopic dermatitis, bronchial asthma solely or in combination)	Der f 1, Der p 1, Der f 2, Der p 2, Der p 5, Der p 7, Der p 10, Der p 11, Der p 20, Der p 21 and Der p 23	Sensitization to at least one HDM allergens has been established in 2875 people, which made up 27.00 % of the studied sample (1993 (69.32 %) children (under the age of 18) vs 882 (30.68 %) adults) Entire group (% of all patients sensitized to corresponding allergen; Mean sIgE, kU/L M $\pm$ σ) Der f 1 (54.02; 15.02 $\pm$ 14.01) Der p 1 (54.5; 15.21 $\pm$ 13.23) Der f 2 (73.25; 27.43 $\pm$ 17.26) Der p 2 (72.1; 24.65 $\pm$ 17.19) Der p 5 (28.45; 14.06 $\pm$ 14.34) Der p 7 (22.57; 16.68 $\pm$ 6.89) Der p 10 (6.16; 13.23 $\pm$ 13.25) Der p 11 (0.56; 1.65 $\pm$ 3.34) Der p 20 (8.14; 9.49 $\pm$ 12.21) Der p 21 (27.34; 19.7 $\pm$ 17.28) Der p 23 (55.72; 16.06 $\pm$ 15.24)	ALEX ²	Rodinkova, V.V. , Yuriev, S.D., Kryvopustova, M. V., Mokin, V.B., Kryzhanovskiy, Y.M., Kurchenko, A.I., 2022. Molecular profile sensitization to house dust mites as an important aspect for predicting the efficiency of allergen immunotherapy. <i>Front. Immunol.</i> 13, 848616.
Italy, Pordenone and Rome	155 consecutive HDM-allergic patients (mean age: 27.5 years; range: 1–62)	Der f 1, Der p 1, Der f 2, Der p 2, Der p 5, Der p 7, Der p 10, Der p 11, Der p 20, Der p 21 and Der p 23	Der f 1 (67.1 %), Der p 1 (67.1 %), Der f 2 (73.5 %), Der p 2 (73.5 %), Der p 5 (26.4 %), Der p 7 (27.7 %), Der p 10 (6.45 %), Der p 11 (1.3 %), Der p 20 (14.2 %) and Der p 21 (30.3 %), Der p 23 (80 %)	ALEX ²	Villalta, D. , Scala, E., Asero, R., Da Re, M., Conte, M., Buzzulini, F., 2022. Evaluation and predictive value of IgE responses toward a comprehensive panel of house dust mite allergens using a new multiplex assay: a real-life experience on an Italian population. <i>Eur. Ann. Allergy Clin.</i> 54, 117–122.
Canada, Europe, South Africa, and the USA	685 HDM-allergic subjects	Der f 1, Der p 1, Der f 2, Der p 2, Der p 4, Der p 5, Der p 7, Der p 10, Der p 11, Der p 14, Der p 15, Der p 18, Der p 21, Der p 23, Der p 37, Blo t 5, Lep d 2	Der f 1, Der p 1, Der f 2, Der p 2 and Der p 23 as major allergens (prevalence above 50 %), Der p 4, p 5, p 7, and p 21 as mid-tier allergens (prevalence between 20 % and 50 %), and the remaining allergens (Der p allergens from groups 10, 11, 14, 15, 18, and 37, Blo t 5 and Lep d 2) as minor allergens (prevalence below 20 %) in the whole study population. With the important exception of the South African cohort, Der p 23 was the dominant HDM allergen (86 % prevalence) and Der p 7 achieved major allergen status (56 %).	ImmunoCAP Immuno Solid-phase Allergen Chip (ISAC) technology	Muddaluru, V. , Valenta, R., Vrtala, S., Schlederer, T., Hindley, J., Hickey, P., Larche, M., Tonti, E., 2021. Comparison of house dust mite sensitization profiles in allergic adults from Canada, Europe, South Africa and USA. <i>Allergy</i> 76, 2177–2188.

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Table 2 (continued)

Region	Subjects tested	Allergens tested	IgE sensitization patterns	Methods	References
Portugal (North and South)	217 HDM-allergic patients	Der p 1, Der p 2, Der p 10 and Der p 23	% Prevalence, Mean (SD) kUA /L Der p 1: 72.4, 21.7 (29.7) Der p 2: 89.4, 30.6 (34.0) Der p 10: 9.7, 1.6 (9.2) Der p 23: 77, 12.1 (19.9)	ImmunoCAP	Lima, R. , Spinola Santos, A., Araujo, L., Cosme, J., Inacio, F., Tomaz, E., Ferrao, A., Santos, N., Sokolova, A., Morete, A., Falcao, H., Cunha, L., Ferreira, A., Bras, A., Ribeiro, F., Lozoya, C., Leiria Pinto, P., Prates, S., Placido, J., Coimbra, A., Taborda-Barata, L., Pereira Santos, M.C., Pereira Barbosa, M., Pineda, F (2021). Molecular profile of sensitization to Dermatophagoides pteronyssinus dust mite in Portugal. J. Investig. Allergol. Clin. Immunol. 32, 33–39.
Spain, Tenerife	93 HDM-allergic patients with a clinical diagnosis of moderate-to-severe persistent asthma	Der p 1, Der p 2, Der p 5, Der p 7, Der p 10, Der p 11, Der p 20, Der p 21 and Der p 23	Der p 1 (74 %), Der p 2 (85.87 %), Der p 23 (85.87 %), Der p 5, Der p 7, and Der p 21 showed a prevalence up to 51 %, minor allergens such as Der p 10, Der p 11, and Der p 20 showed a prevalence up to 14.95 %	ALEX	Gonzalez-Perez, R. , Poza-Guedes, P., Pineda, F., Forstenlechner, P., Castillo, M., Mederos-Luis, E., Aumayr, M., Matheu, V., Alava-Cruz, C., Sanchez-Machin, I., 2021. Mite molecular profile in the Th2-polarized moderate-to-severe persistent asthma endotype subjected to high allergen exposure. Int. Arch. Allergy Immunol. 182, 21–31.
Belgium, Ghent	24 HDM-allergic patients had been treated with conventional HDM subcutaneous immunotherapy (SCIT)	Der f 1, Der p 1, Der f 2, Der p 2, Der p 4, Der p 5, Der p 7, Der p 10, Der p 11, Der p 14, Der p 15, Der p 18, Der p 21, Der p 23 and Der p 37	24 with SCIT , % Prevalence, Mean (SD) ISU Der f 1: 45.83 %, 7.49 (12.15) Der p 1: 58.33 %, 16.04 (27.63) Der f 2: 83.33 %, 26.20 (37.43) Der p 2: 91.67 %, 19.98 (31.83) Der p 4: 33.33 %, 1.05 (0.68) Der p 5: 12.50 %, 0.54 (0.16) Der p 7: 41.67 %, 3.60 (3.96) Der p 10: 20.83 %, 0.51 (0.17) Der p 11: 0.00 %, 0.00 (0.00) Der p 14: 0.00 %, 0.00 (0.00) Der p 15: 4.17 %, 0.00 (0.00) Der p 18: 8.33 %, 14.16 (19.37) Der p 21: 29.17 %, 3.64 (5.52) Der p 23: 45.83 %, 15.09 (34.66) Der p 37: 12.5 %, 2.22 (2.58)	ImmunoCAP Immuno Solid-phase Allergen Chip (ISAC) technology	Rodriguez-Dominguez, A. , Berings, M., Rohrbach, A., Huang, H.J., Curin, M., Gevaert, P., Matricardi, P.M., Valenta, R., Vrtala, S., 2020. Molecular profiling of allergen-specific antibody responses may enhance success of specific immunotherapy. J. Allergy Clin. Immunol. 146, 1097–1108.
Poland (North-Eastern)	323 adult HDM-allergic patients showing respiratory symptoms	nDer p 1, nDer p 2, rDer p 2.0101, rDer p 23	nDer p 1 (72.1 %), nDer p 2 (81.7 %), rDer p 2.0101 (78.3 %) and rDer p 23 (70.9 %)	ELISA	Kowal, K. , Pampuch, A., Siergiejko, G., Siergiejko, Z., Swiebocka, E., Schlachter, C.R., Chruszcz, M., Jacquet, A., 2020. Sensitization to major Dermatophagoides pteronyssinus allergens in house dust mite allergic patients from North Eastern Poland developing rhinitis or asthma. Adv. Med. Sci. 65, 304–309.
Spain, Barcelona	276 children with clinical manifestations of respiratory allergy and sensitization to <i>D. pteronyssinus</i> and/or <i>D. farinae</i>	Der f 1, Der p 1, Der f 2, Der p 2, Der p 10, Der p 23, Blo t 5, Lep d 2	ImmunoCAP: % Prevalence, Median (IQR) kUA /L Der p 1: 86.6, 33.7 (8.3–83.9) Der p 2: 79.3, 42.5 (18.6–96.1) Der p 10: 9.8, 3.6 (1.2–8.5) Der p 23: 75.8, 6.6 (3.1–16.1) ImmunoCAP ISAC: %, Median (IQR) ISU Der f 1: 75.0, 12 (5.2–26.0) Der p 1: 75.4, 12 (5.1–23.0) Der p 2: 79.3, 22 (9.0–43.0) Der f 2: 77.9, 31 (15.0–61.0) Der p 10: 9.4, 10.5 (2.9–28.5) Blo t 5: 15.6, 1.7 (0.7–4.9) Lep d 2: 23.2, 1.95 (0.7–4.7)	ImmunoCAP: nDer p 1, rDer p 2, rDer p 23 and rDer p 10 ImmunoCAP ISAC: nDer p 1, nDer f 1, rDer p 2, rDer f 2, rLep d 2, rBlo t 5, rDer p 10	Jimenez-Feijoo, R. , Pascal, M., Moya, R., Riggioni, C., Dominguez, O., Lozano, J., Alvaro-Lozano, M., Piquert, M., Machinena, A., Folque, M., Dias, M., Carnes, J., Plaza, A.M., 2020. Molecular diagnosis in house dust mite-allergic patients suggests that Der p 23 is clinically relevant in asthmatic children. J. Investig. Allergol. Clin. Immunol. 30, 127–132.

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Table 2 (continued)

Region	Subjects tested	Allergens tested	IgE sensitization patterns	Methods	References
Spain, Tenerife	63 patients with severe persistent allergic rhinitis had a positive SPT result to <i>D. pteronyssinus</i>	Der p 1, Der p 2, Der p 10 and Der p 23	% Prevalence, Median (kUA/L) Der p 1: 75 %, 3.72 Der p 2: 80 %, 10.16 Der p 10: 8.33 %, 0.02 Der p 23: 80 %, 2.42	ImmunoCAP	Gonzalez-Perez, R. , Pineda, F., Poza-Guedes, P., Castillo, M., Matheu, V., Sanchez-Machin, I., 2020. Molecular allergen profiling of dual mite sensitization in severe allergic rhinitis. <i>J. Investig. Allergol. Clin. Immunol.</i> 30, 421–429.
China, Guangzhou	432 patients have been diagnosed to have asthma and/or allergic rhinitis and mite sensitization	Der f 1, Der p 1, Der f 2, Der p 2, Der p 3, Der p 5, Der p 7, Der p 10, Der p 23 and Blo t 5	Der f 1: 74.07 %, Der p 1: 81.48 %, Der f 2: 77.78 %, Der p 2: 66.20 %, Der p 3: 1.85 %, Der p 5: 15.05 %, Der p 7: 29.40 %, Der p 10: 10.65 %, Der p 23: 54.63 %, Blo t 5: 28.01 %	EUROIMMUN system	Huang, Z.F. , Zou, X.W., Chen, H., Liao, C.X., Hu, H.S., Luo, W.T., Sun, B.Q., 2020. Identifying potential co-sensitization and cross-reactivity patterns based on component-resolved diagnosis. <i>Int. Arch. Allergy Immunol.</i> 181, 81–93.
Slovenia	288 HDM-sensitized subjects (118 allergic rhinitis, 53 asthma, 21 dermatitis, 17 urticaria, and 79 subjects, no diagnosis of allergic disease)	Der p 1, Der p 2, Der p 4, Der p 5, Der p 7, Der p 10, Der p 11, Der p 14, Der p 15, Der p 18, Der p 21, Der p 23	Symptomatic patients: Der p 1 (82.3 %), Der p 2 (82.3 %), Der p 5 (41.2 %), Der p 7 (41.2 %), Der p 23 (70.6 %) Asymptomatic subjects: Der p 1 (57.9 %), Der p 2 (57.9 %), Der p 5 (21 %), Der p 7 (5.3 %), Der p 23 (26.3 %) Der p 4, Der p 10, Der p 11, Der p 14, Der p 15, Der p 18 and Der p 21 were rarely recognized	Immuno-dot blot test	Zidarn, M. , Robic, M., Krivec, A., Silar, M., Resch-Marat, Y., Vrtala, S., Kopac, P., Bajrovic, N., Valenta, R., Korosec, P., 2019. Clinical and immunological differences between asymptomatic HDM-sensitized and HDM-allergic rhinitis patients. <i>Clin. Exp. Allergy</i> 49, 808–818.
Austria, Vienna	Cohort 1: 27 HDM-sensitized patients	Der p 1, Der p 2, Der p 4, Der p 5, Der p 7, Der p 10, Der p 11, Der p 14, Der p 15, Der p 18, Der p 21, Der p 23 and Der p 37 (clone 16)	Cohort 1 , % Prevalence, Mean of positive (Min-Max) ISU Der p 1: 85.2 %, 2.4 (0.3–11.3) Der p 2: 81.5 %, 16.7 (0.3–52.4) Der p 4: 14.8 %, 0.7 (0.3–1.5) Der p 5: 51.9 %, 5.0 (0.4–30.0) Der p 7: 25.9 %, 6.0 (0.3–39.1) Der p 10: 14.8 %, 0.3 (0.3–0.3) Der p 11: 0 %, -(—) Der p 14: 0 %, -(—) Der p 15: 0 %, -(—) Der p 18: 18.5 %, 2.2 (0.8–6.4) Der p 21: 48.1 %, 2.8 (0.3–8.9) Der p 23: 70.4 %, 4.7 (0.3–24.8) Der p 37 (clone 16): 11.1 %, 1.7 (1.1–2.3)	ImmunoCAP Immuno Solid-phase Allergen Chip (ISAC) technology	Huang, H.J. , Resch-Marat, Y., Rodriguez-Dominguez, A., Chen, K.W., Kiss, R., Ziegelmayer, P., Ziegelmayer, R., Lemell, P., Horak, F., Valenta, R., Vrtala, S., 2018. Underestimation of house dust mite-specific IgE with extract-based ImmunoCAPs compared with molecular ImmunoCAPs. <i>J. Allergy Clin. Immunol.</i> 142, 1656–1659.
Germany (Berlin, Dusseldorf, Mainz, Freiburg, and Munich)	1314 participants	Der p 1, Der p 2, Der p 4, Der p 5, Der p 7, Der p 11, Der p 14, Der p 15, Der p 18, Der p 21, Der p 23 and Der p 37 (clone 16)	Der p 1 (61.3 %), Der p 2 (77 %), Der p 4 (36.6 %), Der p 5 (37.2 %), Der p 7 (30.9 %), Der p 11 (22 %), Der p 14 (17.8 %), Der p 15 (11.5 %), Der p 18 (12.0 %), Der p 21 (22.5 %), Der p 23 (50.8 %), Der p 37 (clone 16) (11.0 %)	ImmunoCAP Immuno Solid-phase Allergen Chip (ISAC) technology	Posa, D. , Perna, S., Resch, Y., Lupinek, C., Panetta, V., Hofmaier, S., Rohrbach, A., Hatzler, L., Grabenhenrich, L., Tsilochristou, O., Chen, K.W., Bauer, C.P., Hoffman, U., Forster, J., Zepp, F., Schuster, A., Wahn, U., Keil, T., Lau, S., Vrtala, S., Valenta, R., Matricardi, P.M. (2017). Evolution and predictive value of IgE responses toward a comprehensive panel of house dust mite allergens during the first 2 decades of life. <i>J. Allergy Clin. Immunol.</i> 139, 541–549.
USA, Washington	47 mite-allergic patients	Der p 1, Der p 2, Der p 5, Der p 7, Der p 8 and Der p 23	Prevalence, Median (Min-Max) IU/ML Der p 1: 87 %, 5.3 (0–675) Der p 2: 79 %, 5.5 (0.2–782) Der p 5: 47 %, 0.4 (0.2–58) Der p 7: 23 %, 0.5 (0.1–49) Der p 8: 53 %, 0.6 (0–50) Der p 23: 75 %, 1.3 (0.1–23)	ELISA	Mueller, G.A. , Randall, T.A., Glesner, J., Pedersen, Posa, D., Perna, S., Resch, Y., Lupinek, C., Panetta, V., Hofmaier, S., Rohrbach, A., Hatzler, L., Grabenhenrich, L., Tsilochristou, O., Chen, K.W., Bauer, C.P., Hoffman, U., Forster, J., Zepp, F., Schuster, A., Wahn, U., Keil, T., Lau, S., Vrtala, S., Valenta, R., Matricardi, P.M., 2017. Perera, L., Edwards, L.L., DeRose, E.F., Chapman, M.D., London, R.E., Pomes, A., 2016. Serological, genomic and structural analyses of the major mite allergen Der p 23. <i>Clin. Exp. Allergy</i> 46, 365–376.

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Table 2 (continued)

Region	Subjects tested	Allergens tested	IgE sensitization patterns	Methods	References
Germany/Austria	105 allergic children with HDM-associated asthma; 53 children with HDM allergy but without asthma; 53 nonatopic children	Der p 1, Der p 2, Der p 3, Der p 5, Der p 7, Der p 10, Der p 21 and Der p 23	Asthmatic patients: Der p 1 (77 %), Der p 2 (81 %), Der p 5 (39 %), Der p 7 (37 %), Der p 10 (2 %), Der p 21 (29 %), Der p 23 (71 %) Nonasthmatic patients: Der p 1 (74 %), Der p 2 (60 %), Der p 5 (13 %), Der p 7 (19 %), Der p 10 (0 %), Der p 21 (15 %), Der p 23 (59 %) Subjects > 10 yr, % IU/ML (95 % CI) Der p 1: 78.7 %, 101.58 (78.70–124.45) Der p 2: 74.5 %, 40.60 (22.66–58.54) Der p 3: 14.9 %, 7.35 (1.32–16.02) Der p 5: 19.1 %, 17.69 (3.11–32.26) Der p 7: 23.4 %, 9.40 (0.77–18.03) Der p 21: 25.5 %, 11.35 (1.18–21.53) Blo t 2: 21.3 %, 4.92 (1.20–11.05) Blo t 4: 29.8 %, 8.44 (1.92–14.96) Blo t 5: 63.8 %, 41.82 (24.14–59.51) Blo t 7: 51.1 %, 33.63 (17.08–50.18) Blo t 15: 21.3 %, 12.54 (2.20–22.87) Blo t 21: 70.2 %, 57.37 (37.15–77.59)	ImmunoCAP Immuno Solid-phase Allergen Chip (ISAC) technology	Resch, Y., Michel, S., Kabesch, M., Lupinek, C., Valenta, R., Vrtala, S., 2015. Different IgE recognition of mite allergen components in asthmatic and nonasthmatic children. <i>J. Allergy Clin. Immunol.</i> 136, 1083–1091.
Singapore	A total of 253 mite-allergic children, mean age 7.3 yr (range 0.4–18.4), were included, 79 % fulfilled diagnostic criteria for allergic rhinitis, 47 % asthma, 72 % atopic dermatitis and 31 % for all three	Der p 1, Der p 2, Der p 3, Der p 5, Der p 7, Der p 21, Blo t 2, Blo t 4, Blo t 5, Blo t 7, Blo t 15, Blo t 21		Immuno-dot blot test	Kidon, M.L., Chin, C.W., Kang, L.W., Ching, O.T., Seng, T.Y., Ning, W.K., Angus, A.C., Theng, O.S., Feng, G.Y., Reginald, K., Zhi, B.X., Shen, S.H., Chew, F.T., 2011. Mite component-specific IgE repertoire and phenotypes of allergic disease in childhood: The tropical perspective. <i>Pediatr. Allergy Immunol.</i> 22, 202–210.

1 is one of the most abundant allergen molecules present in faecal pellets from *D. pteronyssinus* and exists as a dimer under neutral conditions. The biological function of Der p 1 was identified as cysteine protease, which is produced as a proform and becomes biologically active after cleavage of the propeptide (Lienard et al., 2007). The activation can be obtained by self-cleavage of Der p 1 and the cysteine protease activity of Der p 1 can also activate the other proteolytic HDM allergens, Der p 3, Der p 6 and Der p 9 (Herman et al., 2014). The protease activity of Der p 1 can disrupt the airway epithelial barriers by cutting the transmembrane molecules occludin and claudin, facilitating the allergen to enter the tissue. Because of this disruption, also other allergens without protease activity can enter, thus increasing the danger of sensitization also to those allergens (Kalsheker et al., 1996; Winton et al., 1998). It was also reported that metal ions (Ca^{2+} or Mg^{2+}) are bound to Der p 1, but the exact function of them is unknown. It was speculated that the metal ions Ca^{2+} and Mg^{2+} can increase the catalytic activity of papain (cysteine protease), thus they might assist enzyme activity (Kaul et al., 2002).

3.2. Der p 2

Der p 2 represents a 14 kDa HDM allergen, that shows IgE reactivity with sera from 80 % to 100 % of HDM allergic patients and thus is also classified as major allergen. The allergen is mainly located in the gut and faecal pellets of *D. pteronyssinus* and can therefore easily be inhaled by the patients (Park et al., 2000). Der p 2 shows biological and amino acid sequence similarity to MD-2 (Trompette et al., 2009), which belongs to the ML (MD-2 related lipid binding) domain family, and Der p 2 shows the highest sequence similarity to NPC2 in the ML domain family (Inohara and Nunez, 2002). Because of the similarity of Der p 2 to MD-2, Der p 2 can bind to lipopolysaccharide (LPS) and activate the toll-like receptor 4 (TLR4). This can induce inflammation due to the activation of nuclear factor- κB (NF- κB) and MAPK (Osterlund et al., 2009).

3.3. Der p 5

Der p 5 is a 15 kDa allergen with unknown function and shows IgE reactivity with 30–40 % of HDM allergic patients' sera. The allergen has high allergenic activity and is classified as mid-tier allergen. Der p 5 is localized in secretory granules of midgut epithelial cells of *D. pteronyssinus* and can be found in the faeces of mites (Weghofer et al., 2008b). Monomeric recombinant Der p 5 purified from *Pichia pastoris* under mild acidic pH was able to bind lipid ligands and to stimulate airway epithelial cells by activating TLR-2 dependent pathways (Pulsawat et al., 2019). The three-dimensional structure showed that polymerized Der p 5 creates a hydrophobic cavity which could possibly be a ligand-binding site (Mueller et al., 2010b). Although the amino acid sequence of Der p 5 has 42 % identity with that of Blo t 5, the major allergen from *B. tropicalis*, almost no IgE cross-reactivity was found between these two allergens (Chew et al., 1999; Lahiani et al., 2019; Weghofer et al., 2008b).

3.4. Der p 7

Der p 7 is a 22 kDa allergen with 30–40 % IgE binding frequency. It is considered as mid-tier allergen, but in some regions such as South Africa, it is even recognized by 56 % of HDM-allergic patients and thus a major allergen (Muddaluru et al., 2021). The function of Der p 7 has not been elucidated so far, but it was speculated that it might represent a lipid-binding protein. The structure of Der p 7 has similarity to a human bactericidal permeability increasing protein (BPI) and lipopolysaccharide-binding protein (LBP) which may interact with Toll-like receptors (TLRs) after binding LPS and other bacterially-derived lipid ligands. However, the binding of Der p 7 to LPS was not proven, but it was shown that Der p 7 has a weak affinity to the bacterial lipopeptide polymyxin (Mueller et al., 2010a). The IgE epitopes of Der p 7 are mainly conformational (Curin et al., 2021) and the hydrophobic cavities on Der p 7 might be the positions which bind apolar ligands (Mueller et al., 2010a).

3.5. Der p 21

Der p 21 is a 15 kDa allergen and the prevalence of IgE-reactivity is around 30 %; therefore, Der p 21 is classified as mid-tier HDM allergen. It is localized in the midgut of *D. pteronyssinus* and can also be found in faeces, where it becomes airborne and can be uptaken by allergic patients (Weghofer et al., 2008a). The biological function of Der p 21 is still unknown. However, a study has shown that Der p 21 was able to activate airway epithelial cells through TLR2 signaling, suggesting that the allergenicity of Der p 21 is mediated by interactions with lipid/fatty acid ligands (Pulsawat et al., 2014). Der p 21 has an amino acid sequence similarity of 31 % with Der p 5 and both allergens contain a major conformational IgE epitope located on similar areas of their structure (Curin et al., 2018). However, no IgE cross-reactivity was found between Der p 21 and Der p 5, indicating that they represent two independent allergens (Weghofer et al., 2008a).

3.6. Der p 23

Der p 1 and Der p 2 were considered as the only two major HDM allergens since the 1980s until the identification of Der p 23 in 2013. Der p 23 is a very small allergen with only 8 kDa and it binds IgE from 70 % to 86 % of HDM allergic patients. Because of its high IgE-binding prevalence and its high allergenic activity, this allergen represents a major allergen. Der p 23 is located in the peritrophic matrix on the surface of mite faecal pellets (Weghofer et al., 2013). The amino acid sequence of Der p 23 shows similarities to chitin-binding domains, but so far, no chitin-binding activity was demonstrated (Soh et al., 2015; Weghofer et al., 2013). Although the function of Der p 23 is unknown, Der p 23 shows typical features of peritrophins, like its localization in the peritrophic matrix and the peritrophin-A domain in its sequence (Weghofer et al., 2013). It has been reported that peritrophins can directly activate the innate immune system, but no data are available about the effect of Der p 23 on the innate immune response (Mika et al., 2011). IgE sensitization to Der p 23 in the childhood was found to be significantly associated with asthma, indicating that Der p 23 might be an asthma marker for children (Posa et al., 2017; Resch et al., 2015).

3.7. Cross-reactive allergens

Der p 10, a 37 kDa protein, shows IgE-reactivity with approximately 10 % of HDM allergic patients' sera and low allergenic activity, thus it is of low relevance for HDM allergic patients (Resch et al., 2011). However, in certain areas, considerably higher IgE-binding frequencies were found of sometimes more than 50 % (Westritschnig et al., 2003). Der p 10 represents the alpha-helical muscle protein tropomyosin and the amino acid sequences of tropomyosins are highly conserved among invertebrates, with e.g., 78–84 % sequence identity between the tropomyosins of HDMs and crustacean (Reese et al., 1999). Therefore, a high degree of cross-reactivity is found between tropomyosins of HDMs and those of other invertebrates, e.g., insects, parasites and seafood (Acedo et al., 2009; Wittenman et al., 1994). The high IgE-binding frequencies of Der p 10 found in certain populations might thus be due to cross-reactivity to tropomyosins from crustacean, cockroaches or parasites (Ayuso et al., 2002). Although Der p 10 represents a minor allergen for HDM allergic patients, it was described as the major allergen for seafood allergic patients, where it can induce severe systemic anaphylaxis (Lopata and Lehrer, 2009). Der p 10 might however contribute to shrimp allergy as primary sensitizer via airway, accounting for mild or severe allergies upon consumption of shellfish (Mahammed et al., 2022). A lower sequence homology (55–65 %) was found between Der p 10 and vertebrate tropomyosins and there is no cross-reactivity between HDM and vertebrate tropomyosins.

Der p 20 is the arginine kinase of HDM and similar to tropomyosin, it is a cross-reactive pan-allergen found in all crustaceans and invertebrates (Binder et al., 2001). Patients sensitized to Der p 20 showed

a higher prevalence of asthma symptoms, but little is known about the importance of arginine kinases for other invertebrate allergies (Sarzsinszky et al., 2021).

A series of other HDM allergens (e.g., paramyosin, troponin C, triose-phosphate isomerase and myosin light chain) can be found in other allergen sources and were identified in crustacean as allergens. However, little is known about their role in seafood allergy and cross-reactivity of these allergens (Celi et al., 2020; Giuffrida et al., 2014).

Der p 4 is an alpha amylase of 57 kDa and the IgE binding frequency differs considerably between different populations. It has been shown that Der p 4 binds IgE from sera of scabies infected subjects in the absence of binding to the major HDM allergens, indicating a cross-reactivity of Der p 4 to other amylases (Walton et al., 2015).

Der p 8, the mite glutathione S-transferase has homology to those of cockroaches and parasites, but the low conservation of surface amino acids supports the finding that there is only very low cross-reactivity between different glutathione S-transferases (Mueller et al., 2015).

3.8. House dust mite-related allergic diseases

Early in 1921, Kern reported that HDM sensitization is associated with asthma (Kern, 1921). Since then more and more studies have shown a strong correlation of levels of HDM exposure and HDM sensitization with allergic symptoms such as asthma, rhinitis, conjunctivitis and atopic dermatitis (Asher et al., 2006; Dowse et al., 1985; Sporik et al., 1990). The identification of individual HDM allergens and the development of component-resolved diagnosis allows a correlation between sensitization to specific HDM allergens and certain allergic diseases. Understanding the association of allergen sensitization with disease provides useful information for the clinicians regarding prevention of disease progression and treatment of patients suffering from HDM allergy.

3.9. Asthma

HDM allergic patients commonly show respiratory symptoms such as rhinitis, coughing, wheezing and asthma, by inhaling mite allergens. Exposure to HDMs is known to be strongly associated with rhinitis and asthma symptoms (Wang et al., 2014). A study conducted by Adnan Custovic et al. showed that asthma symptoms of mite-sensitized patients were more severe when high concentrations of Der p 1 and Der p 2 were found in the dust of their beds (Custovic et al., 1996). The German Multicenter Allergy Study monitored HDM sensitization of participants from birth until the age 20 years. It showed that early IgE sensitization to mite allergens during childhood and higher mite exposure was associated with mite polysensitization and a higher risk to develop allergic rhinitis and asthma (Posa et al., 2017). Using recombinant allergens, it was possible to associate asthma with sensitization to certain HDM allergen molecules. In a cross-sectional study of mite-sensitized asthmatic and nonasthmatic children, it was shown that the asthmatic children recognized more HDM allergens than nonasthmatic children. Furthermore, IgE levels to certain HDM allergens (Der p 1, Der p 2, Der p 5, and Der p 23) were significantly higher in asthmatic children compared to the nonasthmatic HDM-sensitized children (Resch et al., 2015). Higher IgE levels to Der p 1 and Der p 23 in HDM-allergic asthmatic patients were also found by another study group (Potapova et al., 2022) and an early life sensitization to Der p 1 or Der p 23 was shown to be a risk factor for the development of asthma (Posa et al., 2017).

Recently, a study showed that sensitization to the newly identified minor HDM allergen, Der p 37, is correlated to asthma, with 43 % of patients with asthma sensitized to Der p 37 compared to 20 % in non-Der p 37-sensitized patients (Huang et al., 2022). The sensitization to another minor HDM allergen, Der p 20, (arginine kinase) was found to be associated with asthma, wheezing and breathing problems (Sarzsinszky et al., 2021).

3.10. Atopic dermatitis

Atopic dermatitis affects 5–20 % of the pediatric population and 2–8 % of adults, causing a global problem (Wollenberg et al., 2018; Wollenberg et al., 2016). Polysensitization to airborne, food-derived, microbial allergens and autoallergens are common in patients suffering from atopic dermatitis (Reginald et al., 2011), but mites are the most relevant allergen sources for atopic dermatitis (Bumbacea et al., 2020). Already in the 1970s, HDMs were considered as a possible allergen source to induce atopic dermatitis (Alani and Haarlov, 1972). The beds of patients provide perfect conditions for mites to grow and reproduce, by obtaining the skin scales from the patients, and they can induce allergic skin symptoms. In forty to eighty percent of patients with atopic dermatitis, HDM-specific IgE antibodies were detected (Huang et al., 2021; Mittermann et al., 2021; Takahashi et al., 1977) and an increase of mast cells was found on patients' skin, indicating that mite sensitization might be a major cause for atopic dermatitis (Mitchell et al., 1986). In the cross-sectional Taiwan Childhood Environment and Allergic diseases Study (TCEAS), skin prick tests with HDMs (*D. pteronyssinus*, *D. farinae*, *D. microceras* and *B. tropicalis*) were performed on 3192 children, showing that mite sensitization was associated with significant increases in the risk of atopic dermatitis (Huang et al., 2021). Using recombinant mite allergens, it was shown that Der p 11 and other allergens that are mainly present in the mite bodies but not in the faeces (e.g., Der p 10, Der p 18) are more frequently recognized by IgE antibodies from patients suffering from atopic dermatitis than by patients with only respiratory symptoms. It was supposed that atopic dermatitis patients become sensitized by exposure to the allergens present in the mite bodies through skin contact instead of inhalation (Banerjee et al., 2015; Resch et al., 2016).

4. HDM allergen molecules for diagnosis and immunotherapy

The clinical evaluation of patients with suspected HDM allergy includes a history of HDM-related symptoms upon exposure with HDMs in the environment. Since this type of history is not specific and can only suspect an association between allergic symptoms and HDM allergy, allergy testing by *in vivo* skin prick test (SPT)/provocation test and *in vitro* serological tests are performed to diagnose HDM allergy. Skin prick tests are used to demonstrate an immediate IgE-mediated allergic reaction to allergens. Provocation tests are used to evaluate local allergic rhinitis upon exposure with HDM allergens by a nasal, a bronchial or a conjunctival provocation test (Agache et al., 2015). Serological testing is performed to detect HDM-specific IgE antibodies in patients' sera, e.g., by ImmunoCAP with HDM extracts (Der p extract, d1 or Der f extract, d2). However, HDM extracts used for SPTs or serological testing are difficult to standardize and contain Der p 1 and Der p 2 in variable amounts. Der p 23 and other clinically relevant HDM molecules such as Der p 5, Der p 7 and Der p 21 are often underrepresented or even absent from the extracts (Casset et al., 2012). Because of this, diagnosis of HDM allergy with HDM extracts might be inconsistent depending on the extract composition and a study showed that HDM allergen-specific IgE was underestimated when HDM extracts were used for diagnosis (Huang et al., 2018). Additionally, HDM-sensitized subjects without Der p 1 and Der p 2 sensitization might not be diagnosed if an extract with only these two allergens is applied. Generally, HDM-allergic patients are polysensitized to several HDM allergens, but HDM allergic patients with monosensitization to HDM allergens different from Der p 1 and Der p 2 can be found. Several studies showed that 2–8 % of HDM-sensitized subjects are mono-sensitized to Der p 23 (Becker et al., 2016; Limao et al., 2021; Lopez-Rodriguez et al., 2022; Muddaluru et al., 2021; Rodinkova et al., 2022), thus it would be crucial to use this allergen for diagnosis of HDM allergic patients, because Der p 23 represents an important allergen that can induce severe symptoms. However, it will not be possible to obtain HDM extracts with sufficient amounts of Der p 23, because the RNA expression level of Der p 23 is thirty-fold less than

Der p 1 and sevenfold less than Der p 2 in mites, resulting in a very low abundance of Der p 23 in HDM extracts (Mueller et al., 2016). Therefore, molecular diagnosis with well characterized individual allergen components represents a major advantage for the correct diagnosis of HDM sensitized patients. Allergen components can easily be standardized and allow the determination of the patients' exact sensitization profile and the component-specific IgE levels. ImmunoCAPs (Thermo Fisher Scientific/Phadia, Uppsala, Sweden) based on individual HDM allergen components are commercially available to detect serum IgE antibodies specific for Der p 1, Der p 2, Der p 10 and Der p 23. The disadvantage of these tests is that every allergen has to be tested individually, therefore, microarray-based allergen tests have been developed that contain several allergens on a small glass plate and thus allow simultaneous detection of specific IgE to different allergen molecules using tiny amounts of serum (van Hage et al., 2017). Microarray-based allergen tests are already commercially available and contain allergens from different allergen sources. The ImmunoCAP ISAC 112 (Thermo Fisher Scientific/Phadia, Uppsala, Sweden) contains 112 allergens from 48 allergen sources and allows measurement of specific IgE to the HDM allergens, Der p 1, Der f 1, Der p 2, Der f 2, Der p 10 and Der p 23 (Gadisseur et al., 2011). Another commercial microarray allergy test, ALEX² (MacroArray Diagnostics, Vienna, Austria), contains 120 extracts from different allergen sources and up to 180 allergen components. Using this test, specific IgE to the HDM components Der p 1, Der f 1, Der p 2, Der f 2, Der p 5, Der p 7, Der p 10, Der p 11, Der p 20, Der p 21 and Der p 23 can be measured (Platteel et al., 2022). Another microarray chip that was used in several studies to detect specific IgE to HDM allergens was developed within the MeDAL (Mechanisms of the Development of ALlergy) project and was based on the ImmunoCAP ISAC. It contained more HDM allergens than the commercially available microarrays, namely Der p 1, Der f 1, Der p 2, Der f 2, Der p 4, Der p 5, Der p 7, Der p 10, Der p 11, Der p 14, Der p 15, Der p 18, Der p 21, Der p 23 and Der p 37 (previously named clone 16) (Lupinek et al., 2014). The different multiplex tests as well as singleplex tests like ImmunoCAPs, dot blot and ELISA assays were widely used worldwide to determine the sensitization profiles of HDM allergic patients and to identify the most important HDM allergens. The studies showed that Der p 1, Der p 2 and Der p 23 are the most important allergens worldwide and that Der p 5, Der p 7 and Der p 21 are also important HDM allergens, although the IgE-binding frequency differed between different regions (Table 2). The determination of the sensitization profile of a certain patient with component-specific diagnosis also would help the clinicians to decide whether the patient should receive immunotherapy or not. Immunotherapy is considered as an efficient treatment to generate allergen-specific blocking IgG antibodies and to obtain a long-term protection from allergic diseases. Additionally, it was shown that allergen-specific immunotherapy administered in early-life can prevent the development of allergic diseases and prevent the progression to more severe disease manifestations (Zeng et al., 2016). However, since immunotherapy is performed with HDM extracts, which often do not contain certain clinically relevant allergens (e.g., Der p 5, Der p 7, Der p 21 and Der p 23) in sufficient amounts (Casset et al., 2012), the success of immunotherapy depends very much on the composition of the extract used and the IgE-sensitization profile of the patient. It was shown that HDM extract-based immunotherapy induced protective IgG antibodies only to those allergens that are present in the extract (mainly Der p 1 and Der p 2) (Rodriguez-Dominguez et al., 2020) and thus only those patients with exclusive sensitization to the allergens present in the extract benefit from the treatment (Chen et al., 2019). Therefore, the success of immunotherapy can be improved by a component-specific diagnosis, to identify those patients that are suitable for the treatment with HDM extracts. It is not possible to obtain HDM extracts that contain all important allergens in sufficient amounts, because some allergens, e.g., Der p 23 are only produced in very small amounts in the mites (Mueller et al., 2016). Therefore, the best way to improve immunotherapy of HDM allergic patients might be to exchange the extracts by individual

allergens, which can be produced easily in the desired quantity. Much effort has already been invested to produce variants of the most important HDM allergens with reduced allergenic activity, to improve the efficacy as well as the safety of the treatment (Durham and Shamji, 2022).

5. Conclusion

Component-resolved diagnosis and immunotherapy with individual HDM allergens are promising tools to improve the current situation for HDM allergic patients. However, they require a thorough characterization of the individual HDM allergens regarding their clinical importance. Although up to date 40 groups of HDM allergens have been identified, it seems that only six of them, the major allergens, Der p 1, Der p 2 and Der p 23, as well as the mid-tier allergens, Der p 5, Der p 7 and Der p 21 are clinically relevant. Using these six allergens, it will be possible to diagnose almost all HDM allergic patients and a mix of these allergens will be sufficient to treat the majority of HDM allergic patients. However, other HDM allergens, e.g., Der p 10, Der p 11, Der p 20 and Der p 37, should be added to diagnostic tests, in order to predict symptoms or possible cross-reactions to unrelated allergen sources.

Data Availability

Data will be made available on request.

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