



Contents lists available at ScienceDirect

Allergology International

journal homepage: <http://www.elsevier.com/locate/alit>

Invited review article

Common food allergens and their IgE-binding epitopes

Hiroaki Matsuo^{a,*}, Tomoharu Yokooji^b, Takanori Taogoshi^a^a Department of Pharmaceutical Services, Hiroshima University Hospital, Hiroshima, Japan^b Department of Pathophysiology and Therapeutics, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

ARTICLE INFO

Article history:

Received 6 May 2015

Received in revised form

18 June 2015

Accepted 23 June 2015

Available online xxx

Keywords:

Allergen

Diagnosis

Epitope

Food allergy

Immunoglobulin E

Abbreviations:

AA, amino acid; AAI, α -amylase inhibitor;

IgE, immunoglobulin E; LMW-GS, low

molecular weight glutenin subunits;

LTP, lipid transfer protein; OM, ovomucoid;

OVA, ovalbumin; WDEIA, wheat-dependent

exercise-induced anaphylaxis

ABSTRACT

Food allergy is an adverse immune response to certain kinds of food. Although any food can cause allergic reactions, chicken egg, cow's milk, wheat, shellfish, fruit, and buckwheat account for 75% of food allergies in Japan. Allergen-specific immunoglobulin E (IgE) antibodies play a pivotal role in the development of food allergy. Recent advances in molecular biological techniques have enabled the efficient analysis of food allergens. As a result, many food allergens have been identified, and their molecular structure and IgE-binding epitopes have also been identified. Studies of allergens have demonstrated that IgE antibodies specific to allergen components and/or the peptide epitopes are good indicators for the identification of patients with food allergy, prediction of clinical severity and development of tolerance. In this review, we summarize our current knowledge regarding the allergens and IgE epitopes in the well-researched allergies to chicken egg, cow's milk, wheat, shrimp, and peanut.

Copyright © 2015, Japanese Society of Allergy. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The prevalence of food allergy in Japan is estimated to be 5%–10% among infants (aged 0–6 years) and 1.5%–3% among school-aged children (aged >6 years), and the prevalence among adults is thought to be similar to that of schoolchildren.^{1,2} The prevalence of food allergy among pediatric patients in the U.S. and Europe is reported to be 8% and 6.9%, respectively, which is similar to that in Japan. The most common foods that induce immediate-type food allergy in Japan are chicken egg (38.2% of food allergy patients), cow's milk (15.9%), wheat (8%), shellfish (6%), fruit (6%), buckwheat (5%), fish (4%), peanut (3%), and fish roe (3%).¹ The frequency of causative foods in the U.S. is different: peanut (25.2%), cow's milk (21.1%), shellfish (17.2%), tree nut (13.1%), chicken egg (9.8%), fin fish (6.2%), strawberry (5.3%), and wheat (5.0%).³ In European patients, the most common causative foods in order of decreasing frequency

are cow's milk, wheat, chicken egg, fish, soy, tree nut, shellfish, and peanut.⁴ Despite these differences, there is a global trend toward an increased prevalence of food allergy.^{5,6}

To understand the pathogenesis of food allergy and establish effective approaches for diagnosis, treatment, and prevention, detailed information on the allergen molecule is essential. Recently, a number of allergen molecules have been identified, and their three-dimensional (3-D) structures have been determined by advanced biological and analytical methods. The immunoglobulin E (IgE) recognition sites (IgE-binding epitopes) in allergens contribute to allergenicity. Therefore, it is important to identify the epitope structure for the development of new strategies for accurate diagnosis and allergen-specific immunotherapy of food allergy as well as the production of hypoallergenic foods. The benefit of component-resolved diagnosis of food allergy using epitope peptides^{7–14} and effective immunotherapy for peanut allergy with IgE-binding epitope modified recombinant allergen¹⁵ have been reported. Here, we provide an overview of the most common food allergen molecules from chicken egg, cow's milk, wheat, shrimp, and peanut, for which IgE-binding epitopes have been well characterized.

* Corresponding author. Department of Pharmaceutical Services, Hiroshima University Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan.

E-mail address: hmatsuo@hiroshima-u.ac.jp (H. Matsuo).

Peer review under responsibility of Japanese Society of Allergy.

<http://dx.doi.org/10.1016/j.alit.2015.06.009>

1323–8930/Copyright © 2015, Japanese Society of Allergy. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Food allergens

Food allergy is an allergen-specific IgE-mediated type I response. Its pathogenesis is divided into two phases: 1) the sensitization phase in which the allergen enters the body through the gastrointestinal tract, skin, or mucosa, where it encounters a naïve immune system under Th2-dominant conditions, resulting in IgE production; and 2) the induction phase, which occurs following the oral intake of the same allergen as in the sensitization phase, and which elicits allergic symptoms such as urticaria, itching, wheezing, dyspnea, and abdominal pain. These responses are caused by the release of chemical mediators such as histamine and leukotrienes from activated mast cells and basophils. Cross-linking of IgE receptors with an allergen is required for the activation of these cells; therefore, more than two IgE antibodies are required to bind to one allergen molecule.

Food allergens include proteins or glycoproteins that have a molecular weight of 5–100 kDa and the ability to cross-link IgE receptors. Although many potential allergens are enzymatically digested and denatured by the acidic environment of the stomach, some are resistant to these conditions.¹⁶ Intact food allergens have been detected in the serum after oral food administration in animals^{17–19} and humans.^{20–22} In addition, anti-ulcer agents that inhibit gastric digestion of the allergen have an effect on the sensitization and induction phases.²³

A number of different forms of plant food allergies have been reported, including pollen-food allergy syndrome and latex-fruit syndromes, in which allergic symptoms are induced mainly in the mucous membranes after ingestion of the causative food.^{24–26} The most comprehensively characterized allergen components associated with plant food allergies are profilins, seed storage proteins (2S albumins, 7S/11S globulins), and pathogenesis related proteins such as non-specific lipid transfer proteins (LTPs). These components, collectively named panallergens, are widely distributed among various plants and have cross-reactivity with related plant species.^{27–29} Carbohydrate determinants have been also reported as cross-reacting IgE-binding motifs in several plant allergens.^{30,31}

IgE-binding epitopes and T-cell epitopes in food allergens

IgE-binding epitopes can be divided into two types, linear (sequential) and conformational (discontinuous). Linear epitopes comprise continuous amino acid (AA) sequences, while conformational epitopes are formed by spatially adjacent AAs that are distantly located in the AA primary sequence of the proteins. Several methods of IgE-binding epitope mapping have been reported.³² Arrays of overlapping peptides synthesized on a

nitrocellulose membrane (SPOT membrane)³³ are frequently used to determine sequential epitopes.^{10,34,35} Peptide microarrays, formed from hundreds of synthetic peptides printed on a glass slide, have been used to determine IgE-binding linear epitopes.^{11,13,36–40} The determination of conformational IgE epitopes, however, requires sophisticated techniques, such as X-ray crystallography of allergens and immunocomplexes, nuclear magnetic resonance, mutant generation, and *in silico* analysis.^{41,42} In such cases, IgE epitopes are predicted based on the 3-D structures of food allergens, which have been determined for lysozyme (Gal d 4), β -lactoglobulin (Bos d 5), latex (Hev b 6), birch pollen (Bet v 1), and peach (Pru p 3).^{29,43,44} Recently, conformational epitopes recognized by monoclonal antibodies specific for almond (Pru du 6) and cashew (Ana o 2) allergens were mapped by hydrogen/deuterium exchange footprint analysis.^{45–47} Although this new technique is not directly applicable to the identification of conformational epitopes recognized by human polyclonal IgE antibodies, the information obtained for the epitopes of monoclonal antibodies is useful to predict the conformational epitopes of human IgE antibodies.

Antigen-specific responses of CD4⁺ T-cells, especially helper T-cells and regulatory T-cells, contribute to the sensitization, desensitization, and tolerance induction of food allergy.⁴⁸ T-cell epitopes that bind to major histocompatibility class II molecules are at least 13 AAs long.⁴⁹ The mapping of T-cell epitopes and IgE-binding epitopes provides useful information for the design of peptide and/or recombinant protein-based immunotherapy for food allergy. T-cell epitopes can be identified using peptides of 10–20 residues that overlap the entire AA sequence of the candidate allergen and allergen-specific T-cell lines derived from peripheral blood mononuclear cells. Then, peptides that induce T-cell proliferation contain T-cell epitopes. T-cell epitope sequences can be also predicted by computer-based *in silico* analysis.⁵⁰ However, numerous synthetic peptides need to be assayed with T-cells from patients to confirm the biological reactivity of the predicted epitopes. Although studies to identify T-cell epitopes are behind those of IgE-binding epitopes, T-cell epitopes of milk (Bos d 5), egg (Gal d 1 and 2), peach (Pru p 3), and peanut (Ara h 1 and 2), among others, have been reported.^{51–57}

Chicken egg

Chicken (*Gallus domesticus*) eggs consist of white and yolk. Ovomucoid (OM, Gal d 1), ovalbumin (OVA, Gal d 2), ovotransferrin (Gal d 3), and lysozyme (Gal d 4) have been identified as egg white allergens⁵⁸ (Table 1), whereas serum albumin (α -livetins, Gal d 5) and a fragment of the vitellogenin-1 precursor (YGP42, Gal d 6) have been reported as egg yolk allergens.^{65,66} In studies of

Table 1
Chicken egg allergens.

Protein name	IUIS name	MW (kDa)	AA length	Accession no.	IgE-binding epitopes (amino acid number)	Year	Ref
Ovomucoid	Gal d 1	28	186	P01005 (Gal d 1.0101)	4–20, 46–59, 91–104	2013	37
					1–10, 11–20, 47–56, 113–122	2007	8
					32–42, 40–50, 56–66, 71–75, 80–90, 101–105, 121–130, 159–174, 179–186	2002	59
					1–14, 11–24, 31–44, 51–64, 61–74, 101–114, 121–134	2001	60
					1–20, 49–56, 85–96, 115–122, 175–186	1997	61
Ovalbumin	Gal d 2	44	386	CAA23682 (Gal d 2.0101)	126–135, 142–155, 160–173, 165–177, 189–199, 327–337, 371–386	2014	62
					39–50, 96–103, 192–201, 244–249, 252–261	2003	63
Ovotransferrin	Gal d 3	77	705	CAA23711 (Gal d 4.0101)	–	–	–
Lysozyme	Gal d 4	14	129		11–27, 57–83, 108–122	2014	64
Serum albumin	Gal d 5	69	615		–	–	–
Fragment of vitellogenin-1 precursor (YGP42)	Gal d 6	35	285		–	–	–

component-resolved diagnosis of chicken egg allergy, measurements of Gal d 1- and/or Gal d 2-specific IgE reactivity improved the sensitivity of a serum-based test.^{67–69} The prevalence of specific IgE to each allergen was 43.5% for Gal d 1, 52.1% for Gal d 2, 13.0% for Gal d 3, 36.9% for Gal d 4, 4.3% for Gal d 5, and 18.5% for Gal d 6 in suspected chicken egg allergy patients.^{65,67}

OM (Gal d 1)

OM accounts for 11% of egg white protein and has three structurally independent tandem domains (DI, DII, and DIII), which exert trypsin-inhibitory activity.⁷⁰ OM is highly heat-stable and protease digestion-resistant, and is the immunodominant allergen in chicken egg.^{71,72} Significant OM-specific IgE antibody levels indicate a risk of clinical reactions to both raw and cooked egg.^{71,73,74} and OM-specific IgE also has some prognostic value in predicting which patients will outgrow egg allergy. The IgE-binding epitopes have been identified by enzyme-linked immunosorbent assay and microarray techniques (Table 1).^{8,37,59–61} The number of epitopes and their locations differed among the studies, possibly because of the population studied, the overlapping peptide length, and the techniques used. Järvinen *et al.*⁸ reported that patients with persistent egg allergy, but not patients who outgrew egg allergy, had IgE antibodies that recognized the AA 1–10, AA11–20, AA47–56, and AA113–122 in OM. These observations indicated that the presence of sequential epitope-specific serum IgE antibodies represents the basis of a screening method for persistent egg allergy. In a recent study using microarray techniques, two major B-cell epitopes (AA4–20 and AA46–59) that coincided with the epitopes described previously were identified,³⁷ indicating that AA4–20 and AA46–59 are clinically relevant epitopes. Although AA4–20 and AA46–59 were recognized by 24% and 32% of patients who tested positive for OM-specific IgE, one third of the patients did not recognize any linear epitopes of OM.³⁷ The 3-D conformation of OM, including carbohydrate modifications, is preferentially recognized by IgE in egg allergy patients. Thus, the detection of conformational epitopes is also of importance for the diagnosis and prognosis of egg OM allergy.

OVA (Gal d 2)

OVA is the most abundant heat-labile phosphoglycoprotein in egg white (approximately 54%) and is a dominant allergen in egg allergy.⁵⁸ Measurement of OVA-specific IgE is helpful for the diagnosis of egg allergy, especially in children with anaphylaxis.⁶⁸ The five IgE-binding epitopes of OVA, AA38–49, AA95–102, AA191–200, AA243–248, and AA251–260, have been mapped by Mine *et al.*⁶³ using SPOT membranes. A recent study using digested OVA with human and simulated gastroduodenal fluids showed that seven IgE-binding peptides, AA125–134, AA141–154, AA159–172, AA164–176, AA188–198, AA326–336, and AA370–385, remained after digestion.⁶² In addition, the importance of AA370–385 was indicated by the observation that this peptide is bound by 80% of sera from egg allergy patients.

Ovotransferrin (Gal d 3)

Ovotransferrin, an iron-binding protein, is a heat-labile and digestible allergen^{75,76} accounting for 12% of egg white proteins. Thirty-seven percent of egg-allergic patients were reportedly sensitized to this component.⁶⁷ Although the 3-D structure has been elucidated,⁷⁷ both linear and conformational IgE-binding epitopes remain to be identified.

Lysozyme (Gal d 4)

Lysozyme is well characterized physicochemically because of its use as an antimicrobial agent in clinical situations and as a food preservative. Jiménez-Saiz *et al.*⁶⁴ reported three possible IgE-binding peptides, AA11–27, AA57–83, and AA108–122, in immunoreactive fragments of lysozyme digested with simulated gastric and duodenal fluids. The lysozyme (AA24–129) fragment, which is linked by disulfide bonds to two immunoreactive peptides, AA57–83 and AA108–122, is resistant to digestive enzymes, and induces basophil activation. Thus, lysozyme contains linear IgE-binding epitopes that are involved in the clinical manifestation of chicken egg allergy.

Chicken serum albumin (Gal d 5)

Chicken serum albumin (α -livetin) was identified as the causative allergen of bird-egg syndrome, which causes respiratory symptoms following exposure to birds, with secondary symptoms of allergy after egg ingestion.⁶⁶ The prevalence of chicken serum albumin-specific IgE is relatively low in chicken egg allergy patients.^{67,68}

YGP42 (Gal d 6)

A 35-kDa fragment of the vitellogenin-1 precursor, known as the YGP42 protein (Gal d 6), was also identified as an egg yolk allergen.⁶⁵ This protein is heat- and reduction-stable; however, IgE-binding of this protein is reduced by treatment with gastric fluid. To date, no B-cell epitopes have been identified.

Cow's milk

The physicochemical properties of allergens from cow's (*Bos domesticus*) milk are well characterized (Table 2). Fractionation of milk yields two fractions, caseins and whey. Caseins (Bos d 8) include α _{s1}- (Bos d 9), α _{s2}- (Bos d 10), β - (Bos d 11), κ - (Bos d 12), and γ -caseins. Whey also called milk serum consists of α -lactalbumin (Bos d 4), β -lactoglobulin (Bos d 5), bovine serum albumin (Bos d 6), immunoglobulin (Bos d 7), and lactoferrin. The prevalence of IgE reactivity to Bos d 8 (46.5%), Bos d 4 (27.6%), Bos d 7 (10.3%), and lactoferrin (10.3%) was demonstrated in patients with suspected cow's milk allergy.⁶⁷ These components, as well as cow's milk protein-specific IgE, are good prognostic markers of the persistence of cow's milk allergy.^{86,87}

α -Lactalbumin (Bos d 4)

α -Lactalbumin, a calcium-binding milk protein, has as a key role in lactose biosynthesis.⁸⁸ Its high thermal stability was revealed by analysis of recombinant α -lactalbumin.⁷⁸ The prevalence of α -lactalbumin-specific IgE in milk allergy patients varies from 27.6% to 62.8% depending on the study population.^{67,78,89} The IgE-binding epitopes of α -lactalbumin, AA1–16, AA13–26, AA47–58, and AA93–102, have been identified.⁷⁹ Hochwallner *et al.*⁷⁸ identified six IgE-reactive peptides using a panel of 19- or 20-mer overlapping peptides spanning the entire protein. Three of these peptides, AA1–19, AA15–34, and AA105–123, are located on the surface of the protein.

β -Lactoglobulin (Bos d 5)

β -Lactoglobulin is the most abundant protein in milk whey. The major IgE-binding epitopes of β -lactoglobulin, AA1–16, AA31–60, AA67–86, and AA127–152, have been identified.⁷⁹ Cerecedo *et al.*³⁸

Table 2
Cow's milk allergens.

Protein name	IUIS name	MW (kDa)	AA length	Accession no.	IgE-binding epitopes (amino acid number)	Year	Ref
α -Lactalbumin	Bos d 4	14.2	123	AAA30615 (Bos d 4.0101)	1–19, 15–34, 45–64, 60–79, 90–109, 105–123	2010	78
β -Lactoglobulin	Bos d 5	18.3	162	CAA32835 (Bos d 5.0101)	1–16, 13–26, 47–58, 93–102	2001	79
					1–16, 56–70, 76–90, 136–150	2012	80
					58–77, 76–95, 121–140	2008	38
					1–16, 31–60, 67–86, 127–152	2001	79
Serum albumin	Bos d 6	67	583		–	–	–
Immunoglobulin	Bos d 7	160	–		–	–	–
Caseins	Bos d 8	20–30	–		–	–	–
(Bos d 9–Bos d 12)							
α _{s1} -Casein	Bos d 9	23.6	199	NP_851372 (Bos d 9.0101)	6–20, 11–35, 126–140, 171–185	2013	81
					16–35, 28–50, 73–92	2008	38
					17–36, 39–48, 69–78, 83–102, 109–120,	2001	82
					122–132, 139–154, 159–174, 173–194		
					181–199	1998	83
					19–30, 93–98, 141–150	1996	84
α _{s2} -Casein	Bos d 10	25.2	207	NP_776953 (Bos d 10.0101)	1–20, 13–32, 67–82, 106–125, 122–141,	2008	38
					157–182, 181–207		
					31–44, 43–56, 83–100, 93–108, 105–114,	2001	85
					117–128, 143–158, 157–172, 165–188,		
					191–200		
β -Casein	Bos d 11	24	209	XP_005902099 (Bos d 11.0101)	25–50, 52–74, 121–140, 154–173	2008	38
					1–16, 45–54, 55–70, 83–92, 107–120,	2001	34
					135–144, 149–164, 167–184, 185–208		
κ -Casein	Bos d 12	19	169	NP_776719 (Bos d 12.0101)	16–35, 34–53	2008	38
					9–26, 21–44, 47–68, 67–78, 95–116,	2001	34
					111–126, 137–148, 149–166		

also used a panel of overlapping peptides in a microarray-based immunoassay to analyze the IgE-binding epitopes of β -lactoglobulin. The identified IgE epitopes, AA58–77, AA76–95, and AA121–140, are recognized by more than 75% of milk allergy patients. AA58–77 is significantly associated with milk protein-reactive patients. Recent studies identified AA1–16, AA56–70, and AA76–90 as epitopes in Chinese patients.⁸⁰ These sequences are roughly in accordance with the epitopes detected in European patients described previously.

Bovine serum albumin (Bos d 6)

Bovine serum albumin is an important allergen in milk, meat, and epithelia allergy.^{90–92} There is cross-reactivity between serum albumin from cow, sheep, deer, pig, dog, and cat (meat and/or epithelia)⁹⁰; therefore, albumins are implicated as panallergens in mammals. Although bovine serum albumin is the major allergen in beef allergy,⁹³ bovine serum albumin-specific IgE is found in only 3.8% of patients with cow's milk allergy.⁸⁹ Structural modification by heat treatment and chemical denaturation does not affect the allergenicity of bovine serum albumin,⁹⁴ and several IgE-binding epitope sequences have been reported in beef allergy.^{95,96}

Bovine gamma globulin (Bos d 7)

Bovine gamma globulin is also an allergen in cow's milk and beef allergy.⁹⁷ Approximately 10% of patients with cow's milk allergy are bovine gamma globulin-specific IgE positive.⁶⁷

Caseins (Bos d 8–12)

Casein (Bos d 8) constitutes approximately 80% of the proteins present in cow's milk. These phosphorylated proteins are heat-stable but are susceptible to digestive enzymes.⁹⁸ Casein is composed of four major proteins, α _{s1}-casein (Bos d 9), α _{s2}-casein (Bos d 10), β -casein (Bos d 11), and κ -casein (Bos d 12), most of which exist in a colloidal particle known as the casein micelle. The molecular weight and AA length of caseins are listed in Table 2. The

proportions of casein in milk protein are 37% for α _{s1}-casein, 37% for α _{s2}-casein, 13% for β -casein, and 13% for κ -casein.

α _{s1}-Casein (Bos d 9)

Approximately 50% of serum samples from patients with cow's milk allergy react with α _{s1}-casein, which has an unordered molecular structure.⁸⁹ Nakajima-Adachi *et al.*⁸³ identified AA181–199 in the C-terminal region as the immunodominant IgE-binding region. Three regions of α _{s1}-casein, corresponding to AA19–30, AA93–98, and AA141–150, were also identified as IgE-binding peptides.⁸⁴ In recent studies, several IgE-binding epitopes were identified by overlapping peptide mapping.^{38,81,82}

α _{s2}-Casein (Bos d 10)

Busse *et al.*⁸⁵ identified 10 sequential IgE-binding epitopes of α _{s2}-casein, four of which AA83–100, AA143–158, AA157–172, and AA165–188, were detected in 77% of patients. Cerecedo *et al.*³⁸ mapped seven IgE-binding epitopes and showed that four, AA1–20, AA13–32, AA67–86, and AA181–207, were significantly associated with the reactive group of patients.

β -Casein (Bos d 11)

Six major and three minor IgE-binding epitopes of β -casein were identified by Chatchatee *et al.*³⁴ Cerecedo *et al.*³⁸ also identified four B-cell epitopes, three of which, AA25–50, AA52–74, and AA154–73, were found to be associated with allergic symptoms. Several IgE-binding epitopes remain as fragments of β -casein after gastrointestinal digestion.⁹⁹

κ -Casein (Bos d 11)

Using overlapping peptide mapping, eight major IgE-binding peptides of κ -casein were identified, three of which, AA9–26, AA21–44, and AA47–68, were recognized by 93% of patients with cow's milk allergy.³⁴ AA16–35 and AA34–53 in κ -casein were also

identified as IgE-binding dominant epitopes.³⁸ Thus, the N-terminal region (AA9–68) of κ -casein may play an important role in the allergenicity of this protein. The critical AAs for IgE-binding to linear epitopes of κ -casein were identified by Han *et al.*¹⁰⁰

Time-related differences in the binding of IgE and IgG4 to epitopes of β -lactoglobulin, α -lactalbumin, and caseins between patients with early recovery or persistent cow's milk allergy have been investigated.^{101,102} Furthermore, IgE and IgG4 epitope binding was also analyzed to predict the outcome of oral immunotherapy in cow's milk allergy using peptide arrays.¹⁰³ The results of this study showed that monitoring the binding of IgE and IgG4 to epitope peptides of caseins has predictive value for the development of tolerance to cow's milk or the outcome of oral immunotherapy.

Wheat

Wheat (*Triticum aestivum*) is an important allergen source that elicits various clinical types of food allergy, such as immediate

wheat allergy, baker's asthma, wheat contact dermatitis, and wheat-dependent exercise-induced anaphylaxis (WDEIA). The total protein content of wheat flour ranges from 8% to 12%, and can be classified as water/salt-soluble proteins (albumin and globulin) and the insoluble protein, gluten. Wheat profilin (Tri a 12), non-specific LTP (Tri a 14), α -amylase inhibitors (AAI, Tri a 15, Tri a 28–30), wheat germ agglutinin (Tri a 18), thioredoxin (Tri a 25), thiol reductase homolog (Tri a 27), triosephosphate isomerase (Tri a 31), 1-cys-peroxiredoxin (Tri a 32), serpin (Tri a 33), glyceraldehyde-3-phosphate dehydrogenase (Tri a 34), dehydrin (Tri a 35), α -pur-othionin (Tri a 37), serine proteinase inhibitor (Tri a 39), thaumatin-like protein, peroxidase, and glutathione S-transferase in the soluble fraction have been identified as allergens in patients with baker's asthma, wheat food allergy and wheat contact urticaria (Table 3).^{112–115} α/β -Gliadin (Tri a 21), γ -gliadin (Tri a 20), ω 1,2-gliadin, ω 5-gliadin (Tri a 19), low molecular weight glutenin subunits (LMW-GS, Tri a 36), and high molecular weight glutenin subunits (Tri a 26) in wheat gluten have been reported as allergens

Table 3
Wheat allergens.

Protein name	IUIS name	MW (kDa)	AA length	Accession no.	IgE-binding epitopes (AA sequence or number)	Year	Ref
Water/salt-soluble protein							
Profilin	Tri a 12	14	—	—	—	—	—
Non-specific lipid transfer protein 1	Tri a 14	9	90	P24296	24–33, 37–46, 81–90	2011	104
α -Amylase inhibitors							
Monomeric	Tri a 15	12	—	—	—	—	—
Dimeric	Tri a 28	13	—	—	—	—	—
Tertameric	CM1/CM2	13	—	—	—	—	—
	CM3	16	—	—	—	—	—
	CM16/CM17	17	—	—	—	—	—
Agglutinin	Tri a 18	17	—	—	—	—	—
Thioredoxin	Tri a 25	13	—	—	—	—	—
Thiol reductase homologue	Tri a 27	27	—	—	—	—	—
Triosephosphate isomerase	Tri a 31	26	—	—	—	—	—
1-Cys-peroxiredoxin	Tri a 32	24	—	—	—	—	—
Serpin	Tri a 33	40	398	CAB52710	46–68, 76–92, 271–293, 364–384	2012	105
Glyceraldehyde-3-phosphate-dehydrogenase	Tri a 34	40–42	—	—	—	—	—
Dehydrin	Tri a 35	12	—	—	—	—	—
α -Purothionin	Tri a 37	12	111	AFQ60540	2–31, 42–71, 62–91	2014	106
Serine protease inhibitor-like protein	Tri a 39	9	—	—	—	—	—
Glutathione transferase	—	25	—	—	—	—	—
Thaumatococcus protein	—	18	—	—	—	—	—
Peroxidase	—	36	—	—	—	—	—
Water/salt-insoluble protein							
α/β -Gliadin	Tri a 21	28–35	299	P04725	VRVPVPLQLP, QEQVPLVQQQ, VQQQQPFGQQ, QQQPFGQQQQ, YLQLQFPFPQ, QILQQILQQQ, LQIPEQSQSQ, QEQKQQLQQQ, SFQQPQQQYP, LALQTLPLAMC, YIPPHCSTTI, QPQQPFPQ	2011, 2005	104,107
γ -Gliadin	Tri a 20	28–35	280	BAN29066 (Tri a 20.0101)	QPQQPFPQ	2013	108
			308	P08453	QPQQPFPQ QQX ₃ X ₄ PQ (X ₃ = L, S, Q; X ₄ = L, V, F)	2012 2005	109 107
			261	Q9FUW7	QPQQPFPQ QQPX ₅ PX ₆ Q (X ₅ = I, T, F; X ₆ = V, Q, I)	2012 2011, 2005	109 104,107
ω 1,2-Gliadin	—	40	261	Q9FUW7	QQX ₁ PX ₂ QQ (X ₁ = L, F, S, I; X ₂ = Q, E)	2011, 2005	104,107
ω 5-Gliadin	Tri a 19	65	420	BAE20328 (Tri a 19.0101)	QQIPQQQ, QQFPQQQ, QQSPEQQ, QQSPPQQ, QQYPPQQ, PYPP, QQFHQQQ, QSPQQQ, YQQYPPQ, QQPQQQ	2005, 2004	35,110
High molecular weight glutenin subunits	Tri a 26	88	827	Q9ZNY0	QQPGQ, QQPGQGGQ, QQSQQGQ	2005	10
Low molecular weight glutenin subunits	Tri a 36	32–40	369	Q9ZNY0	HQQQPIQQP, QQPIQQPQQ, QQFPQQPCS, PFVHPSILQQ, QCSVPAMPQS, LPQIPQQSRY, QSRYEAIRAI, QQQPP	2011 1996	104 111

that cause WDEIA.^{113,116,117} Gliadins and glutenins are allergens that also cause baker's asthma and common immediate wheat allergy in some cases.^{118,119} In addition, LTP in the water/salt-soluble fraction was reported to cause WDEIA.^{112,113} These findings demonstrate the comparative specificity of the causative allergens to each clinical type of wheat allergy, although some allergens contribute to the development of two or more clinical types of this allergy. It should be noted that the biological activity of some wheat allergens reported in this review have not been determined using techniques such as the skin prick test or the basophil histamine release test.

Water/salt-soluble wheat allergens

Tri a 12 is recognized by specific IgE antibodies in patients with baker's asthma, grass pollen allergy, and food allergy to wheat.^{115,120–122} However, the prevalence of IgE reactivity to wheat profilin in patients with food allergy and respiratory allergy is low.¹¹⁵ Tri a 14 was identified as an allergen in food allergy patients after ingestion of wheat products,^{123–126} as well as in patients with baker's asthma¹²⁷ and WDEIA.¹¹⁸ Monomeric AAI 0.28 (Tri a 15), dimeric AAI 0.19 (Tri a 28), tetrameric AAI CM1/CM2 (Tri a 29), AAI CM3 (Tri a 30), and AAI CM16 are allergens in pediatric patients with wheat allergy,¹²⁶ patient's with baker's asthma,^{121,128} and those with work-related wheat dermatitis.¹²⁹

Tri a 18, 25, 32–35, and 39 were identified as allergens in patients with baker's asthma and/or food allergy.^{103,105,122,130–133} Four IgE-binding epitopes of Tri a 33, AA46–48, AA76–92, AA271–293, and AA364–384, were identified using overlapping peptide mapping,¹⁰⁵ and 3-D modeling showed that these epitopes are partially located on the surface of the protein. No differences were identified in the IgE-binding epitope peptides associated with food allergy and baker's asthma.¹⁰⁵

Tri a 27 was identified as an allergen that causes wheat protein contact dermatitis and wheat food allergy.^{114,134,135} It is considered that the N-linked glycan moieties with fucose residues contained in this allergen are involved in IgE-binding.¹³⁶ The highest frequencies of Tri a 27-specific IgE were reported in patients with baker's asthma.¹²¹ Tri a 37 was recently reported as a novel wheat allergen specific for patients with wheat food allergy.¹³⁷ Twenty percent of patients with wheat food allergy had Tri a 37-specific IgE, whereas the frequency was only 3% among patients with baker's asthma.¹³⁷ The IgE-binding epitopes in this allergen have been mapped to three regions of the protein, AA2–31, AA42–71, and AA62–91.¹⁰⁶

Water/salt-insoluble wheat allergens

Gliadins and glutenins are water/salt-insoluble wheat proteins that have been identified as causative allergens in patients with wheat food allergy, baker's asthma, and WDEIA.^{10,35,107,113,117} ω 5-Gliadin (Tri a 19) is a major allergen in WDEIA^{138,139} and children with immediate allergy to ingested wheat.¹⁴⁰ Because of the presence of a repetitive domain, there are many IgE epitope sequences in ω 5-gliadin; however, the consensus sequence comprising QXX₁PX₂QQ (X₁ = L, F, S, I; X₂ = Q, E, G) has been identified as the IgE-binding epitope in Japanese and European patients.^{35,104,107,110} The measurement of specific IgE to ω 5-gliadin and its IgE-binding epitopes in the diagnosis of patients with wheat food allergy including WDEA has been reported.^{10,141–145} However, the Tri a 19-specific IgE test alone could not be used to diagnose all patients with wheat food allergy.^{146,147} γ -Gliadin (Tri a 20) is a causative allergen in patients with food allergy to wheat and those with baker's asthma.^{113,117} Furthermore, γ -gliadin-specific IgE was also detected in Japanese patients with WDEIA following transdermal sensitization with hydrolyzed wheat protein.^{108,148} The IgE-binding epitope sequence of QPQQPFPQ in γ -gliadin identified in Japanese

patients sensitized via the dermal route was identical to the epitope sequence identified in European patients sensitized orally with hydrolyzed wheat proteins.¹⁰⁹ α/β -Gliadin (Tri a 21) and α 1,2-gliadin are also important causative allergens in wheat food allergy, WDEIA, and baker's asthma.^{104,107,113,146} The IgE-binding epitopes for these allergens were identified in patients with wheat allergy^{104,107} and in addition, the sequences of QQPFP and PQQPF in gliadin were epitopes in atopic dermatitis-related wheat allergy.¹⁴⁹

LMW-GS (Tri a 36) was identified as an allergen that induces wheat food allergy^{123,150,151} and WDEIA¹⁵² in European patients. There are several types of LMW-GS encoded by genes located on group 1 chromosomes at the Glu-A3, Glu-B3, and Glu-D3 loci,¹⁵³ and patients with wheat allergy exhibited IgE-reactivity to different LMW-GS.¹⁵⁰ Although the LMW-GS GluB3-23, B16, and P73 epitopes are well characterized,^{147,150,152} only GluB3-23 is defined as Tri a 36 in the IUIS allergen database.¹⁴⁷ Tanabe *et al.*¹¹¹ identified the QQQPP motif in LMW-GS as a major IgE-binding epitope responsible for atopic dermatitis in patients sensitized with wheat.

High molecular weight glutenin subunits (Tri a 26) has been identified as an allergen responsible for WDEIA in Japanese patients and its IgE-binding epitopes, QQPQG, QQPQGQQ, and QQSGQQG, have been fine-mapped.¹⁰ We showed that the combined detection of IgE antibodies specific to epitope peptides or recombinant proteins of Tri a 26 and Tri a 19 improved the sensitivity and specificity of the diagnosis of WDEIA.^{10,154}

Shrimp

Seafood allergy is a common food allergy. The prevalence of fish and shellfish allergies is estimated at 0.2%–0.3% and 0.6%, respectively.¹⁵⁵ Allergy to crustacean shellfish, which include shrimp, prawns, lobsters, and crabs, seems to affect school-aged children and adults predominantly.¹ Crustacean-allergic patients can show cross-reactivity to different types of shellfish as well as molluscan shellfish, such as gastropods (abalones, limpets, snails), bivalves (scallops, oysters, mussels), and cephalopods (squid, octopus).

Studies of shrimp allergens are the most advanced among the shellfish allergies.¹⁵⁶ There are various types of edible shrimp worldwide, with White Pacific shrimp (*Litopenaeus vannamei*), black tiger (*Penaeus monodon*), kuruma prawn (*Marsupenaeus japonicus*), and Japanese spiny lobster (*Panulirus japonicus*) the most commonly eaten in Japan. The allergens responsible for crustacean allergies are also well studied. Tropomyosin, arginine kinase, sarcoplasmic calcium-binding protein, myosin light chain, troponin C, and triosephosphate isomerase have been identified as allergens in *Penaeus monodon*, *L. vannamei*, *Crangon crangon* (North Sea shrimp), *Homarus americanus* (American lobster), and some crabs (Table 4).^{156,159–161}

Tropomyosin (group 1)

Tropomyosin is associated with the actin and troponin components of muscle cells, and isoforms of tropomyosin were identified in several shrimp species, including *Pandalus borealis* (Pan b 1), *Penaeus monodon* (Pen m 1), *Penaeus aztecus* (Pen a 1), *Penaeus indicus* (Pen i 1), *Metapenaeus ensis* (Met e 1), *L. vannamei* (Lit v 1), *Crangon crangon* (Cra c 1), and *H. americanus* (Hom a 1). Although tropomyosins from crustaceans share high homology (up to 98%), the AA sequence identity of crustacean and molluscan tropomyosin is much lower (approximately 60%).¹⁶⁰ The major continuous IgE epitopes were identified in Pen a 1¹⁵⁷ and Lit v 1¹⁵⁸ using overlapping peptide mapping. Nine IgE-binding peptides in Pen a 1 were identified, five of which, AA37–63, AA82–105, AA115–150,

Table 4
Shrimp allergens.

Protein name	IUIS name	MW (kDa)	AA length	Accession no.	IgE-binding epitopes (amino acid number)	Year	Ref
Tropomyosin							
<i>Penaeus aztecus</i> (Brown shrimp)	Pen a 1	37	284	AAZ76743 (Pen a 1.0101)	1–36, 37–63, 61–81, 82–105, 115–150, 142–162, 157–183, 190–210, 246–284	2002	157
<i>Litopenaeus vannamei</i> (White shrimp)	Lit v 1	37	284	ACB38288 (Lit v 1.0101)	43–57, 85–105, 133–148, 187–202, 247–284	2010	158
<i>Pandalus borealis</i> (Northern shrimp)	Pan b 1	–	–	–	–	–	–
<i>Metapenaeus ensis</i> (Greasyback shrimp)	Met e 1	–	–	–	–	–	–
<i>Penaeus indicus</i> (Indian white shrimp)	Pen i 1	–	–	–	–	–	–
<i>Penaeus monodon</i> (Black tiger shrimp)	Pen m 1	–	–	–	–	–	–
<i>Crangon crangon</i> (North sea shrimp)	Cra c 1	–	–	–	–	–	–
Arginine kinase	Lit v 2	40	356	ABI98020 (Lit v 2.0101)	1–18, 25–42, 64–96, 121–141, 142–159, 160–192, 232–255	2010	158
	Pen m 2	–	–	–	–	–	–
	Cra c 2	–	–	–	–	–	–
Myosin light chain 2	Lit v 3	20	177	ACC76803 (Lit v 3.0101)	13–30, 22–48, 49–66, 58–90, 79–99, 118–141	2010	158
	Pen m 3	–	–	–	–	–	–
Sarcoplasmic calcium-binding protein	Lit v 4	20	193	ACM89179 (Lit v 4.0101)	10–36, 49–72, 130–147	2010	158
	Pen m 4	–	–	–	–	–	–
	Cra c 4	–	–	–	–	–	–
Myosin light chain 1	Cra c 5	18	–	–	–	–	–
Troponin C	Cra c 6	20	–	–	–	–	–
	Pen m 6	–	–	–	–	–	–
Triosephosphate isomerase	Cra c 8	28	–	–	–	–	–

AA190–210, and AA246–284, corresponded with the epitopes of Lit v 1. The sequences LEX₁X₂L or LEX₁X₂N (X₁ = D, E, N or K, X₂ = D or E) in AA1–36 (LEKDN), AA37–63 (LENDL), AA82–105 (LEEDL), and AA246–284 (LEDLE) were identified as common IgE-binding motifs in Lit v 1.¹⁵⁸ The immunodominant regions of Pan b 1 were also mapped by Myrset et al.¹⁶²

Arginine kinase (group 2)

Arginine kinase was identified in three types of shrimp (Cra c 2,¹⁶³ Lit v 2,¹⁶⁴ Pen m 2¹⁶⁵). Eight IgE-binding epitopes were identified in Lit v 2,¹⁵⁸ with the highest diagnostic efficiency shown in the test for AA232–255 peptide-specific IgE.¹³ Recent studies showed that Pen m 2 is an important allergen recognized by Th2 cells in patients with shrimp allergy.¹⁶⁶

Myosin light chain (group 3 and Cra c 5)

Myosin light chain (Lit v 3, Pen m 3) was first identified in *L. vannamei*¹⁶⁷ and *Penaeus monodon*.¹⁶⁸ Cra c 5 was also confirmed as a novel type of IgE-binding myosin light chain with only 13% AA sequence identity to Lit v 3.¹⁶³ Six IgE-binding sequences were identified in Lit v 3.¹⁵⁸

Sarcoplasmic calcium-binding protein

Sarcoplasmic calcium-binding protein was identified as an allergen in three types of shrimp (Cra c 4,¹⁶³ Lit v 4,¹⁶⁹ and Pen m 4¹⁷⁰). Three IgE-binding regions were identified in Lit v 4.¹⁵⁸

Troponin C (group 6) and triosephosphate isomerase (Cra c 8)

Troponin C (Cra c 6¹⁶³ and Pen m 6¹⁷¹) and triosephosphate isomerase (Cra c 8¹⁶³) were identified as allergens in patients with shrimp allergy but have not been reported in *L. vannamei* and

Penaeus monodon, suggesting they are minor or local shrimp allergens.

Several studies conducted to investigate component-resolved diagnosis using recombinant shrimp allergens and IgE-binding epitope peptides showed that measuring IgE binding to tropomyosin and sarcoplasmic calcium-binding protein is useful for the prediction of clinical reactivity in patients with shrimp allergy although the measurement of IgE specific for other allergens and epitopes is necessary for the accurate diagnosis of shrimp allergy.^{7,13}

Peanut

Twelve allergens have been identified in association with peanut (*Arachis hypogaea*) allergy (Table 5). These are designated Ara h 1 to Ara h 13, with the exception of Ara h 4, which has been renamed Ara h 3.02.¹⁷⁶ Ara h 2, Ara h 6, and Ara h 7, which belong to the 2S albumin family, are seed storage proteins and have homologous AA sequences and secondary structures.¹⁷⁷ Ara h 2 and Ara h 6 are the most clinically relevant allergens in peanut allergy.^{178,179} Ara h 1 (7S globulin) and Ara h 3 (11S globulin) are seed proteins belonging to the cupin superfamily, which contains a conserved barrel domain.^{180,181} Ara h 5 is a member of the profilin family with 72% AA sequence identity to birch pollen profilin (Bet v 2), and is a class II type labile food allergen.¹⁸² Ara h 8, a pathogenesis related protein-10 (Bet v 1) homolog, is also a class II food allergen. It is a major allergen and produces allergic symptoms in birch pollen-allergic patients after the ingestion of peanuts.^{183,184} Ara h 9, a non-specific LTP, was identified as a peanut allergen in patients who have peach allergy and are positive for Pru p 3-specific IgE.^{185,186} Most of these patients did not have IgE antibodies specific to Ara h 1, Ara h 2, and Ara h 3, indicating that Ara h 9 is an important allergen in peanut allergy. Oleosins (Ara h 10 and Ara h 11) are obtained from peanut oil bodies.^{187,188} In a recent study, the IgE-binding epitopes of Ara h 10 and Ara h 11 were identified using

Table 5
Peanut allergens.

Protein name	IUIS name	MW (kDa)	AA length	Accession no.	IgE-binding epitopes (amino acid number)	Year	Ref
Cupin (Vicillin-type, 7S globulin)	Ara h 1	64	626	AAB00861 (Ara h 1.0101)	139–147, 175–183 (most dominant)	2008	12
					26–33*, 48–57, 66–73*, 90–97*, 98–104, 108–115, 124–131, 134–143, 144–151, 295–302, 312–319, 325–334, 345–352, 361–385, 393–402, 409–418, 463–468, 498–507*, 525–534, 539–548, 551–560, 559–568, 578–587, 598–605 (* dominant epitope)	2004, 1997	11,172
Conglutin (2S albumin)	Ara h 2	17.5	160	ABQ96212 (Ara h 2.01)	31–36, 43–53, 63–68, 92–103, 106–118, 120–128, 130–139, 140–152	2014	173
					31–36 (most dominant)	2008	12
					30–39, 44–59, 62–67, 70–80, 92–103, 110–116, 130–136	2005	39
					18–27, 24–31, 30–39, 42–51, 52–59, 62–67, 68–75, 120–125, 130–135, 146–152	1997	174
					1–13, 23–33, 41–47, 58–70, 73–85, 97–106, 107–119	2014	173
Cupin (Legumin-type, 11S globulin, Glycinin)	Ara h 6	15	124	ABQ96216 (Ara h 6.0101)	—	—	—
	Ara h 7	16–17	—	—	—	—	—
Profilin	Ara h 3	60	510	AAC63045 (Ara h 3.0101)	301–309 (most dominant)	2008	12
	Ara h 5	14	—	—	30–44, 237–251, 276–290, 300–312	1999	175
Pathogenesis-related protein 10 (PR-10)	Ara h 8	17	—	—	—	—	—
Non-specific lipid-transfer protein type 1	Ara h 9	9.1	—	—	—	—	—
Oleosin	Ara h 10	18	—	—	—	—	—
	Ara h 11	14	—	—	—	—	—
Defensin	Ara h 12	5.2	—	—	—	—	—
	Ara h 13	8.4	—	—	—	—	—

in silico methods.¹⁸⁹ In addition, Kobayashi *et al.*¹⁹⁰ identified the IgE-binding epitope of peanut oleosin 3, which differs from those of Ara h 10 and Ara h 11. Ara h 12 and Ara h 13, which are defensins directed against fungal pathogens, were identified as allergens by Petersen *et al.*¹⁹¹ Although they have been listed as peanut allergens by the WHO/IUIS Allergen Nomenclature Subcommittee, the details have not been reported. The prevalence of IgE binding to Ara h 10–13 has not yet been elucidated. From the viewpoint of component-resolved diagnosis of peanut allergy, Ara h 1, 2, 3, 6, and 9 are significant allergens that correlate with reactivity and/or severity, although the sensitivity and specificity of each component is population-dependent.^{192–194}

7S globulin (Ara h 1)

Ara h 1 is a glycosylated seed storage protein. IgE binding to Ara h 1 has a low sensitivity to heating and digestion with pepsin.^{195,196} Twenty-three IgE-binding epitopes were identified throughout the protein by overlapping peptide mapping,¹⁷² and a further epitope, AA361–385, was reported by Shreffler *et al.*¹¹ Six of these epitopes, AA90–97, AA98–104, AA108–115, AA124–131, AA134–143, and AA144–151, are pepsin-resistant.¹⁹⁷ Bøgh *et al.*¹⁹⁸ identified five conformational epitope motifs in Ara h 1 by competitive immunoscreening of a phage-displayed random peptide library, and epitope mimics were found to cluster in three areas of Ara h 1. Furthermore, phage-display technology was used to analyze the difference between IgE and IgG epitopes of Ara h 1.¹⁹⁹ Elucidation of IgE and IgG epitope recognition patterns could be a valuable tool for the diagnosis of peanut allergy.

11S globulin (Ara h 3)

Ara h 3 is post-transcriptionally cleaved to form two protein fragments by an asparaginyl endopeptidase after the formation of an intermolecular disulfide bond. Thus, 23-kDa and 36-kDa spots

are observed by 2D-PAGE under reducing conditions.¹⁸¹ Analysis of the IgE-binding epitope sequences in Ara h 3 in three different overlapping peptide array experiments showed that four epitopes, AA30–44, AA237–251, AA276–290, and AA300–312, were important in peanut allergy.^{12,175}

2S albumin (Ara h 2 and 6)

Ara h 2, which consists of two isoforms, Ara h 2.01 and Ara h 2.02, is highly resistant to boiling and proteolytic digestion.^{200,201} Seven to ten IgE-binding epitopes were identified in Ara h 2 using overlapping peptide immunoassays.^{12,39,173,174} In addition, post-translational proline hydroxylation of Ara h 2 contributes to linear IgE epitopes.²⁰²

Ara h 6 shares 55% identity with the AA sequence of Ara h 2 and some of the IgE epitopes of Ara h 6 are cross-reactive with those of Ara h 2.¹⁷³ As with Ara h 2, the resistance of Ara h 6 to heat and digestive enzymes was reported.²⁰¹ Seven IgE-binding epitopes were identified for Ara h 6 by Otsu *et al.*,¹⁷³ and the linear IgE-binding epitopes of Ara h 2 and Ara h 6 were useful in predicting clinical reactions in patients with peanut allergy.

Protein structures of Ara h 1–3, 5, and 8 were elucidated by X-ray crystal structure analysis.^{181,203–206} B-cell epitopes of Ara h 1–3, 5–13 were predicted using *in silico* methods, and the predicted epitope sequences of Ara h 1–3 correlated with the epitopes identified experimentally,¹⁸⁹ suggesting that computational prediction of epitopes may contribute to improved accuracy of peanut allergy diagnosis.

Conclusions

Advances in molecular biology and analytical chemistry in the past three decades have facilitated the identification of food allergens and their sequential IgE-binding epitopes. The production of recombinant allergens and the use of 3-D structural analysis have

also contributed to this progress. The results of these studies have enhanced our understanding of the mechanisms of food allergy at the molecular level. Although there are a number of limitations associated with studies of food allergen components and epitopes, the detection and quantification of serum IgE antibodies specific to allergen components and epitope peptides are useful for the diagnosis and prognosis of food allergy. In addition, clarification of the sensitization patterns of allergen components in individual patients might facilitate allergen-specific immunotherapy of food allergy. However, numerous issues remain to be investigated. For example, conformational IgE epitopes and T-cell epitopes have not yet been identified for most food allergens, even those for which the 3-D structure has been determined. Furthermore, many allergens remain unidentified because of biodiversity, especially in seafood, and the disposition and digestion of food allergens after ingestion have not been clarified. Future studies should focus on full IgE and T-cell epitope mapping in individual patients to improve the diagnosis, therapy, and prevention of food allergy.

Conflict of interest

The authors have no conflict of interest to declare.

References

- Urisu A, Ebisawa M, Ito K, Aihara Y, Ito S, Mayumi M, et al. Japanese guideline for food allergy 2014. *Allergol Int* 2014;**63**(3):399–419.
- Ebisawa M, Nishima S, Ohnishi H, Kondo N. Pediatric allergy and immunology in Japan. *Pediatr Allergy Immunol* 2013;**24**(7):704–14.
- Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011;**128**(1):e9–17.
- Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy* 2014;**69**(1):62–75.
- Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy* 2014;**69**(8):992–1007.
- Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. *J Allergy Clin Immunol* 2014;**133**(2):291–307.
- Pascal M, Grishina G, Yang AC, Sánchez-García S, Lin J, Towle D, et al. Molecular diagnosis of shrimp allergy: efficiency of several allergens to predict clinical reactivity. *J Allergy Clin Immunol Pract* 2015. <http://dx.doi.org/10.1016/j.jaip.2015.02.001>.
- Järvinen KM, Beyer K, Vila L, Bardina L, Mishoe M, Sampson HA. Specificity of IgE antibodies to sequential epitopes of hen's egg ovomucoid as a marker for persistence of egg allergy. *Allergy* 2007;**62**(7):758–65.
- Beyer K, Järvinen KM, Bardina L, Mishoe M, Turjanmaa K, Niggemann B, et al. IgE-binding peptides coupled to a commercial matrix as a diagnostic instrument for persistent cow's milk allergy. *J Allergy Clin Immunol* 2005;**116**(3):704–5.
- Matsuo H, Kohno K, Niihara H, Morita E. Specific IgE determination to epitope peptides of omega-5 gliadin and high molecular weight glutenin subunit is a useful tool for diagnosis of wheat-dependent exercise-induced anaphylaxis. *J Immunol* 2005;**175**(12):8116–22.
- Shreffler WG, Beyer K, Chu TH, Burks AW, Sampson HA. Microarray immunoassay: association of clinical history, in vitro IgE function, and heterogeneity of allergenic peanut epitopes. *J Allergy Clin Immunol* 2004;**113**(4):776–82.
- Flinterman AE, Knol EF, Lencer DA, Bardina L, den Hartog Jager CF, Lin J, et al. Peanut epitopes for IgE and IgG4 in peanut-sensitized children in relation to severity of peanut allergy. *J Allergy Clin Immunol* 2008;**121**(3):737–43.
- Ayuso R, Sánchez-García S, Pascal M, Lin J, Grishina G, Fu Z, et al. Is epitope recognition of shrimp allergens useful to predict clinical reactivity? *Clin Exp Allergy* 2012;**42**(2):293–304.
- Lin J, Sampson HA. The role of immunoglobulin E-binding epitopes in the characterization of food allergy. *Curr Opin Allergy Clin Immunol* 2009;**9**(4):357–63.
- Wood RA, Sicherer SH, Burks AW, Grishin A, Henning AK, Lindblad R, et al. A phase 1 study of heat/phenol-killed, *E. coli*-encapsulated, recombinant modified peanut proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) for the treatment of peanut allergy. *Allergy* 2013;**68**(6):803–8.
- Moreno FJ. Gastrointestinal digestion of food allergens: effect on their allergenicity. *Biomed Pharmacother* 2007;**61**(1):50–60.
- Tsume Y, Taki Y, Sakane T, Nadai T, Sezaki H, Watabe K, et al. Quantitative evaluation of the gastrointestinal absorption of protein into the blood and lymph circulation. *Biol Pharm Bull* 1996;**19**(10):1332–7.
- Yokooji T, Nouma H, Matsuo H. Characterization of ovalbumin absorption pathways in the rat intestine, including the effects of aspirin. *Biol Pharm Bull* 2014;**37**(8):1359–65.
- Yokooji T, Hamura K, Matsuo H. Intestinal absorption of lysozyme, an egg-white allergen, in rats: kinetics and effect of NSAIDs. *Biochem Biophys Res Commun* 2013;**438**(1):61–5.
- Matsuo H, Morimoto K, Akaki T, Kaneko S, Kusatake K, Kuroda T, et al. Exercise and aspirin increase levels of circulating gliadin peptides in patients with wheat-dependent exercise-induced anaphylaxis. *Clin Exp Allergy* 2005;**35**(4):461–6.
- Matsuo H, Kaneko S, Tsujino Y, Honda S, Kohno K, Takahashi H, et al. Effects of non-steroidal anti-inflammatory drugs (NSAIDs) on serum allergen levels after wheat ingestion. *J Dermatol Sci* 2009;**53**(3):241–3.
- Kohno K, Matsuo H, Takahashi H, Niihara H, Chinuki Y, Kaneko S, et al. Serum gliadin monitoring extracts patients with false negative results in challenge tests for the diagnosis of wheat-dependent exercise-induced anaphylaxis. *Allergol Int* 2013;**62**(2):229–38.
- Untersmayr E, Jensen-Jarolim E. The role of protein digestibility and antacids on food allergy outcomes. *J Allergy Clin Immunol* 2008;**121**(6):1301–8.
- Kondo Y, Urisu A. Oral allergy syndrome. *Allergol Int* 2009;**58**(4):485–91.
- Price A, Ramchandran S, Smith GP, Stevenson ML, Pomeranz MK, Cohen DE. Oral allergy syndrome (pollen-food allergy syndrome). *Dermatitis* 2015;**26**(2):78–88.
- Ricci G, Piccinno V, Calamelli E, Giannetti A, Pession A. Latex-fruit syndrome in Italian children and adolescents with natural rubber latex allergy. *Int J Immunopathol Pharmacol* 2013;**26**(1):263–8.
- Hauser M, Roulias A, Ferreira F, Egger M. Panallergens and their impact on the allergic patient. *Allergy Asthma Clin Immunol* 2010;**6**:1.
- Andersen MB, Hall S, Dragsted LO. Identification of European allergy patterns to the allergen families PR-10, LTP, and profilin from Rosaceae fruits. *Clin Rev Allergy Immunol* 2011;**41**(1):4–19.
- Sinha M, Singh RP, Kushwaha GS, Iqbal N, Singh A, Kaushik S, et al. Current overview of allergens of plant pathogenesis related protein families. *ScientificWorldJournal* 2014;**2014**:543195.
- Soh JY, Huang CH, Lee BW. Carbohydrates as food allergens. *Asia Pac Allergy* 2015;**5**(1):17–24.
- Altmann F. The role of protein glycosylation in allergy. *Int Arch Allergy Immunol* 2007;**142**(2):99–115.
- Hensen SM, Derksen M, Pruijn GJ. Multiplex peptide-based B cell epitope mapping. *Methods Mol Biol* 2014;**1184**:295–308.
- Frank R. The SPOT-synthesis technique. Synthetic peptide arrays on membrane supports—principles and applications. *J Immunol Methods* 2002;**267**(1):13–26.
- Chatchatee P, Järvinen KM, Bardina L, Vila L, Beyer K, Sampson HA. Identification of IgE and IgG binding epitopes on beta- and kappa-casein in cow's milk allergic patients. *Clin Exp Allergy* 2001;**31**(8):1256–62.
- Matsuo H, Morita E, Tatham AS, Morimoto K, Horikawa T, Osuna H, et al. Identification of the IgE-binding epitope in omega-5 gliadin, a major allergen in wheat-dependent exercise-induced anaphylaxis. *J Biol Chem* 2004;**279**(13):12135–40.
- Lin J, Bardina L, Shreffler WG, Andree DA, Ge Y, Wang J, et al. Development of a novel peptide microarray for large-scale epitope mapping of food allergens. *J Allergy Clin Immunol* 2009;**124**(2):315–22.
- Martínez-Botas J, Cerecedo I, Zamora J, Vlaicu C, Dieguez MC, Gómez-Coronado D, et al. Mapping of the IgE and IgG4 sequential epitopes of ovomucoid with a peptide microarray immunoassay. *Int Arch Allergy Immunol* 2013;**161**(1):11–20.
- Cerecedo I, Zamora J, Shreffler WG, Lin J, Bardina L, Dieguez MC, et al. Mapping of the IgE and IgG4 sequential epitopes of milk allergens with a peptide microarray-based immunoassay. *J Allergy Clin Immunol* 2008;**122**(3):589–94.
- Shreffler WG, Lencer DA, Bardina L, Sampson HA. IgE and IgG4 epitope mapping by microarray immunoassay reveals the diversity of immune response to the peanut allergen, Ara h 2. *J Allergy Clin Immunol* 2005;**116**(4):893–9.
- Perez-Gordo M, Lin J, Bardina L, Pastor-Vargas C, Cases B, Vivanco F, et al. Epitope mapping of Atlantic salmon major allergen by peptide microarray immunoassay. *Int Arch Allergy Immunol* 2012;**157**(1):31–40.
- Pomés A. Relevant B cell epitopes in allergic disease. *Int Arch Allergy Immunol* 2010;**152**(1):1–11.
- Sharma P, Gaur SN, Arora N. In silico identification of IgE-binding epitopes of osmotin protein. *PLoS One* 2013;**8**(1):e54755.
- Dall'antonia F, Pavkov-Keller T, Zangger K, Keller W. Structure of allergens and structure based epitope predictions. *Methods* 2014;**66**(1):3–21.
- Pacios LF, Tordesillas L, Cuesta-Herranz J, Compes E, Sánchez-Monge R, Palacín A, et al. Mimotope mapping as a complementary strategy to define allergen IgE-epitopes: peach Pru p 3 allergen as a model. *Mol Immunol* 2008;**45**(8):2269–76.
- Coales SJ, Tuske SJ, Tomasso JC, Hamuro Y. Epitope mapping by amide hydrogen/deuterium exchange coupled with immobilization of antibody, on-line proteolysis, liquid chromatography and mass spectrometry. *Rapid Commun Mass Spectrom* 2009;**23**(5):639–47.
- Willison LN, Zhang Q, Su M, Teuber SS, Sathe SK, Roux KH. Conformational epitope mapping of Pru du 6, a major allergen from almond nut. *Mol Immunol* 2013;**55**(3–4):253–63.
- Xia L, Willison LN, Porter L, Robotham JM, Teuber SS, Sathe SK, et al. Mapping of a conformational epitope on the cashew allergen Ana o 2: a discontinuous

- large subunit epitope dependent upon homologous or heterologous small subunit association. *Mol Immunol* 2010;**47**(9):1808–16.
48. Berin MC, Mayer L. Can we produce true tolerance in patients with food allergy? *J Allergy Clin Immunol* 2013;**131**(1):14–22.
 49. Jardtzyk TS, Brown JH, Gorga JC, Stern LJ, Urban RG, Strominger JL, et al. Crystallographic analysis of endogenous peptides associated with HLA-DR1 suggests a common, polyproline II-like conformation for bound peptides. *Proc Natl Acad Sci U S A* 1996;**93**(2):734–8.
 50. Nielsen M, Lund O, Buus S, Lundegaard C. MHC class II epitope predictive algorithms. *Immunology* 2010;**130**(3):319–28.
 51. Bohle B. T-cell epitopes of food allergens. *Clin Rev Allergy Immunol* 2006;**30**(2): 97–108.
 52. Tordesillas L, Cuesta-Herranz J, Gonzalez-Muñoz M, Pacios LF, Compés E, Garcia-Carrasco B, et al. T-cell epitopes of the major peach allergen, Pru p 3: Identification and differential T-cell response of peach-allergic and non-allergic subjects. *Mol Immunol* 2009;**46**(4):722–8.
 53. Pastorello EA, Monza M, Pravettoni V, Longhi R, Bonara P, Scibilia J, et al. Characterization of the T-cell epitopes of the major peach allergen Pru p 3. *Int Arch Allergy Immunol* 2010;**153**(1):1–12.
 54. DeLong JH, Simpson KH, Wambre E, James EA, Robinson D, Kwok WW, Ara h 1-reactive T cells in individuals with peanut allergy. *J Allergy Clin Immunol* 2011;**127**(5):1211–8.
 55. Pascal M, Konstantinou GN, Masilamani M, Lieberman J, Sampson HA. In silico prediction of Ara h 2 T cell epitopes in peanut-allergic children. *Clin Exp Allergy* 2013;**43**(1):216–27.
 56. Ravkov EV, Pavlov IY, Martins TB, Gleich GJ, Wagner LA, Hill HR, et al. Identification and validation of shrimp-tropomyosin specific CD4 T cell epitopes. *Hum Immunol* 2013;**74**(12):1542–9.
 57. Meulenbroek LA, den Hartog Jager CF, Lebens AF, Knulst AC, Bruijnzeel-Koomen CA, Garssen J, et al. Characterization of T cell epitopes in bovine α -lactalbumin. *Int Arch Allergy Immunol* 2014;**163**(4):292–6.
 58. Mine Y, Yang M. Recent advances in the understanding of egg allergens: basic, industrial, and clinical perspectives. *J Agric Food Chem* 2008;**56**(13): 4874–900.
 59. Mine Y, Wei Zhang J. Identification and fine mapping of IgG and IgE epitopes in ovomucoid. *Biochem Biophys Res Commun* 2002;**292**(4):1070–4.
 60. Hohen E, Bolann B, Elsayed S. Novel B and T cell epitopes of chicken ovomucoid (Gal d 1) induce T cell secretion of IL-6, IL-13, and IFN- γ . *Clin Exp Allergy* 2001;**31**(6):952–64.
 61. Cooke SK, Sampson HA. Allergenic properties of ovomucoid in man. *J Immunol* 1997;**159**(4):2026–32.
 62. Benedité S, López-Expósito I, López-Fandiño R, Molina E. Identification of IgE-binding peptides in hen egg ovalbumin digested in vitro with human and simulated gastroduodenal fluids. *J Agric Food Chem* 2014;**62**(1):152–8.
 63. Mine Y, Rupa P. Fine mapping and structural analysis of immunodominant IgE allergenic epitopes in chicken egg ovalbumin. *Protein Eng* 2003;**16**(10): 747–52.
 64. Jiménez-Saiz R, Benedité S, Miralles B, López-Expósito I, Molina E, López-Fandiño R. Immunological behavior of in vitro digested egg-white lysozyme. *Mol Nutr Food Res* 2014;**58**(3):614–24.
 65. Amo A, Rodríguez-Pérez R, Blanco J, Villota J, Juste S, Moneo I, et al. Gal d 6 is the second allergen characterized from egg yolk. *J Agric Food Chem* 2010;**58**(12):7453–7.
 66. Quirce S, Marañón F, Umpiérrez A, de las Heras M, Fernández-Caldas E, Sastre J. Chicken serum albumin (Gal d 5) is a partially heat-labile inhalant and food allergen implicated in the bird-egg syndrome. *Allergy* 2001;**56**(8): 754–62.
 67. D'Urbano LE, Pellegrino K, Artesani MC, Donnanno S, Luciano R, Riccardi C, et al. Performance of a component-based allergen-microarray in the diagnosis of cow's milk and hen's egg allergy. *Clin Exp Allergy* 2010;**40**(10):1561–70.
 68. Tosca MA, Pistorio A, Accogli A, Silvestri M, Rossi GA, Ciprandi G. Egg allergy: the relevance of molecular-based allergy diagnostics. *Clin Exp Allergy* 2014;**44**(8):1094–5.
 69. Caubet JC, Kondo Y, Urisu A, Nowak-Węgrzyn A. Molecular diagnosis of egg allergy. *Curr Opin Allergy Clin Immunol* 2011;**11**(3):210–5.
 70. Kato I, Schrodde J, Kohr WJ, Laskowski Jr M. Chicken ovomucoid: determination of its amino acid sequence, determination of the trypsin reactive site, and preparation of all three of its domains. *Biochemistry* 1987;**26**(1):193–201.
 71. Urisu A, Ando H, Morita Y, Wada E, Yasaki T, Yamada K, et al. Allergenic activity of heated and ovomucoid-depleted egg white. *J Allergy Clin Immunol* 1997;**100**(2):171–6.
 72. Matsuda T, Watanabe K, Nakamura R. Immunochemical and physical properties of peptic-digested ovomucoid. *J Agric Food Chem* 1983;**31**(5): 942–6.
 73. Ando H, Movérare R, Kondo Y, Tsuge I, Tanaka A, Borres MP, et al. Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy. *J Allergy Clin Immunol* 2008;**122**(3):583–8.
 74. Lemon-Mulé H, Sampson HA, Sicherer SH, Shreffler WG, Noone S, Nowak-Węgrzyn A. Immunologic changes in children with egg allergy ingesting extensively heated egg. *J Allergy Clin Immunol* 2008;**122**(5):977–83.
 75. Shin M, Han Y, Ahn K. The influence of the time and temperature of heat treatment on the allergenicity of egg white proteins. *Allergy Asthma Immunol Res* 2013;**5**(2):96–101.
 76. Astwood JD, Leach JN, Fuchs RL. Stability of food allergens to digestion in vitro. *Nat Biotechnol* 1996;**14**(10):1269–73.
 77. Mizutani K, Toyoda M, Mikami B. X-ray structures of transferrins and related proteins. *Biochim Biophys Acta* 2012;**1820**(3):203–11.
 78. Hochwallner H, Schulmeister U, Swoboda I, Focke-Tejkl M, Civaj V, Balic N, et al. Visualization of clustered IgE epitopes on alpha-lactalbumin. *J Allergy Clin Immunol* 2010;**125**(6):1279–85.
 79. Järvinen KM, Chatchatee P, Bardina L, Beyer K, Sampson HA. IgE and IgG binding epitopes on alpha-lactalbumin and beta-lactoglobulin in cow's milk allergy. *Int Arch Allergy Immunol* 2001;**126**(2):111–8.
 80. Cong YJ, Li LF. Identification of the critical amino acid residues of immunoglobulin E and immunoglobulin G epitopes in β -lactoglobulin by alanine scanning analysis. *J Dairy Sci* 2012;**95**(11):6307–12.
 81. Cong Y, Yi H, Qing Y, Li L. Identification of the critical amino acid residues of immunoglobulin E and immunoglobulin G epitopes on α s1-casein by alanine scanning analysis. *J Dairy Sci* 2013;**96**(11):6870–6.
 82. Chatchatee P, Järvinen KM, Bardina L, Beyer K, Sampson HA. Identification of IgE- and IgG-binding epitopes on alpha(s1)-casein: differences in patients with persistent and transient cow's milk allergy. *J Allergy Clin Immunol* 2001;**107**(2):379–83.
 83. Nakajima-Adachi H, Hachimura S, Ise W, Honma K, Nishiwaki S, Hirota M, et al. Determinant analysis of IgE and IgG4 antibodies and T cells specific for bovine alpha(s1)-casein from the same patients allergic to cow's milk: existence of alpha(s1)-casein-specific B cells and T cells characteristic in cow's-milk allergy. *J Allergy Clin Immunol* 1998;**101**(5):660–71.
 84. Spuergerin P, Mueller H, Walter M, Schiltz E, Forster J. Allergenic epitopes of bovine alpha S1-casein recognized by human IgE and IgG. *Allergy* 1996;**51**(5): 306–12.
 85. Busse PJ, Järvinen KM, Vila L, Beyer K, Sampson HA. Identification of sequential IgE-binding epitopes on bovine alpha(s2)-casein in cow's milk allergic patients. *Int Arch Allergy Immunol* 2002;**129**(1):93–6.
 86. Ahrens B, Lopes de Oliveira LC, Grabenhenrich L, Schulz G, Niggemann B, Wahn U, et al. Individual cow's milk allergens as prognostic markers for tolerance development? *Clin Exp Allergy* 2012;**42**(11):1630–7.
 87. Järvinen KM, Beyer K, Vila L, Chatchatee P, Busse PJ, Sampson HA. B-cell epitopes as a screening instrument for persistent cow's milk allergy. *J Allergy Clin Immunol* 2002;**110**(2):293–7.
 88. Permyakov EA, Berliner LJ. alpha-Lactalbumin: structure and function. *FEBS Lett* 2000;**473**(3):269–74.
 89. Hochwallner H, Schulmeister U, Swoboda I, Balic N, Geller B, Nystrand M, et al. Microarray and allergenic activity assessment of milk allergens. *Clin Exp Allergy* 2010;**40**(12):1809–18.
 90. Vicente-Serrano J, Caballero ML, Rodríguez-Pérez R, Carretero P, Pérez R, Blanco JG, et al. Sensitization to serum albumins in children allergic to cow's milk and epithelia. *Pediatr Allergy Immunol* 2007;**18**(6):503–7.
 91. Restani P, Ballabio C, Cattaneo A, Isoardi P, Terracciano L, Flocchi A. Characterization of bovine serum albumin epitopes and their role in allergic reactions. *Allergy* 2004;**59**(Suppl. 78):21–4.
 92. Flocchi A, Restani P, Riva E, Qualizza R, Bruni P, Restelli AR, et al. Meat allergy: I-Specific IgE to BSA and OSA in atopic, beef sensitive children. *J Am Coll Nutr* 1995;**14**(3):239–44.
 93. Flocchi A, Restani P, Riva E. Beef allergy in children. *Nutrition* 2000;**16**(6): 454–7.
 94. Restani P, Flocchi A, Beretta B, Velonà T, Giovannini M, Galli CL. Effects of structure modifications on IgE binding properties of serum albumins. *Int Arch Allergy Immunol* 1998;**117**(2):113–9.
 95. Tanabe S, Kobayashi Y, Takahata Y, Morimatsu F, Shibata R, Nishimura T. Some human B and T cell epitopes of bovine serum albumin, the major beef allergen. *Biochem Biophys Res Commun* 2002;**293**(5):1348–53.
 96. Beretta B, Conti A, Flocchi A, Gaiaichi A, Galli CL, Giuffrida MG, et al. Antigenic determinants of bovine serum albumin. *Int Arch Allergy Immunol* 2001;**126**(3): 188–95.
 97. Werfel SJ, Cooke SK, Sampson HA. Clinical reactivity to beef in children allergic to cow's milk. *J Allergy Clin Immunol* 1997;**99**(3):293–300.
 98. Wal JM. Structure and function of milk allergens. *Allergy* 2001;**56**(Suppl. 67): 35–8.
 99. Lisson M, Lochnit G, Erhardt G. Genetic variants of bovine β - and κ -casein result in different immunoglobulin E-binding epitopes after in vitro gastrointestinal digestion. *J Dairy Sci* 2013;**96**(9):5532–43.
 100. Han N, Järvinen KM, Cocco RR, Busse PJ, Sampson HA, Beyer K. Identification of amino acid critical for IgE-binding to sequential epitopes of bovine kappa-casein and the similarity of these epitopes to the corresponding human kappa-casein sequence. *Allergy* 2008;**63**(2):198–204.
 101. Savilahti EM, Kuitunen M, Valori M, Rantanen V, Bardina L, Gimenez G, et al. Use of IgE and IgG4 epitope binding to predict the outcome of oral immunotherapy in cow's milk allergy. *Pediatr Allergy Immunol* 2014;**25**(3):227–35.
 102. Matsumoto N, Okochi M, Matsushima M, Kato R, Takase T, Yoshida Y, et al. Peptide array-based analysis of the specific IgE and IgG4 in cow's milk allergens and its use in allergy evaluation. *Peptides* 2009;**30**(10):1840–7.
 103. Savilahti EM, Rantanen V, Lin JS, Karinen S, Saarinen KM, Goldis M, et al. Early recovery from cow's milk allergy is associated with decreasing IgE and increasing IgG4 binding to cow's milk epitopes. *J Allergy Clin Immunol* 2010;**125**(6):1315–21.
 104. Denery-Papini S, Bodinier M, Pineau F, Triballeau S, Tranquet O, Adel-Patient K, et al. Immunoglobulin E-binding epitopes of wheat allergens in patients with food allergy to wheat and in mice experimentally sensitized to wheat proteins. *Clin Exp Allergy* 2011;**41**(10):1478–92.

105. Mameri H, Denery-Papini S, Pietri M, Tranquet O, Larré C, Drouet M, et al. Molecular and immunological characterization of wheat Serpin (Tri a 33). *Mol Nutr Food Res* 2012;**56**(12):1874–83.
106. Pahr S, Selb R, Weber M, Focke-Tejkl M, Hofer G, Dordić A, et al. Biochemical, biophysical and IgE-epitope characterization of the wheat food allergen, Tri a 37. *PLoS One* 2014;**9**(11):e111483.
107. Battais F, Mothes T, Moneret-Vautrin DA, Pineau F, Kanny G, Popineau Y, et al. Identification of IgE-binding epitopes on gliadins for patients with food allergy to wheat. *Allergy* 2005;**60**(6):815–21.
108. Yokooji T, Kurihara S, Murakami T, Chinuki Y, Takahashi H, Morita E, et al. Characterization of causative allergens for wheat-dependent exercise-induced anaphylaxis sensitized with hydrolyzed wheat proteins in facial soap. *Allergol Int* 2013;**62**(4):435–45.
109. Denery-Papini S, Bodinier M, Larré C, Brossard C, Pineau F, Triballeau S, et al. Allergy to deamidated gluten in patients tolerant to wheat: specific epitopes linked to deamidation. *Allergy* 2012;**67**(8):1023–32.
110. Matsuo H, Kohno K, Morita E. Molecular cloning, recombinant expression and IgE-binding epitope of omega-5 gliadin, a major allergen in wheat-dependent exercise-induced anaphylaxis. *FEBS J* 2005;**272**(17):4431–8.
111. Tanabe S, Arai S, Yanagihara Y, Mita H, Takahashi K, Watanabe M. A major wheat allergen has a Gln-Gln-Gln-Pro-Pro motif identified as an IgE-binding epitope. *Biochem Biophys Res Commun* 1996;**219**(2):290–3.
112. Salcedo G, Quirce S, Diaz-Perales A. Wheat allergens associated with Baker's asthma. *J Invest Allergol Clin Immunol* 2011;**21**(2):81–92.
113. Tatham AS, Shewry PR. Allergens to wheat and related cereals. *Clin Exp Allergy* 2008;**38**(11):1712–26.
114. Matsuo H, Uemura M, Yorozuya M, Adachi A, Morita E. Identification of IgE-reactive proteins in patients with wheat protein contact dermatitis. *Contact Dermat* 2010;**63**(1):23–30.
115. Constantin C, Quirce S, Poorafshar M, Touraev A, Niggemann B, Mari A, et al. Micro-arrayed wheat seed and grass pollen allergens for component-resolved diagnosis. *Allergy* 2009;**64**(7):1030–7.
116. Morita E, Matsuo H, Chinuki Y, Takahashi H, Dahlström J, Tanaka A. Food-dependent exercise-induced anaphylaxis - importance of omega-5 gliadin and HMW-glutenin as causative antigens for wheat-dependent exercise-induced anaphylaxis-. *Allergol Int* 2009;**58**(4):493–8.
117. Hofmann SC, Fischer J, Eriksson C, Bengtsson Gref O, Biedermann T, Jakob T. IgE detection to $\alpha/\beta/\gamma$ -gliadin and its clinical relevance in wheat-dependent exercise-induced anaphylaxis. *Allergy* 2012;**67**(11):1457–60.
118. Pastorello EA, Farioli L, Stafylaraki C, Scibilia J, Mirone C, Pravettoni V, et al. Wheat-dependent exercise-induced anaphylaxis caused by a lipid transfer protein and not by ω -5 gliadin. *Ann Allergy Asthma Immunol* 2014;**112**(4):386–7.
119. Romano A, Scala E, Rumi G, Gaeta F, Caruso C, Alonzi C, et al. Lipid transfer proteins: the most frequent sensitizer in Italian subjects with food-dependent exercise-induced anaphylaxis. *Clin Exp Allergy* 2012;**42**(11):1643–53.
120. Sander I, Rozynek P, Rihs HP, van Kampen V, Chew FT, Lee WS, et al. Multiple wheat flour allergens and cross-reactive carbohydrate determinants bind IgE in baker's asthma. *Allergy* 2011;**66**(9):1208–15.
121. Sander I, Rihs HP, Doekes G, Quirce S, Krop E, Rozynek P, et al. Component-resolved diagnosis of baker's allergy based on specific IgE to recombinant wheat flour proteins. *J Allergy Clin Immunol* 2015. <http://dx.doi.org/10.1016/j.jaci.2014.11.021>.
122. Pahr S, Constantin C, Mari A, Scheibhofer S, Thalhamer J, Ebner C, et al. Molecular characterization of wheat allergens specifically recognized by patients suffering from wheat-induced respiratory allergy. *Clin Exp Allergy* 2012;**42**(4):597–609.
123. Pastorello EA, Farioli L, Conti A, Pravettoni V, Bonomi S, Iametti S, et al. Wheat IgE-mediated food allergy in European patients: alpha-amylase inhibitors, lipid transfer proteins and low-molecular-weight glutenins. Allergenic molecules recognized by double-blind, placebo-controlled food challenge. *Int Arch Allergy Immunol* 2007;**144**(1):10–22.
124. Battais F, Pineau F, Popineau Y, Aparicio C, Kanny G, Guerin L, et al. Food allergy to wheat: identification of immunoglobulin E and immunoglobulin G-binding proteins with sequential extracts and purified proteins from wheat flour. *Clin Exp Allergy* 2003;**33**(7):962–70.
125. Palacin A, Bartra J, Muñoz R, Diaz-Perales A, Valero A, Salcedo G. Anaphylaxis to wheat flour-derived foodstuffs and the lipid transfer protein syndrome: a potential role of wheat lipid transfer protein Tri a 14. *Int Arch Allergy Immunol* 2010;**152**(2):178–83.
126. Mäkelä MJ, Eriksson C, Kotaniemi-Syrjänen A, Palosuo K, Marsh J, Borres M, et al. Wheat allergy in children - new tools for diagnostics. *Clin Exp Allergy* 2014;**44**(11):1420–30.
127. Palacin A, Quirce S, Armentia A, Fernández-Nieto M, Pacios LF, Asensio T, et al. Wheat lipid transfer protein is a major allergen associated with baker's asthma. *J Allergy Clin Immunol* 2007;**120**(5):1132–8.
128. Gómez-Casado C, Garrido-Arandia M, Pereira C, Catarino M, Parro V, Armentia A, et al. Component-resolved diagnosis of wheat flour allergy in baker's asthma. *J Allergy Clin Immunol* 2014;**134**(2):480–3.
129. Olivieri M, Biscardo CA, Palazzo P, Pahr S, Malerba G, Ferrara R, et al. Wheat IgE profiling and wheat IgE levels in bakers with allergic occupational phenotypes. *Occup Environ Med* 2013;**70**(9):617–22.
130. Sutton R, Skerritt JH, Baldo BA, Wrigley CW. The diversity of allergens involved in bakers' asthma. *Clin Allergy* 1984;**14**(1):93–107.
131. Weichel M, Glaser AG, Ballmer-Weber BK, Schmid-Grendelmeier P, Cramer R. Wheat and maize thioredoxins: a novel cross-reactive cereal allergen family related to baker's asthma. *J Allergy Clin Immunol* 2006;**117**(3):676–81.
132. Sander I, Flagge A, Merget R, Halder TM, Meyer HE, Baur X. Identification of wheat flour allergens by means of 2-dimensional immunoblotting. *J Allergy Clin Immunol* 2001;**107**(5):907–13.
133. Constantin C, Quirce S, Grote M, Touraev A, Swoboda I, Stoecklinger A, et al. Molecular and immunological characterization of a wheat serine proteinase inhibitor as a novel allergen in baker's asthma. *J Immunol* 2008;**180**(11):7451–60.
134. Kimoto M, Suzuki M, Komiyama N, Kunitomo A, Yamashita H, Hiemori M, et al. Isolation and molecular cloning of a major wheat allergen, Tri a Bd 27K. *Biosci Biotechnol Biochem* 2009;**73**(1):85–92.
135. Sotkovský P, Hubálek M, Hernychová L, Novák P, Havranová M, Setinová I, et al. Proteomic analysis of wheat proteins recognized by IgE antibodies of allergic patients. *Proteomics* 2008;**8**(8):1677–91.
136. Hiemori M, Yosida Y, Kimoto M, Yamashita H, Takahashi K, Takahashi K, et al. Investigation of multiple forms of Tri a Bd 27K, a major wheat allergen, by immunoblotting analysis. *Biosci Biotechnol Biochem* 2010;**74**(1):199–202.
137. Pahr S, Constantin C, Papadopoulos NG, Giavi S, Mäkelä M, Pelkonen A, et al. α -Purothionin, a new wheat allergen associated with severe allergy. *J Allergy Clin Immunol* 2013;**132**(4):1000–3.
138. Palosuo K, Alenius H, Varjonen E, Kalkkinen N, Reunala T. Rye gamma-70 and gamma-35 secalins and barley gamma-3 hordein cross-react with omega-5 gliadin, a major allergen in wheat-dependent, exercise-induced anaphylaxis. *Clin Exp Allergy* 2001;**31**(3):466–73.
139. Morita E, Matsuo H, Mihara S, Morimoto K, Savage AW, Tatham AS. Fast omega-gliadin is a major allergen in wheat-dependent exercise-induced anaphylaxis. *J Dermatol Sci* 2003;**33**(2):99–104.
140. Palosuo K, Varjonen E, Kekki OM, Klemola T, Kalkkinen N, Alenius H, et al. Wheat omega-5 gliadin is a major allergen in children with immediate allergy to ingested wheat. *J Allergy Clin Immunol* 2001;**108**(4):634–8.
141. Brans R, Sauer I, Czaja K, Pfütznner W, Merk HF. Microarray-based detection of specific IgE against recombinant ω -5 gliadin in suspected wheat-dependent exercise-induced anaphylaxis. *Eur J Dermatol* 2012;**22**(3):358–62.
142. Ebisawa M, Shibata R, Sato S, Borres MP, Ito K. Clinical utility of IgE antibodies to ω -5 gliadin in the diagnosis of wheat allergy: a pediatric multicenter challenge study. *Int Arch Allergy Immunol* 2012;**158**(1):71–6.
143. Shibata R, Nishima S, Tanaka A, Borres MP, Morita E. Usefulness of specific IgE antibodies to ω -5 gliadin in the diagnosis and follow-up of Japanese children with wheat allergy. *Ann Allergy Asthma Immunol* 2011;**107**(4):337–43.
144. Ito K, Futamura M, Borres MP, Takaoka Y, Dahlström J, Sakamoto T, et al. IgE antibodies to omega-5 gliadin associate with immediate symptoms on oral wheat challenge in Japanese children. *Allergy* 2008;**63**(11):1536–42.
145. Matsuo H, Dahlström J, Tanaka A, Kohno K, Takahashi H, Furumura M, et al. Sensitivity and specificity of recombinant omega-5 gliadin-specific IgE measurement for the diagnosis of wheat-dependent exercise-induced anaphylaxis. *Allergy* 2008;**63**(2):233–6.
146. Beyer K, Chung D, Schulz G, Mishoe M, Niggemann B, Wahn U, et al. The role of wheat omega-5 gliadin IgE antibodies as a diagnostic tool for wheat allergy in childhood. *J Allergy Clin Immunol* 2008;**122**(2):419–21.
147. Baar A, Pahr S, Constantin C, Scheibhofer S, Thalhamer J, Giavi S, et al. Molecular and immunological characterization of Tri a 36, a low molecular weight glutenin, as a novel major wheat food allergen. *J Immunol* 2012;**189**(6):3018–25.
148. Chinuki Y, Morita E. Wheat-dependent exercise-induced anaphylaxis sensitized with hydrolyzed wheat protein in soap. *Allergol Int* 2012;**61**(4):529–37.
149. Tanabe S. IgE-binding abilities of pentapeptides, QQPF and PQQP, in wheat gliadin. *J Nutr Sci Vitaminol* 2004;**50**(5):367–70.
150. Snégoff J, Branlard G, Bouchez-Mahiot I, Laudet B, Tylichova M, Chardot T, et al. Recombinant proteins and peptides as tools for studying IgE reactivity with low-molecular-weight glutenin subunits in some wheat allergies. *J Agric Food Chem* 2007;**55**(24):9837–45.
151. Baar A, Pahr S, Constantin C, Giavi S, Manoussaki A, Papadopoulos NG, et al. Specific IgE reactivity to Tri a 36 in children with wheat food allergy. *J Allergy Clin Immunol* 2014;**133**(2):585–7.
152. Bouchez-Mahiot I, Snégoff J, Tylichova M, Pecquet C, Branlard G, Laurière M. Low molecular weight glutenins in wheat-dependant, exercise-induced anaphylaxis: allergenicity and antigenic relationships with omega 5-gliadins. *Int Arch Allergy Immunol* 2010;**153**(1):35–45.
153. Liu L, Ikeda TM, Branlard G, Peña RJ, Rogers WJ, Lerner SE, et al. Comparison of low molecular weight glutenin subunits identified by SDS-PAGE, 2-DE, MALDI-TOF-MS and PCR in common wheat. *BMC Plant Biol* 2010;**10**:124.
154. Takahashi H, Matsuo H, Chinuki Y, Kohno K, Tanaka A, Maruyama N, et al. Recombinant high molecular weight-glutenin subunit-specific IgE detection is useful in identifying wheat-dependent exercise-induced anaphylaxis complementary to recombinant omega-5 gliadin-specific IgE test. *Clin Exp Allergy* 2012;**42**(8):1293–8.
155. Chafen JJ, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttrop MJ, et al. Diagnosing and managing common food allergies: a systematic review. *JAMA* 2010;**303**(18):1848–56.
156. Leung NY, Wai CY, Shu S, Wang J, Kenny TP, Chu KH, et al. Current immunological and molecular biological perspectives on seafood allergy: a comprehensive review. *Clin Rev Allergy Immunol* 2014;**46**(3):180–97.

157. Ayuso R, Lehrer SB, Reese G. Identification of continuous, allergenic regions of the major shrimp allergen Pen a 1 (tropomyosin). *Int Arch Allergy Immunol* 2002;**127**(1):27–37.
158. Ayuso R, Sánchez-García S, Lin J, Fu Z, Ibáñez MD, Carrillo T, et al. Greater epitope recognition of shrimp allergens by children than by adults suggests that shrimp sensitization decreases with age. *J Allergy Clin Immunol* 2010;**125**(6):1286–93.
159. Giuffrida MG, Villalta D, Mistrello G, Amato S, Asero R. Shrimp allergy beyond Tropomyosin in Italy: clinical relevance of Arginine Kinase, Sarcoplasmic calcium binding protein and Hemocyanin. *Eur Ann Allergy Clin Immunol* 2014;**46**(5):172–7.
160. Tsaouri S, Triga M, Makris M, Kalogeromitos D, Church MK, Priftis KN. Fish and shellfish allergy in children: review of a persistent food allergy. *Pediatr Allergy Immunol* 2012;**23**(7):608–15.
161. Hajeb P, Selamat J. A contemporary review of seafood allergy. *Clin Rev Allergy Immunol* 2012;**42**(3):365–85.
162. Myrset HR, Fæste CK, Kristiansen PE, Dooper MM. Mapping of the immunodominant regions of shrimp tropomyosin Pan b 1 by human IgE-binding and IgE receptor crosslinking studies. *Int Arch Allergy Immunol* 2013;**162**(1):25–38.
163. Bauermeister K, Wangorsch A, Garoffo LP, Reuter A, Conti A, Taylor SL, et al. Generation of a comprehensive panel of crustacean allergens from the North Sea Shrimp *Crangon crangon*. *Mol Immunol* 2011;**48**(15–16):1983–92.
164. García-Orozco KD, Aispuro-Hernández E, Yepiz-Plascencia G, Calderón-de-la-Barca AM, Sotelo-Mundo RR. Molecular characterization of arginine kinase, an allergen from the shrimp *Litopenaeus vannamei*. *Int Arch Allergy Immunol* 2007;**144**(1):23–8.
165. Yu CJ, Lin YF, Chiang BL, Chow LP. Proteomics and immunological analysis of a novel shrimp allergen, Pen m 2. *J Immunol* 2003;**170**(1):445–53.
166. Renand A, Newbrough S, Wambre E, DeLong JH, Robinson D, Kwok WW. Arginine kinase Pen m 2 as an important shrimp allergen recognized by TH2 cells. *J Allergy Clin Immunol* 2014;**134**(6):1456–9.
167. Ayuso R, Grishina G, Bardina L, Carrillo T, Blanco C, Ibáñez MD, et al. Myosin light chain is a novel shrimp allergen, Lit v 3. *J Allergy Clin Immunol* 2008;**122**(4):795–802.
168. Abdel Rahman AM, Kamath S, Lopata AL, Helleur RJ. Analysis of the allergenic proteins in black tiger prawn (*Penaeus monodon*) and characterization of the major allergen tropomyosin using mass spectrometry. *Rapid Commun Mass Spectrom* 2010;**24**(16):2462–70.
169. Ayuso R, Grishina G, Ibáñez MD, Blanco C, Carrillo T, Bencharitiwong R, et al. Sarcoplasmic calcium-binding protein is an EF-hand-type protein identified as a new shrimp allergen. *J Allergy Clin Immunol* 2009;**124**(1):114–20.
170. Shiomoto K, Sato Y, Hamamoto S, Mita H, Shimakura K. Sarcoplasmic calcium-binding protein: identification as a new allergen of the black tiger shrimp *Penaeus monodon*. *Int Arch Allergy Immunol* 2008;**146**(2):91–8.
171. Kalyanasundaram A, Santiago TC. Identification and characterization of new allergen tropomyosin C (Pen m 6.0101) from Indian black tiger shrimp *Penaeus monodon*. *Eur Food Res Technol* 2015;**240**:509–15.
172. Burks AW, Shin D, Cockrell G, Stanley JS, Helm RM, Bannan GA. Mapping and mutational analysis of the IgE-binding epitopes on Ara h 1, a legume vicilin protein and a major allergen in peanut hypersensitivity. *Eur J Biochem* 1997;**245**(2):334–9.
173. Otsu K, Guo R, Dreskin SC. Epitope analysis of Ara h 2 and Ara h 6: characteristic patterns of IgE-binding fingerprints among individuals with similar clinical histories. *Clin Exp Allergy* 2015;**45**(2):471–84.
174. Stanley JS, King N, Burks AW, Huang SK, Sampson H, Cockrell G, et al. Identification and mutational analysis of the immunodominant IgE binding epitopes of the major peanut allergen Ara h 2. *Arch Biochem Biophys* 1997;**342**(2):244–53.
175. Rabjohn P, Helm EM, Stanley JS, West CM, Sampson HA, Burks AW, et al. Molecular cloning and epitope analysis of the peanut allergen Ara h 3. *J Clin Invest* 1999;**103**(4):535–42.
176. Radauer C, Nandy A, Ferreira F, Goodman RE, Larsen JN, Lidholm J, et al. Update of the WHO/IUIS Allergen nomenclature database based on analysis of allergen sequences. *Allergy* 2014;**69**(4):413–9.
177. Kleber-Janke T, Cramer R, Appenzeller U, Schlaak M, Becker WM. Selective cloning of peanut allergens, including profilin and 2S albumins, by phage display technology. *Int Arch Allergy Immunol* 1999;**119**(4):265–74.
178. Flinterman AE, van Hoven E, den Hartog Jager CF, Koppelman S, Pasmans SG, Hoekstra MO, et al. Children with peanut allergy recognize predominantly Ara h2 and Ara h6, which remains stable over time. *Clin Exp Allergy* 2007;**37**(8):1221–8.
179. Koid AE, Chapman MD, Hamilton RG, van Ree R, Versteeg SA, Dreskin SC, et al. Ara h 6 complements Ara h 2 as an important marker for IgE reactivity to peanut. *J Agric Food Chem* 2014;**62**(1):206–13.
180. Barre A, Borges JP, Rougé P. Molecular modelling of the major peanut allergen Ara h 1 and other homotrimeric allergens of the cupin superfamily: a structural basis for their IgE-binding cross-reactivity. *Biochimie* 2005;**87**(6):499–506.
181. Jin T, Guo F, Chen YW, Howard A, Zhang YZ. Crystal structure of Ara h 3, a major allergen in peanut. *Mol Immunol* 2009;**46**(8–9):1796–804.
182. Kleber-Janke T, Cramer R, Scheurer S, Vieths S, Becker WM. Patient-tailored cloning of allergens by phage display: peanut (*Arachis hypogaea*) profilin, a food allergen derived from a rare mRNA. *J Chromatogr B Biomed Sci Appl* 2001;**756**(1–2):295–305.
183. Mittag D, Akkerdaas J, Ballmer-Weber BK, Vogel L, Wensing M, Becker WM, et al. Ara h 8, a Bet v 1-homologous allergen from peanut, is a major allergen in patients with combined birch pollen and peanut allergy. *J Allergy Clin Immunol* 2004;**114**(6):1410–7.
184. Asarnoj A, Movérare R, Ostblom E, Poorafshar M, Lilja G, Hedlin G, et al. IgE to peanut allergen components: relation to peanut symptoms and pollen sensitization in 8-year-olds. *Allergy* 2010;**65**(9):1189–95.
185. Krause S, Reese G, Randow S, Zennaro D, Quarantino D, Palazzo P, et al. Lipid transfer protein (Ara h 9) as a new peanut allergen relevant for a Mediterranean allergic population. *J Allergy Clin Immunol* 2009;**124**(4):771–8.
186. Javaloyes G, Goikoetxea MJ, García Nuñez I, Aranda A, Sanz ML, Blanca M, et al. Pru p 3 acts as a strong sensitizer for peanut allergy in Spain. *J Allergy Clin Immunol* 2012;**130**(6):1432–4.
187. Bublin M, Breiteneder H. Cross-reactivity of peanut allergens. *Curr Allergy Asthma Rep* 2014;**14**(4):426.
188. Cabanos C, Katayama H, Tanaka A, Utsumi S, Maruyama N. Expression and purification of peanut oleosins in insect cells. *Protein J* 2011;**30**(7):457–63.
189. Mishra A, Jain A, Arora N. Mapping B-cell epitopes of major and minor peanut allergens and identifying residues contributing to IgE binding. *J Sci Food Agric* 2015. <http://dx.doi.org/10.1002/jsfa.7121>.
190. Kobayashi S, Katsuyama S, Wagatsuma T, Okada S, Tanabe S. Identification of a new IgE-binding epitope of peanut oleosin that cross-reacts with buckwheat. *Biosci Biotechnol Biochem* 2012;**76**(6):1182–8.
191. Petersen A, Rennert S, Bottger M, Krause S, Gutsmann T, Lindner B, et al. Defensin: a novel allergen in peanuts. *Allergy* 2012;**67**(Suppl. 96):374.
192. Ebisawa M, Movérare R, Sato S, Maruyama N, Borres MP, Komata T. Measurement of Ara h 1-, 2-, and 3-specific IgE antibodies is useful in diagnosis of peanut allergy in Japanese children. *Pediatr Allergy Immunol* 2012;**23**(6):573–81.
193. Surattanont N, Ngamphaiboon J, Wongpiyabovorn J, Puripokai P, Chatchatee P. Component-resolved diagnostics for the evaluation of peanut allergy in a low-prevalence area. *Pediatr Allergy Immunol* 2013;**24**(7):665–70.
194. Sicherer SH, Wood RA. Advances in diagnosing peanut allergy. *J Allergy Clin Immunol Pract* 2013;**1**(1):1–13.
195. Koppelman SJ, Bruijnzeel-Koomen CA, Hessing M, de Jongh HH. Heat-induced conformational changes of Ara h 1, a major peanut allergen, do not affect its allergenic properties. *J Biol Chem* 1999;**274**(8):4770–7.
196. Eiwegger T, Rigby N, Mondoulet L, Bernard H, Krauth MT, Boehm A, et al. Gastro-duodenal digestion products of the major peanut allergen Ara h 1 retain an allergenic potential. *Clin Exp Allergy* 2006;**36**(10):1281–8.
197. van Bostel EL, Koppelman SJ, van den Broek LA, Gruppen H. Determination of pepsin-susceptible and pepsin-resistant epitopes in native and heat-treated peanut allergen Ara h 1. *J Agric Food Chem* 2008;**56**(6):2223–30.
198. Bøgh KL, Nielsen H, Madsen CB, Mills EN, Rigby N, Eiwegger T, et al. IgE epitopes of intact and digested Ara h 1: a comparative study in humans and rats. *Mol Immunol* 2012;**51**(3–4):337–46.
199. Bøgh KL, Nielsen H, Eiwegger T, Madsen CB, Mills EN, Rigby NM, et al. IgE versus IgG4 epitopes of the peanut allergen Ara h 1 in patients with severe allergy. *Mol Immunol* 2014;**58**(2):169–76.
200. Chatel JM, Bernard H, Orson FM. Isolation and characterization of two complete Ara h 2 isoforms cDNA. *Int Arch Allergy Immunol* 2003;**131**(1):14–8.
201. Lehmann K, Schweimer K, Reese G, Randow S, Suhr M, Becker WM, et al. Structure and stability of 2S albumin-type peanut allergens: implications for the severity of peanut allergic reactions. *Biochem J* 2006;**395**(3):463–72.
202. Bernard H, Guillon B, Drumare MF, Paty E, Dreskin SC, Wal JM, et al. Allergenicity of peanut component Ara h 2: contribution of conformational versus linear hydroxyproline-containing epitopes. *J Allergy Clin Immunol* 2014. <http://dx.doi.org/10.1016/j.jaci.2014.10.025>.
203. Chruszcz M, Maleki SJ, Majorek KA, Demas M, Bublin M, Solberg R, et al. Structural and immunologic characterization of Ara h 1, a major peanut allergen. *J Biol Chem* 2011;**286**(45):39318–27.
204. Mueller GA, Gosavi RA, Pomés A, Wünschmann S, Moon AF, London RE, et al. Ara h 2: crystal structure and IgE binding distinguish two subpopulations of peanut allergic patients by epitope diversity. *Allergy* 2011;**66**(7):878–85.
205. Wang Y, Fu TJ, Howard A, Kothary MH, McHugh TH, Zhang Y. Crystal structure of peanut (*Arachis hypogaea*) allergen Ara h 5. *J Agric Food Chem* 2013;**61**(7):1573–8.
206. Hurlburt BK, Offermann LR, McBride JK, Majorek KA, Maleki SJ, Chruszcz M. Structure and function of the peanut panallergen Ara h 8. *J Biol Chem* 2013;**288**(52):36890–901.