
3 Identification and characterisation of food allergens

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3.1 INTRODUCTION

As part of its normal humoral immune responses, in a process generally known as sensitisation, the body produces various different types of molecules called immunoglobulins (Igs or antibodies) which are designated as IgA, IgG, IgM and IgE. These molecules comprise a binding domain which is capable of recognising, usually with high affinity and specificity, ‘non-self’ molecules which include those found in microbes, parasites, environmental agents such as pollen and dust, as well as dietary proteins. In one type of allergic disease known as type I hypersensitivity, the repertoire of antibodies is altered, the body producing larger quantities of IgE, the antibody class normally produced in response to parasitic infections. These IgE responses are directed towards a variety of environmental agents, the target molecules recognised by IgE being termed allergens. It is these molecules that are responsible for triggering an allergic reaction, a process also known as elicitation. IgE works by becoming associated with cells, such as mast cells, which are packed full of inflammatory mediators like histamine. On binding multivalent allergen, the surface bound IgE becomes ‘cross-linked’, triggering release of the mediators, such as histamine, which actually cause the symptoms associated with allergic reactions.

Allergens are usually proteinaceous in nature, the sites recognised by the IgE being known as epitopes. These epitopes can comprise either linear sequences of amino acids (also termed continuous) or disparate portions of a protein’s amino acid sequence which are brought together by the folding of the polypeptide chain to form a discontinuous, or conformational, epitope. It is thought that the majority of epitopes are conformational in nature (Van Regenmortel, 1992) and consequently can be difficult to define in relation to food allergens where processing may either disrupt conformational epitopes found in the native, unprocessed protein, or even introduce new epitopes.

In the absence of any treatment, the only option for food allergic individuals is to avoid the food they are allergic to, and, if appropriate, rescue medication is given in case of an accidental consumption of a problem food. Such food avoidance strategies can be difficult to implement. As a consequence, legislation has been brought in around the world which makes it mandatory to label certain foods and derived ingredients, irrespective of the level to which they are added to a foodstuff (Mills *et al.*, 2004c). The list of ingredients which must be labelled does vary across the world and in the European Union it has already been updated to include molluscs and lupin. Table 3.1 shows the major foods that have to be labelled under this legislation, together with the allergens that have been isolated and characterised from them. In addition to these foods, there are many fresh fruits and vegetables that trigger food allergies and are associated with allergies to other substance such as pollen.

Table 3.1 The major foods that have to be labelled under EU labelling legislation, together with the allergens that have been isolated and characterised from them.

Food	IUIS allergen name	Other names	Protein family	Sequence accessions	Reference
Soybean (<i>Glycine max</i>)	Gly m 1	P34	Vacuolar thiol protease	AAB34755, ABA7, ABA54898	Gonzalez <i>et al.</i> (1995)
	Gly m 2		Not known	A57106 (partial sequence only)	Codina <i>et al.</i> (2002)
	Gly m 3		Profilin	O65809, CAA11755	Rihs <i>et al.</i> (1999)
	Gly m 4	SAM22, PR-10 protein	Bet v 1	CAA42646	Crowell <i>et al.</i> (1992)
	None	11S seed storage globulin, Glycine Glycinin, individual gene products known as G1, G2, G3, G4 and G5.	Cupin	CAA26723, CAA 332154895 (G1), CAA33216 (G2), CAA33217 (G3), CAA37044, CAA26478, CAA60533 (G4), AA33964, AAA33965, CAA55977 (G5)	Nielsen <i>et al.</i> (1989)
Peanut (<i>Arachis hypogaea</i>)	None	Gly m Bd 30 k	C-protease	P22895, AAB09252, BAA25899	Bando <i>et al.</i> (1996)
	None	Gly m Bd 28 k	C-protease (unconfirmed)	BAB21619, P22895, AAB09252	Ogawa <i>et al.</i> (1991), Hiemori <i>et al.</i> (2004)
	Ara h 1	Conarachin, vicillin, 7S seed storage globulin	Cupin	P43237, AAT00596, AAT00595, P43238	Koppelman <i>et al.</i> (2004)
	Ara h 2	2S albumin	Prolamin; 2S albumin	AAM78596, AAN77576, CAC41202	Clarke <i>et al.</i> (1998)
	Ara h 6	Conglutin, 2S albumin n	Prolamin; 2S albumin	AAL37561, 1W2Q_A, AAD56337	Koppelman <i>et al.</i> (2005)
Ara h 3,4	Arachin, 7S seed storage globulin	Cupin	AAC63045, AAD47382, AAM46958, AAM93157, ABI17154	Restani <i>et al.</i> (2005)	
Ara h 5	Actin-binding proteins	Profilin	AF059616	Kleber-Janke <i>et al.</i> (1999)	

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Table 3.1 (Continued)

Food	IUIS allergen name	Other names	Protein family	Sequence accessions	Reference
	Ara h 8		Bet v 1	AAQ91847	Mittag <i>et al.</i> (2004b)
	None	Oleosin	Oleosin-like	G6J1J8	Pons <i>et al.</i> (2002)
Lupin (<i>Lupinus luteus</i>)	Lup an 1	Conglutin- β	Cupin	EU352876	Peeters <i>et al.</i> (2007)
Tree nuts					
Almond (<i>Prunus dulcis</i>)	Pru du 4		Profilin	AAL91662, AAD29411, CAD37201	Scheurer <i>et al.</i> (2001)
	None	2S, Prunus Seed allergenic protein 1	Prolamin; 2S albumin	P82944.1, P82944.2 (partial sequences only)	Poltronieri <i>et al.</i> (2002)
	None	Prunus Seed allergenic protein 2, Conglutin- γ	Prolamin; 2S albumin	P82952 (partial sequences only)	Poltronieri <i>et al.</i> (2002)
	None	Major almond protein, Amandin, 11S seed storage globulin	Cupin	S51942, CAA55009	Garcia-Mas <i>et al.</i> (1995), Sathe <i>et al.</i> (2002)
	Pru du 5	60S acidic ribosomal protein	Ribosomal 60S superfamily	DQ836316	Abolhassani and Roux (2007)
Cashew nut (<i>Anacardium occidentale</i>)	Ana o 1	Vicilin-like, 7S seed storage globulin	Cupin	AAM73729, AAM73730	Wang <i>et al.</i> (2002)
	Ana o 2	Legumin-like, 11S seed storage globulin	Cupin	AAN76862	Wang <i>et al.</i> (2003)
	Ana o 3	2S albumin	Prolamin	AAL91665	Robotham <i>et al.</i> (2005)

Hazelnut (<i>Corylus avellana</i>)	Cor a 1	Bet v 1	CAA50325, CAA50326, CAA50328, Q08407, CAA96548, CAA96549, AAD48405, AAG40329, AAG40330, AAG40331	Lüttkopf <i>et al.</i> (2002)
	Cor a 2	Profilin	Q9AXH5	Flinterman <i>et al.</i> (2008a)
	Cor a 8	Prolamin; LTP family	AAK28533	Schocker <i>et al.</i> (2004)
	Cor a 9	Non-specific lipid transfer protein (nsLTP)	AAI73404	Beyer <i>et al.</i> (2002a)
	Cor a 11	Legumin-like, 11S seed storage globulin	AAI86739	Lauer <i>et al.</i> (2004)
	Gly m 1	Vicilin-like, 7S seed storage globulin	AAI86739	Lauer <i>et al.</i> (2004)
	Gly m 2	P34, Hydrophobic protein	AAI86739	Lauer <i>et al.</i> (2004)
	Gly m 3	Defensin	Not known	Codina <i>et al.</i> (2002)
	Gly m 4	SAM22, PR-10 protein	Profilin	Rihs <i>et al.</i> , 1999
	None	11S seed storage globulin, Glycine Glycinin, individual gene products known as G1, G2, G3, G4 and G5.	BetV1 family Cupin	Crowell <i>et al.</i> (1992) Nielsen <i>et al.</i> (1989)
	Soybean (<i>Glycine max</i>)	None	Gly m Bd 30k, P34	CAA60533 (G4); AAA33964, AAA33965, CAA55977 (G5).
None		Gly m Bd 28 k	P22895, AAB09252, BAA25899	Ogawa <i>et al.</i> (1991), Hiemori <i>et al.</i> (2004)
None		Cysteine protease	P22895, AAB09252, BAA25899	Bando <i>et al.</i> (1996)

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Table 3.1 (Continued)

Food	IUIS allergen name	Other names	Protein family	Sequence accessions	Reference
Peanut (<i>Arachis hypogaea</i>)	Ara h 1	Conarachin, vicillin, 7S seed storage globulin	Cupin	P43237, AAT00596, AAT00595, P43238	Koppelman <i>et al.</i> (2004)
	Ara h 2	2S albumin	Prolamin	AAM78596, AAN77576, CAC41202	Clarke <i>et al.</i> (1998)
	Ara h 6	Conglutin, 2S albumin	Prolamin	AAI37561, 1W2Q.A, AAD56337	Koppelman <i>et al.</i> (2005)
	Ara h 3,4	Arachin, 7S seed storage globulin	Cupin	AAC63045, AAD47382, AAM46958, AAM93157, ABI17154	Restani <i>et al.</i> (2005)
Lupin (<i>Lupinus luteus</i>)	Ara h 5	Actin-binding protein	Profilin	AF059616	Kleber-Janke <i>et al.</i> (1999)
	Ara h 8	PR-10 protein	Bet v 1 family	AAQ91847	Mittag <i>et al.</i> (2004aa, 2004bb)
Tree nuts	None	Oleoin	Oleoin-like	Q611J8	Pons <i>et al.</i> (2002)
	Lup an 1	Conglutin beta	Cupin	EU352876	Peeters <i>et al.</i> (2007)
Almond (<i>Prunus dulcis</i>)	Pru du 4	2S albumin, Prunus Seed allergenic protein 1	Profilin	AAI91662, AAD29411, CAD37201	Scheurer <i>et al.</i> (2001), Tawde <i>et al.</i> (2006)
	None	2S albumin, Prunus Seed allergenic protein 2,	Prolamin	P82944.1, P82944.2 (partial sequences only)	Poltronieri <i>et al.</i> (2002)
	None	Conglutin gamma	Prolamin	P82952 (partial sequences only)	Poltronieri <i>et al.</i> (2002)
	None	Amandin, Pru du amandin, 11S globulin	Cupin	S51942, CAA55009	Garcia-Mas <i>et al.</i> (1995), Sathe <i>et al.</i> (2002)
	Pru du 5	60S acidic ribosomal prot. P2	Ribosomal 60S superfamily	DQ836316	Abolhassani and Roux (2007)

Cashew nut (<i>Anacardium occidentale</i>)	Ana o 1	Vicilin-like, 7S seed storage globulin	Cupin	AAM73729, AAM73730	Wang <i>et al.</i> (2002)
	Ana o 2	Legumin-like, 11S seed storage globulin	Cupin	AAN76862	Wang <i>et al.</i> (2003)
	Ana o 3	2S albumin	Prolamin	AAL91665	Robotham <i>et al.</i> (2005)
Hazelnut (<i>Corylus avellana</i>)	Cor a 1	PR-10 protein	Bet v 1 family	CAA50325, CAA50326, CAA50328, Q08407, CAA96548, CAA96549, AAD48405, AAG40329, AAG40330, AAG40331	Lüttkopf <i>et al.</i> (2002)
	Cor a 2		Profilin	Q9AXH5	Flinterman <i>et al.</i> (2008b)
	Cor a 8	Non-specific lipid transfer protein (nsLTP)	Prolamin	AAK28533	Schocker <i>et al.</i> (2004)
	Cor a 9	Legumin-like, 11S seed storage globulin	Cupin	AAL73404	Beyer <i>et al.</i> (2002b)
	Cor a 11	Vicilin-like, 7S seed storage globulin	Cupin	AAL86739	Lauer <i>et al.</i> (2004)
	Cor a 12	Oleosin (17 kDa)	Oleosin-like	AY224679	Akkerdaas <i>et al.</i> (2006)
	Cor a 13	Oleosin (14–16 kDa)	Oleosin-like	AY224599	Akkerdaas <i>et al.</i> (2006)
Macadamia nut	No allergens characterised, clinically relevant				Pallares (2000)
(<i>Macadamia integrifolia</i> ,	type-1 hypersensitivity observed				
<i>Macadamia tetraphylla</i>)					
Walnut (<i>Juglans regia</i>)	Jug r 1	2S albumin	Prolamin	AA841308	Teuber <i>et al.</i> (1998)

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Table 3.1 (Continued)

Food	IUIS allergen name	Other names	Protein family	Sequence accessions	Reference
	Jug r 2	Vicilin-like, 7S seed storage globulin	Cupin	AAF18269	Teuber <i>et al.</i> (1999)
	Jug r 4	Legumin-like, 11S seed storage globulin	Cupin	AAW29810	Wallowitz <i>et al.</i> (2006)
Mustard					
White mustard (<i>Sinapis alba</i>)	Sin a 1	2S albumin	Prolamin	CAA62909, CAA62910, CAA62911, CAA62912, CAA62908, P15322	Monsalve <i>et al.</i> (1993)
	Sin a 2	11S-type or legumin-like globulin	Cupin	AAW77383, AAX77384	Palomares <i>et al.</i> (2007)
Black Mustard (<i>Brassica nigra</i>)	Bra i 1	2S albumin	Prolamin	P80207	Palomares <i>et al.</i> (2005)
Sesame (<i>Sesamum indicum</i>)		Seed maturation protein	Glucose and ribitol dehydrogenases	AF449242	Beyer <i>et al.</i> (2002a)
	Ses i 1	2S albumin	Prolamin	AF240005, AF091841	Tai <i>et al.</i> (1999), Pastorello <i>et al.</i> (2001b)
	Ses i 2		Beta-globulin	Q9XHP1	Tai <i>et al.</i> (2001)
	Ses i 3	7S globulin	Cupin	Q9AUD0	Beyer <i>et al.</i> (2002b)
Celery (<i>Apium graveolens</i>)	Api g 1		Bet v 1 family	P49372, P92918	Breiteneder <i>et al.</i> (1995)
	Api g 4		Profilin	Q9XF37	Scheurer <i>et al.</i> (2000), Scheurer <i>et al.</i> (2001)
	Api g 5	FAD binding oxidase homologue	Unknown	P81943	Ganglbberger <i>et al.</i> (2000)
Wheat (<i>Triticum aestivum</i>)		Alpha gliadins	Prolamin	Q41545, Q41509, P04721, P04723, P04725, P18573, Q9M4M1, Q9M4L7, G9M4M6	Sandiford <i>et al.</i> (1997)

	Alpha-amylase inhibitor 0.53	Trypsin/alpha-amylase inhibitor	P01084	Carbonero and Garcia-Olmedo (1999)
	CM3	Trypsin/alpha-amylase inhibitor	P17314	Salcedo <i>et al.</i> (2004)
Tri α 12	Profilin-1	Profilin	P49232	Rihs <i>et al.</i> (1994)
Tri α 18	Isolectin A, WGA1			Sutton <i>et al.</i> (1984)
Tri α 14	Lipid Transfer Protein (LTP1)	Prolamin	P24296	Asero <i>et al.</i> (2000)
Tri α 19	Omega-5-gliadin	Prolamin	Q40215	DuPont <i>et al.</i> (2000), Lehto <i>et al.</i> (2003)
	Serine protease inhibitor	Serine protease inhibitor family	EU051824	Constantin <i>et al.</i> (2008)
Tri α 25	Thioredoxin	Thoredoxin-fold family	AJ404845	Weichel <i>et al.</i> (2006)
Tri α 26	glutenin		X12928	Battais <i>et al.</i> (2003)
Bos d 8	Alpha S1-Casein	Casein	P02662 (minor variants)	Mercier <i>et al.</i> (1971), Bernard <i>et al.</i> (1998)
Bos d 8	Alpha S2-Casein	Casein	P02663	Busse <i>et al.</i> (2002)
Bos d 8	Kappa-Casein	Casein	P02668	Chatchatee <i>et al.</i> (2001)
Bos d 8	Beta-Casein	Casein	P02666	Jimenez-Flores <i>et al.</i> (1987)
Bos d 4	Alpha-Lactalbumin	lysozyme/alpha-lactalbumin	P00711	Hurley and Schuler (1987), Neyestani <i>et al.</i> (2003).
Bos d 5	Beta-Lactoglobulin	lipocalin	P02754	Kontopidis <i>et al.</i> (2004)
Bos d 7	Immunoglobulin	Immunoglobulin family	XP_593266, AAB37381.2, AAB37380.1, XP_587538.1, AAC18409.1	Bernhisel-Broadbent <i>et al.</i> (1991)
Bos d 6	Bovine Serum Albumin	Serum albumin family	P02769	Restani <i>et al.</i> (2004)
None	Lactoferrin	Transferrin	P24627	Pierce <i>et al.</i> (1991)

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Table 3.1 (Continued)

Food	IUIS allergen name	Other names	Protein family	Sequence accessions	Reference
Hen's egg	Gal d 1	Ovomucoid	Kazal-type srine protease inhibitor	P01005	Besler <i>et al.</i> (1997)
	Gal d 2	Ovalbumin	Serpin	P01012	Honma <i>et al.</i> (1996)
	Gal d 3	Ovo transferrin	Transferrin	P02789	Awade <i>et al.</i> (1994)
	Gal d 4	Lysozyme	C-type lysozyme	P00698	Mohan <i>et al.</i> (2003)
	Gal d 5	α -livetin	Serum albumin family	P19121	de Blay <i>et al.</i> (1994)
Fish					
Alaska pollack (<i>Theragra chalcogramma</i>)		The c 1, β -parvalbumin	Calcium-binding EF-hand	Q90YK7	Van Do <i>et al.</i> (2005)
Cod (<i>Gadus morhua</i>)	Gad c 1	β -parvalbumin	Calcium-binding EF-hand	P02622	Bugajska-Schreiter <i>et al.</i> (1998)
Carp (<i>Cyprinus carpi</i>)		Cyp c 1, β -parvalbumin	Calcium-binding EF-hand	CAC83658	Bugajska-Schreiter <i>et al.</i> (2000)
Mackerel (<i>Scomber japonicus</i>)		Sco j 1, β -parvalbumin	Calcium-binding EF-hand	P59747	Hamada <i>et al.</i> (2003)
Salmon (<i>Salmo salar</i>)	Sal s 1	β -parvalbumin	Calcium-binding EF-hand	X97824	Lindstrøm <i>et al.</i> (1996)
Tuna (<i>Thunnus tonggol</i>)		Thu o 1, β -parvalbumin	Calcium-binding EF-hand	n.d.	Bugajska-Schreiter <i>et al.</i> (1998)
		Gelatine (denatured collagen aggregate)	Collagen	U23822 (red seabream), O93484 (rainbow trout)	Hansen <i>et al.</i> (2004)

Crustacea							
Shrimp	Pen m 1, Pen α 1, Met e 1	Tropomyosin	Calcium-binding EF-hand	AAZ76743, Q25456	Daul <i>et al.</i> (1994)		
American lobster (<i>Homarus americanus</i>)	Pen m 2	Arginine kinase	Phosphagen kinase	Q819P7	France <i>et al.</i> (1997), Binder <i>et al.</i> (2001)		
Spiny lobster (<i>Panulirus stimpsoni</i>)	Hom α 1	Tropomyosin	Calcium-binding EF-hand	O441119	Leung <i>et al.</i> (1998a)		
Crab	Pan s 1	Tropomyosin	Calcium-binding EF-hand	Q61379	Leung <i>et al.</i> (1998a)		
	Cha f 1	Tropomyosin	Calcium-binding EF-hand	Q9N2R3	Leung <i>et al.</i> (1998b)		
Molluscs							
Squid (<i>Todarodes Pacificus</i>)	Tod p 1	Tropomyosin	Calcium-binding EF-hand	n. d.	Miyazawa <i>et al.</i> (1996)		
Snail (<i>Helix aspersa</i>)	He as 1	Tropomyosin	Calcium-binding EF-hand	Y14855	Asturias <i>et al.</i> (2002)		
Abalone (<i>Haliotis midae</i>)	Hal m 1	Unknown	Unknown	n. d.	Lopata <i>et al.</i> (1997)		
Oyster (<i>Crassostrea gigas</i>)	Cra g 1	Tropomyosin	Calcium-binding EF-hand	Q95WYO	Ishikawa <i>et al.</i> (1998)		

n. d., not determined.

The World Health Organization and the International Union of Immunological Societies (IUIS) produce an official list of allergens, which is designated by the Allergen Nomenclature Sub-Committee (Hoffman *et al.*, 1994). Allergens included in this listing must induce IgE-mediated (atopic) allergy in humans with a prevalence of IgE reactivity above 5%. An allergen is termed major if it is recognised by IgE from at least 50% of a cohort of allergic individuals but does not carry any connotation of allergenic potency; allergens are otherwise termed 'minor'. The allergen designation is then based on the Latin name of the species from which it originates and is composed of the first three letters of the genus, followed by the first letter of the species finishing with an Arabic number, for example Ara h 1 relates to an allergen from *Arachis hypogea* (peanuts). The numbers are determined by the order in which allergens are identified and are common to all homologous allergens (also known as isoallergens) in a given species. Isoallergens are defined on the basis of having a similar molecular mass, an identical biological function, if known, for example enzymatic action and >67% identity of amino acid sequences. For those species where the first three letters of a genus and the first letter of a species are identical, the second letter of the species is also used. The IUIS designations for those allergens in foods for which labelling is mandatory are also given in Table 3.1.

3.2 CLASSIFICATION OF FOOD ALLERGENS

It is generally held that the vast majority of food allergies are caused by a limited number of foods (Bush and Hefle, 1996), but a large number of foods have been documented as causing food allergies, reflecting the diversity of species that humans consume. Over the past 20 years, there has been an explosion in the number of allergens that have been identified and characterised and subsequently there have been efforts to classify them in order to identify common properties and motifs which may be predictive of allergenicity.

Observations have been made that food allergens are restricted to certain protein families (Mills *et al.*, 2004a), and subsequently a classification of plant food allergens based on the membership of allergens to certain protein families and superfamilies has been proposed (Breiteneder and Radauer, 2004). Using post-genomic bioinformatic tools such as Pfam (Bateman *et al.*, 2004), an analysis of plant food allergen families showed that they belonged to only 27 of the then identified 8183 Pfam families, indicating that conserved structures and biological activities play a role in determining or promoting allergenic properties of proteins (Jenkins *et al.*, 2005). Three plant food allergen protein families/superfamilies were found to predominate: the prolamin superfamily, the cupin superfamily and the Bet v 1 family, which together with the profilins accounted for more than 65% of all plant food allergens. A similar situation was found for pollen allergens which were classified into 29 Pfam families representing a 0.35% section of today's classified protein universe (Radauer and Breiteneder, 2006). A similar distribution was found for food allergens of animal origin (Jenkins *et al.*, 2007) with three protein families: the tropomyosins, parvalbumins and caseins dominating. Thus, the repertoire of allergenic proteins identified is small compared to the vast array of different proteins found in biology. The explanations for this are lacking but may in part result from conservation of surface structures in certain families, such as the Bet v 1 and parvalbumin superfamilies, which promotes IgE cross-reactivity (Jenkins *et al.*, 2005, 2007).

3.3 PLANT FOOD ALLERGENS

3.3.1 Fresh fruits and vegetables

Allergy to fresh fruits and vegetables is frequently associated with inhalant allergies to agents such as birch and grass pollen and latex. It is thought that individuals initially become sensitised to the inhalant allergens in pollen and latex and subsequently go on to develop allergies to foods because of IgE cross-reactivity to closely related homologues of the pollen and latex allergens. Symptoms are often mild and confined to the oral cavity, which has given rise to the term oral allergy syndrome (OAS) and frequently (although not always) processing removes allergenicity. Thus, many individuals with the fruit/vegetable-pollen or fruit/vegetable-latex allergies can safely consume cooked fruits and vegetables but not fresh produce. The pollen-related fruit and vegetable allergies tend to have a geographic distribution related to pollen distribution. Allergens involved include those homologous to the major birch pollen allergen, Bet v 1, whose role in plants has yet to be defined, although it does belong to family 10 of the pathogenesis-related proteins (Breiteneder *et al.*, 1989; Hoffmann-Sommergruber, 2002). As it can bind plant steroids in a central tunnel, one suggestion is that it functions as a steroid carrier in plants (Markovic-Housley *et al.*, 2003) (see Plate 3.1). Homologues involved in pollen-fruit cross-reactive allergies have been identified in a very large number of fruits and vegetables, some of the most important include the Rosaceae fruits such as apple (Mal d 1; Vanek-Krebitz *et al.*, 1995), cherry (Pru av 1; Neudecker *et al.*, 2001) and peach (Pru p 1; Gaier *et al.*, 2008). Homologues have also been identified in fruits such as kiwi fruit which are emerging as important allergenic foods in Europe (Act d 8; Oberhuber *et al.*, 2008) and exotic fruits not generally consumed in Europe which may pose a risk such as Sharon fruit (Bolhaar *et al.*, 2005) and jackfruit (Bolhaar *et al.*, 2004). In addition, allergenic Bet v 1 homologues have also been identified in vegetables notably celery (Api g 1; Breiteneder *et al.*, 1995) and carrot (Dau c 1; Hoffmann-Sommergruber *et al.*, 1999). In general, the IgE-binding sites on Bet v 1 are conformational in nature (Gajhede *et al.*, 1996; Neudecker *et al.*, 2001) and consequently IgE reactivity is lost following processing that causes unfolding of the protein. They are also labile to gastrointestinal digestion. A second group of widespread IgE cross-reactive allergens involved in pollen-fruit cross-reactive allergies are the profilins, which were originally identified as the birch pollen allergen Bet v 2 (Valenta *et al.*, 1991). Profilins have a key role in biological systems promoting the polymerisation of actin, but whilst being widespread in nature only those found in plants have been described as allergens. Whilst some studies have cast doubt about the clinical relevance of IgE to profilins (Wensing *et al.*, 2002), others have demonstrated that profilins play an important role in eliciting symptoms in certain patients (Radauer *et al.*, 2006).

There is a second type of fruit and vegetable allergy which is generally found in the Mediterranean area which is not associated with pollen allergy and tends to be expressed with much more severe, even life-threatening allergic reactions. It involves a distinctly different group of allergens, the non-specific lipid transfer proteins (LTPs) (Fernandez-Rivas *et al.*, 2006). These proteins have been characterised as allergens in fruits such as apple (Mal d 3; Sanchez-Monge *et al.*, 1999b), peach (Pru p 3; Pastorello *et al.*, 1999) and grape (Vit v 1; Pastorello *et al.*, 2003), and vegetables such as asparagus (Diaz-Perales *et al.*, 2002) and cabbage (Bra o 3; Palacín *et al.*, 2006). Whilst originally identified in plants through their ability to transfer lipids in an *in vitro* system, their function *in vivo* is probably quite different and they appear to have some role in plant protection as they belong to PR group 14 (Breiteneder and Mills, 2005). The observation that those LTPs involved in food

allergies are located in epidermal tissues (Douliez *et al.*, 2000) along with their lipid-binding characteristics has led to suggestions that they play a role in transporting cutin and suberin monomers to the outer layers where they are polymerised to form the outer waxy layers. Like many other members of the prolamin superfamily, they are highly resistant to gastric and duodenal digestion (Asero *et al.*, 2000), with major IgE-binding sites remaining intact as indicated by the fact that simulated gastrointestinal digestion does not alter their ability to elicit skin reactions *in vivo* as observed for grape LTP (Vassilopoulou *et al.*, 2006).

A third group of relevant fruit allergens are those involved in the latex-fruit cross-reactive allergy syndrome which include the class-I chitinases. A group of carbohydrases with a role in protecting plants from pathogens, these proteins are found widely in plants they have been termed panallergens (Salcedo *et al.*, 2001). A number of allergens have been described including ones from avocado (Pers a 1, Sowka *et al.*, 1998), banana (Mus p 1.2 Sanchez-Monge *et al.*, 1999a) and chestnut (Cas s 1, Diaz-Perales *et al.*, 1998). Other allergens involved in IgE cross-reactive allergies between foods and latex include patatin; a storage protein from potato has also been shown to be cross-reactive with the latex allergen Hev b 7 along with other proteins from avocado and banana (Sowka *et al.*, 1999).

Other minor fruit allergens include the highly disulphide-bonded proteins known as thaumatin-like proteins (TLPs), C-proteases (Pastorello *et al.*, 1998a) and a variety of lectins and Kunitz inhibitors identified in potato (Seppala *et al.*, 2001). Many have anti-fungal and/or anti-bacterial activity and therefore may have a role in plant protection. One example of an important emerging allergenic fruit which contains several of these is kiwi fruit in which is found both a TLP (Act d 2; Gavrovic-Jankulovic *et al.*, 2002) and a thiol-protease actinidin (Act c 1; Pastorello *et al.*, 1998a). The eight disulphide bonds in TLP are probably responsible for their stability to proteolysis (Smole *et al.*, 2008) and the fact that grape TLP retains its allergenicity even after fermentation during wine production (Flamini and De Rosso, 2006). Other less widely found allergens include the flavin adenine dinucleotide (FAD)-containing oxidase allergen of celery, Api g 5, an M_r 53-57-kDa protein which is extensively glycosylated and possesses cross-reactive glycans (Bublin *et al.*, 2003) and a germin-like protein which has been identified in bell pepper (Leitner *et al.*, 1998) and orange (Cit s 1, Crespo *et al.*, 2006) for which the N-linked glycans have been found to be important for IgE binding (Pörtl *et al.*, 2007).

3.3.2 Nuts and seeds

In addition to the pollen-fruit cross-reactive allergy syndromes, it is emerging that Bet v 1 homologues in various nuts and seeds can cause similar allergies. These have been especially well documented for hazelnut where an isoform, Cor a 1.04, has been identified in the nut which resembles Bet v 1 more closely than the allergenic Bet v 1 homologue from hazelnut pollen Cor a 1.01 (Lüttkopf *et al.*, 2002). There are also reports of LTPs found in nuts and seeds triggering allergies similar to those observed in fruits such as peach, including LTP allergens from walnut (Jug r 3; Pastorello *et al.*, 2004) and hazelnut (Cor a 8; Pastorello *et al.*, 2002) the latter having been shown to be an allergen in a population from Northern Europe (Flinterman *et al.*, 2008a). However, the major allergens in these foods include other members of the prolamin superfamily, the 2S albumins and the cupin seed globulins, both of which often function as a protein store in the seed (Jenkins *et al.*, 2005) (see Plate 3.2).

The 2S albumins are usually synthesised in the seed as single chains of M_r 10,000–15,000 which maybe post-translationally processed to give small and large subunits which usually

remain joined by disulfide bonds. The type of this processing depends on the plant species with those in sunflower being single chain albumins, whilst those in Brazil nut are two-chain albumins (Shewry and Pandya, 1999). They have been identified as important allergens in nuts including walnut allergen Jug r 1 (Teuber *et al.*, 1998), almond (Poltronieri *et al.*, 2002) and Ber e 1 from Brazil nut (Pastorello *et al.*, 1998b), and in seeds such as oriental and yellow mustard allergens Bra j 1 and Sin a 1 (Monsalve *et al.*, 1993; Menendez-Arias *et al.*, 1988), Ses i 1 and 2 from sesame (Pastorello *et al.*, 2001b; Beyer *et al.*, 2002b; Wolf *et al.*, 2004) and the 2S albumin from sunflower seeds SFA-8 (Kelly *et al.*, 2000).

In addition to the 2S albumins, a major group of allergens found in nuts and seeds are the 11S and 7S seed storage globulins which belong to the cupin superfamily. The 11S globulins, sometimes termed legumins because they are particularly found in legume seeds, are hexameric proteins of $M_r \sim 300,000\text{--}450,000$. Each subunit is synthesised in the seed as a single chain of M_r about 60,000, which is post-translationally processed to give rise to acidic (M_r about 40,000) and basic (M_r about 20,000) chains, linked by a single disulfide bond and are rarely, if ever, glycosylated (Mills *et al.*, 2004b). The 7/8S globulins, also termed vicilins, are somewhat simpler, comprising three subunits of $M_r \sim 40,000\text{--}80,000$, but typically about 50,000. Seed storage protein allergens have been described in a variety of nuts and seeds with both 11S and 7S proteins having been reported as allergens in hazelnut (Cor a 11 (7S globulin) and Cor a 9 (11S globulin); Pastorello *et al.*, 2002; Beyer *et al.*, 2002a, b), cashew nut (Ana c 1 and Ana c 2; Wang *et al.*, 2002, 2003), whilst only the 7S globulins of walnut (Jug r 2; Teuber *et al.*, 1999), sesame seed (Ses i; Beyer *et al.*, 2002b) and mustard seed (Palomares *et al.*, 2005, 2007) having been identified. The 11S globulins have also been shown to be allergens in almond, also known as almond major protein (AMP) (Roux *et al.*, 2003).

Another group of potentially important allergens that has been identified in the last few years is the oleosins, a group of proteins associated with oil bodies where they play an important role in packaging and stabilising the oil droplet surface, having a portion of the protein structure buried in the oil phase with a second domain on the aqueous facing surface. These have been identified as allergens in sesame (Leduc *et al.*, 2006) and hazelnut (Akkerdaas *et al.*, 2006). They may be important if they find their way into crudely refined oil which, unlike highly refined oils, has sufficient protein to trigger allergic reactions (Crevel *et al.*, 2000).

3.3.3 Legumes

Many of the types of allergens found in other plant foods have also been identified in allergenic legumes. Thus, allergens involved in the cross-reactive pollen syndromes have been identified in several legumes including the Bet v 1 homologues in soybean (Kleine-Tebbe *et al.*, 2002; Mittag *et al.*, 2004a), peanut (Ara h 8; Mittag *et al.*, 2004b) and mung bean (Mittag *et al.*, 2005) and peanut profilin (Kleber-Janke *et al.*, 1999). In addition, the 7S (β -congrucinin) and 11S (glycinin) seed storage globulins have been described as allergens in soybean (Ogawa *et al.*, 1995; Burks *et al.*, 1988; Beardslee *et al.*, 2000) (see Plate 3.3). There is also some evidence that the 2S albumins of soy (Shibasaki *et al.*, 1980) and chickpea (Vioque *et al.*, 1999) are allergenic. In addition, the 7S (Ara h 1; Burks *et al.*, 1991) and 11S (Ara h 3; Rabjohn *et al.*, 1999; Beardslee *et al.*, 2000) seed storage globulins as well as the prolamin superfamily albumin, Ara h 2, 6 and 7 (Burks *et al.*, 1992; Kleber-Janke *et al.*, 1999), are important allergens in peanut. In contrast to the 2S albumins which are relatively resistant to simulated gastrointestinal proteolysis (Suhr *et al.*, 2004), the 7S globulins are

highly susceptible to pepsinolysis. A number of lower molecular weight polypeptides appear to persist following digestion of the peanut Ara h 1, although they retain their IgE-binding capacity following proteolysis (Shin *et al.*, 1998) and simulated gastrointestinal digestion (Eiwegger *et al.*, 2006). Seed storage globulin allergens have also been identified as allergens in lentil (Len c 1; Lopez-Torrejon *et al.*, 2003) and pea (Pis s 1; Sanchez-Monge *et al.*, 2004) which can be cross-reactive with peanut (Wensing *et al.*, 2003). Such cross-reactivity is particularly problematic with lupin (Moneret-Vautrin *et al.*, 1999) with proteins such as conglutin- β having been identified as a major allergen, Lup an 1 (Goggin *et al.*, 2008). Lup an 1 is a 7S seed storage globulin with significant homology to the peanut allergen Ara h 1 and hence may be responsible for the clinical cross-reactivity observed between these two legumes.

Other allergens identified in peanut include an oleosin (Pons *et al.*, 2002) and a lectin, peanut agglutinin (Burks *et al.*, 1994), whilst in soybean a Kunitz trypsin inhibitor (Moroz and Yang, 1980; Burks *et al.*, 1994) and a member of the cysteine protease family, the 34 kDa so-called oil body-associated protein, known as Gly m 1, and Glym Bd 30 k (Ogawa *et al.*, 1993), have been identified as allergens in soybean. Another soybean allergen which is of relevance in countries such as Japan is the M_r 23 kDa protein known as Gly m 28 k which is glycosylated and contains important IgE-reactive glycans also found in a derived 23 kDa peptide (Hiemori *et al.*, 2004). Found in the protein storage vacuoles, the protein has an as yet unknown function in the plant.

3.3.4 Cereals

Cereals have been found to trigger two types of IgE-mediated allergic disease: the occupational allergy known as Baker's asthma, which results from inhalation of flour particles in dusty working environments such as bakeries, and food allergies resulting from ingestion of cereal containing foods. There also appear to be some individuals who react to wheat proteins as a result of prior sensitisation to grass pollen, who are serologically distinct from those who are exposed to flour in a work environment (Sander *et al.*, 1997). However, IgE-mediated allergy to wheat products does not appear to be as widespread as allergies to foods such as egg and peanut, despite a public perception that wheat allergy is prominent. Diagnosis of wheat allergy is further complicated by the low solubility of cereal seed storage prolamins in the dilute salt solutions routinely used in clinical diagnosis, which may mean that cereal allergy may remain undiagnosed.

The seed storage prolamins of cereals, also known more commonly as gluten, are usually associated with causing the food intolerance syndrome, coeliac disease, but can also trigger allergies to cereals, both by ingestion and through inhalation (Sandiford *et al.*, 1997) including conditions such as atopic dermatitis (Varjonen *et al.*, 1995, 1997) and exercise-induced anaphylaxis (EIA) (Varjonen *et al.*, 2000). The latter is a severe allergic reaction that certain patients experience only if they exercise after eating a problem food; two allergens have been described as triggering such reactions, including γ -, α - and ω -5 gliadins (Palosuo *et al.*, 1999, 2001; Matsuo *et al.*, 2004). Other prolamins storage proteins have been identified as major cereal allergens, including both the polymeric HMW and LMW subunits of glutenin as well as the monomeric γ and an α -gliadins (Watanabe *et al.*, 1995; Tanabe *et al.*, 1996; Maruyama *et al.*, 1998; Simonato *et al.*, 2001a). Cooking appears to affect allergenicity, and one study suggested baking may be essential for allergenicity of cereal prolamins (Simonato *et al.*, 2001b).

In addition to the gluten protein fraction, other wheat proteins have been implicated as food allergens including a single $M_r \sim 15,000$ subunit corresponding to an trypsin/ α -amylase inhibitor identified as an allergen (James *et al.*, 1997), whilst another trypsin/ α -amylase inhibitor, termed CM3, has been identified as an allergen triggering atopic dermatitis (Kusaba-Nakayama *et al.*, 2000). α -Amylase inhibitors have also been implicated in allergies to other cereal-based foods, including an M_r 16,000 beer allergen which originates from barley (Curioni *et al.*, 1999) and an M_r 16,000 protein which is a major allergen in maize (Pastorello *et al.*, 2000). A number of α -amylase inhibitors with M_r of about 14,000–16,000 including one $M_r \sim 16,000$ subunit, termed RA 17, have been described as allergens in rice (Nakase *et al.*, 1994). Another group of proteins which have been described as cereal allergens is the type 1 non-specific lipid transfer proteins (LTPs), including ones from maize (Pastorello *et al.*, 2000), spelt (Pastorello *et al.*, 2001a) and wheat (Tri 14; Pastorello *et al.*, 2007). Species differences in response to processing are emerging, since cooking wheat did not modify the IgE-binding capacity of the α -amylase inhibitors but some patients lost their IgE-binding capacity towards the LTP, in contrast to maize (Pastorello *et al.*, 2007). In addition, barley LTP has been found to trigger allergic reactions in beer (Curioni *et al.*, 1999; Asero *et al.*, 2001; Garcia-Casado *et al.*, 2001).

3.4 ANIMAL FOOD ALLERGENS

3.4.1 Cow's milk

The major allergens in cow's milk are the caseins, a group of structurally mobile proteins which bind calcium through clusters of phosphoserine and/or phosphothreonine residues. Caseins are a heterogeneous mixture of proteins, the product of expression of a polymorphic multigene family which undergoes post-translational proteolysis and phosphorylation. They show a heterogeneity of IgE-binding properties. Thus, IgE cross-reactivity studies in a group of cow's milk allergic infants showed that whilst all but 10% had serum IgE against α_{S2} -casein, only around half recognised α_{S1} -casein and only a small proportion (15%) had IgE against β -casein (Natale *et al.*, 2004). The high level of homology between caseins from different mammalian species explains their IgE cross-reactivity. Extensive cross-reactivity has been observed between the milks of cow, sheep and goat (Spuergin *et al.*, 1997) and between the milks of cow, ewe, goat and buffalo, but not of camel (Restani *et al.*, 1999). Thus individuals with cows' milk allergy generally reacting when undergoing oral challenge with goat's milk (Bellioni-Businco *et al.*, 1999) whose caseins have sequence identities of over 90% with bovine caseins. Lower sequence identities of 22–66% may be associated with reduced IgE cross-reactivity, which may explain why some individuals with cow's milk allergy can tolerate mare's milk (Businco *et al.*, 2000) and do not show IgE cross-reactivity to milk proteins from species such as camel (Restani *et al.*, 1999). In addition, it has also been suggested that mare's milk and donkey's milk might be used in selected cases of cow's milk allergy after appropriate modification to make them suitable for human infants (Businco *et al.*, 2000; Muraro *et al.*, 2002). More recently, allergies to goats' or sheep's milk have been emerging, although the IgE reactivity appears to be confined to the casein fraction (Ah-Leung *et al.*, 2006).

The other important allergens in cows' milk are the whey proteins β -lactoglobulin, the only lipocalin which acts as a food allergen (Virtanen, 2001), and α -lactalbumin, which like the egg allergen lysozyme belongs to the glycoside hydrolase family 22 clan of the

O-glycosyl hydrolase superfamily (Wal, 2002). Lastly, one minor allergen identified in milk is the iron-binding protein, lactoferrin (Wal, 2002).

3.4.2 Egg

A number of allergens have been described in egg, in particular the Kazal inhibitor known as ovomucoid, the dominant hen's egg white allergen Gal d 3 (Bernhisel-Broadbent *et al.*, 1994), which is extensively glycosylated and may act to stabilise the protein against proteolysis (Cooke and Sampson, 1997). Another egg allergen is also a protease inhibitor, the serpin serine protease inhibitor namely ovalbumin Gal d 1 (Bernhisel-Broadbent *et al.*, 1994). A third type of hydrolase, this time a glycosidase belonging to the glycoside hydrolase family 22 clan of the *O*-glycosyl hydrolase superfamily, namely lysozyme has been described as a minor hen's egg allergen, known as Gal d 4 (Nitta and Sugai, 1989). It probably acts as a muramidase, hydrolysing peptidoglycans found in bacterial cell wall. Lastly, the sulphur-rich iron-binding glycoprotein ovotransferrin has also been identified as minor allergens in hen egg white (Holen and Elsayed, 1990; Aabin *et al.*, 1996).

3.4.3 Fish

The major allergen identified so far in fish is the white muscle protein known as parvalbumin, a protein which contains a calcium-binding domain known as an EF-hand which is widely found throughout living systems (Lewit-Bentley and Rety, 2000). Loss of calcium results in a major change in conformation which also results in a loss of IgE binding capacity (Bugajska-Schretter *et al.*, 1998, 2000). The parvalbumins family comprises two distinct subtypes, known as α - and the β -parvalbumins, and whilst their three-dimensional structures are very similar, with only one exception all food allergens belong to the β -parvalbumin family (Jenkins *et al.*, 2007) (see Plate 3.4). The only α -parvalbumin reported to be an allergen is that of frog (Hilger *et al.*, 2002). The codfish allergen, Gad c 1, was the first allergenic fish parvalbumin to be described (Aas and Jebsen, 1967; Elsayed and Bennich, 1975) but a number have now been identified in many different fish species and can therefore be considered to be the pan-allergens in fish (Bernhisel-Broadbent, 1992). Clinical cross-reactivity to multiple fish in individuals with fish allergy based on the major fish allergen parvalbumin is a common observation (Sicherer, 2001).

3.4.4 Shellfish and Crustacea

A family of closely related proteins present in muscle and non-muscle cells, tropomyosins are major allergens in the two invertebrate groups, Crustacea and Mollusca, which are generally known as shellfish and are generally assumed to be responsible for seafood allergies. The first to be characterised were those identified in shrimp, and are now acknowledged to be invertebrate pan-allergens by several laboratories (Shanti *et al.*, 1993; Daul *et al.*, 1994; Leung *et al.*, 1994; Reese *et al.*, 1999). The first two residues of the IgE binding region (epitope) in the C-terminal portion of the protein appear to be crucial for IgE binding and is not found in vertebrate tropomyosin. As a consequence of the lack of homology in the IgE epitopes, there is no reported cross-reactivity between IgE from shellfish allergic individuals, and animal muscle tropomyosins. As a result of their extensive homology, tropomyosins exhibit IgE cross-reactivity between various crustacean and mollusc species

(Motoyama *et al.*, 2006), but whilst clinical reactions to multiple crustacean species seem to be fairly common, this is less clear regarding mollusc reactivity which may be restricted to cross-sensitisation (Sicherer, 2001). The proteins appear to be generally heat stable, their allergenicity being unaltered by boiling (Naqpal *et al.*, 1989), with tropomyosins being detected in the cooking water (Lehrer *et al.*, 1990). A minor group of allergens identified in shrimp is the arginine kinases (Yu *et al.*, 2003) which have also been identified as cross-reactive allergens in the Indian meal moth, king prawn, lobster and mussel (Binder *et al.*, 2001).

3.5 CONCLUSIONS

The last 20 years have seen a great expansion in our knowledge of food allergens, particularly with regard to their identification and characterisation with most of the allergens identified in the major allergenic foods. This knowledge is facilitating development of novel diagnostic approaches, in particular component resolved diagnosis using individual purified and highly characterised allergens to relate specific symptoms with the profile of allergens recognised. Such approaches, should they prove effective, have many benefits, as currently the most effective way to diagnose a food allergy is to undertake a food challenge with all its attendant risks to the patient their with time-consuming nature. Novel diagnostic platforms, such as protein arrays, have the potential to deliver improved diagnostic capability whilst utilising only small quantities of serum (Asero *et al.*, 2007). This knowledge of allergens is also leading to the development of new approaches regarding the development of therapeutics, in particular allergens engineered to lose their IgE epitopes, yet retain sufficient immunological activity to allow them to be used to desensitise allergic individuals. Such approaches appear promising, based on studies in animal models using fish parvalbumins (Swoboda *et al.*, 2007).

This large body of knowledge is also allowing us to begin to study what makes one protein become an allergen, but not another. There are indications that the food processing and the matrix itself may modulate any intrinsic allergenic potential of an allergen per se. For example, the potency of peanut allergens in a chocolate matrix to elicit an allergic reaction was shown some years ago to be modulated by addition of vegetable fat, the higher fat content masking early oral reactions, resulting in greater consumption of the food and subsequently more severe reactions (Grimshaw *et al.*, 2003). Our extensive knowledge of the allergens responsible for food allergies will make it possible to begin tackling such issues, despite the lack of adequate animal models for food allergy. This will be important for managing the risks associated with food allergies, whether it be predicting the allergenic potential of a novel protein or food, or managing allergens in foods within existing factory environments. Certainly, new methods for detecting allergens on foods based on the revolution in protein mass spectroscopy that has taken place in the past 10 years will need to draw on this body of knowledge in the future.

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