

## Review article

# Allergic cross-reactivity: from gene to the clinic

A large number of allergenic proteins have now their complete cDNA sequences determined and in some cases also the 3D structures. It turned out that most allergens could be grouped into a small number of structural protein families, regardless of their biological source. Structural similarity among proteins from diverse sources is the molecular basis of allergic cross-reactivity. The clinical relevance of immunoglobulin E (IgE) cross-reactivity seems to be influenced by a number of factors including the immune response against the allergen, exposure and the allergen. As individuals are exposed to a variable number of allergenic sources bearing homologous molecules, the exact nature of the antigenic structure inducing the primary IgE immune response cannot be easily defined. In general, the 'cross-reactivity' term should be limited to defined clinical manifestations showing reactivity to a source without previous exposure. 'Co-recognition', including by definition 'cross-reactivity', could be used to describe the large majority of the IgE reactivity where co-exposure to a number of sources bearing homologous molecules do not allow unequivocal identification of the sensitizing molecule. The analysis of reactivity clusters in diagnosis allows the interpretation of the patient's reactivity profile as a result of the sensitization process, which often begins with exposure to a single allergenic molecule.

**F. Ferreira<sup>1</sup>, T. Hawranek<sup>2</sup>, P. Gruber<sup>1</sup>,  
N. Wopfner<sup>1</sup>, A. Mari<sup>3</sup>**

<sup>1</sup>Department of Genetics and General Biology, University of Salzburg; <sup>2</sup>Department of Dermatology, Landeskliniken Salzburg, Salzburg, Austria; <sup>3</sup>Allergy Unit, National Health Service, Rome, Italy

Key words: allergen structure; allergenicity; arthropod allergens; cross-reactive carbohydrate determinant; cross-reactivity; food allergens; immunoglobulin E antibodies; insect venom allergens; latex allergens; pollen allergens.

Dr Fátima Ferreira  
Institut für Genetik und Allgemeine Biologie  
Universität Salzburg  
Hellbrunnerstr. 34  
A-5020 Salzburg  
Austria

Accepted for publication 3 September 2003

Allergenic proteins originate from a great variety of sources (pollen, mites, moulds, animal products, venom, foods and latex) and are able to induce the immune system to produce high-affinity immunoglobulin E (IgE) antibodies and/or to trigger allergic symptoms in a sensitized individual. The phenomenon of allergen cross-reactivity occurs when IgE antibodies originally raised against one allergen binds or recognizes a similar protein from another source (1–3). The interaction with such homologous protein can then trigger allergic reactions or can be completely irrelevant for the patient. Such cross-reacting allergens are usually discovered in epidemiological studies or clinical observations. Cloning and sequencing of allergen genes provides the molecular basis of cross-reactivity. For example, it is well known that some pollen allergic patients often display adverse reactions after ingestion of certain fresh fruits, vegetables and nuts. Several clinical syndromes have been described such as those associated with birch, mugwort, and ragweed pollen. They can be collectively termed pollen-food syndrome (PFS) (4). For instance, molecular cloning led to the identification of the Bet v 1 and Bet v 2 group of proteins as the molecules involved in the birch PFS.

Two (or more) allergens are cross-reactive if IgE antibodies or a T cell receptor reacts with both (2). However, as high affinity IgE antibodies are central for

the clinical manifestation of cross-reactivity, here we will only discuss cross-reactions at the antibody level.

### Cross-reactivity, co-sensitization and co-recognition

The clinical relevance of cross-reactivity seems to be influenced by a number of factors including the host (the immune response against the allergen), exposure and the allergen (1). In general, repeated exposure to the allergen is required for allergic reactions. In addition, the levels of specific IgE antibodies and their affinity are important aspects for allergic cross-reactions. High affinity antibodies are necessary to trigger IgE-mediated cellular responses by trace amounts of allergens. However, data concerning affinity threshold for triggering reactions by cross-reactive proteins is still insufficient.

The structural characteristics of proteins are major determinants of cross-reactivity. The IgE cross-reactions are because of shared features at the level of primary and tertiary structure of proteins. In general, cross-reactivity seems to require more than 70% sequence identity. Proteins having <50% sequence identity are very seldom cross-reactive (1). Another important aspect to be considered is sequence similarities of allergens to human homologues, which could lead to autoreactive

IgE antibodies. For instance, IgE antibodies reacting with human profilin and manganese-superoxide dismutase (MnSOD) have been described in some patients with pollinosis and fungal allergy, respectively (5, 6). Exceptions occur when postsynthetic modifications (e.g. glycosylation) are involved in cross-reactivity between unrelated proteins. These cross-reactive carbohydrate determinants (CCD) will be briefly discussed below.

The exact nature of the antigenic structure inducing the primary IgE immune response cannot be easily defined. Usually, subjects are exposed to a variable number of allergenic sources bearing homologous molecules (e.g. several grass species). Even in the case of a mono-exposure to a single species (e.g. birch pollen without exposure to other Fagales pollen), very likely subjects are exposed to a variable number of different isoforms from a particular allergen (7). In the routine diagnostic approach, patients are tested with allergenic extracts or molecules showing the highest IgE reactivity and it is usually assumed that those are the sensitizers. This assumption has not been unequivocally demonstrated. For instance, it is possible to record stronger skin test reactivity with pollen extracts to which patients are not exposed to, although such findings could be linked to the quality of extracts used for testing (8). More striking are the observations that certain genetically engineered molecules obtained by site-directed mutagenesis or gene shuffling can display higher IgE-binding activity than the original wild type allergens (9). In the latter case, patients have not been exposed to such molecules. Thus it is conceivable that homologous allergens found in sources to which patients are not exposed could show higher IgE binding activity than the primary sensitizer.

In general, the term 'cross-reactivity' should be used to describe clearly defined clinical features showing the reactivity to a source without previous exposure (10). The more comprehensive term 'co-recognition', including by definition 'cross-reactivity', could be usefully adopted to define the large majority of the IgE reactivity where co-exposure to a number of sources bearing homologous molecules does not allow the identification of the sensitizer. There are a few exceptions (i.e. cat Fel d 1, Api m 1 from bee venom and chicken egg proteins) where the sensitizing source can be identified with a high degree of certainty. For example, the reactivity to Fel d 1-homologous molecules from 'big cats' is certainly determined by primary sensitization to Fel d 1 via exposure to cat-derived material (11). In such limited number of cases the term cross-reactivity could be appropriate, as the primary sensitizer is known. In most of the cases the sensitizing source is postulated because of the high level of exposure (e.g. peanut allergen). Thus, assuming that IgE antibodies are the essential part in the reactivity, they should be central to evaluate the relationships among molecules. Recently, an interesting report from Fernandes et al. (10) clearly highlights how IgE co-recognition of allergenic

molecules might lead to a potential reactivity without prior exposure. Mite or other arthropods tropomyosin sensitization via the inhalation route is suspected to lead to reactivity to shrimp tropomyosin without any previous exposure via the digestive tract. The IgE reactivity to mite group 10 allergenic epitopes that are present in different allergenic sources, as well as IgE to cockroach Per a 7 might thus lead to cross-reactivity to crustacean homologous molecules (Pen a 1). A similar example is reported in a recent study dealing with the IgE reactivity to Bet v 1 in a birch-free area (12). As in the tropomyosin story with Orthodox Jews, IgE reactivity to the major birch allergen has been detected without prior exposure to the related source. Again, considering IgE toward epitopes shared by molecules of the Fagales group 1 as the central point, the phenomenon of reactivity to an 'absent' source can be regarded as 'normal' or even an 'expected' one. Many other examples reported in the literature may have a similar interpretation (e.g. cockroach sensitization in Norway (13)).

Finally, the term 'co-sensitization' underlies the presence of IgE toward epitopes that are not shared between allergenic sources or molecules. The co-sensitization to allergenic sources detected by means of allergenic extracts is a common finding (e.g. grasses and mites) but it does not reflect the pattern of allergenic molecules and of specific IgE antibodies. A subject with isolated grass sensitization might have IgE to several allergenic molecules (e.g. grass group 1, 2, 4, 5) all restricted to the grass family (14). Conversely, a subject sensitized to olive and pellitory pollen and to cat and *Alternaria* might react to Ole e 1, Par j 2, Fel d 1 and Alt a 1 allergens. Co-sensitization to four different molecules is detected in the latter case as well, although they belong to four different sources. Even if the subjects in both cases are co-sensitized to the same number of molecules they will experience different patterns of symptoms, as their triggering allergens can be present at different time points. It is up to the clinical allergologist to differentiate what is relevant in the interventional approach for patients with multiple sensitization and how their immunological reactivity can be interpreted using different criteria.

### Cross-reactive molecules

Presently, the allergen databank (<http://www.allergen.org>) from the Allergen Nomenclature Sub-Committee of the International Union of Immunological Societies (IUIS) contains a list with more than 400 allergens and almost 200 isoallergens. For most of these allergenic proteins originating from various sources, the complete cDNA sequences have been determined and in some cases also the 3D structures (see selected examples in Fig. 1). From these data it is now clear that most allergens can be grouped into a small number of structural protein families, regardless of their biological

source. As mentioned above, structural similarity among proteins from diverse sources is the molecular basis of cross-reactivity.

Tables 1–4 list 28 major groups of cross-reactive proteins from various sources. Allergens in six of these groups belong to some families of pathogenesis-related (PR) proteins from plants (PR-2, PR-3, PR-5, PR-10, PR-12 and PR-14). The PR proteins are divided into 14 families. They are induced in response to infections by pathogens (fungi, bacteria and viruses), by wounding or other stresses including drought, flooding, freezing temperature, ozone and ultraviolet B light (UV-B). Plants expressing higher levels of certain PR proteins are more resistant to environmental stress and disease and their selection for agricultural use could then contribute to an increase in the allergenicity of cultivated plants (15). The aspects of plant PR proteins as allergens and environmental issues have been addressed in several review articles (16–19).

Eleven groups of allergens show sequence homology to a variety of enzymes including proteases (plant and mites cysteine proteases, Grass pollen group 1), glycolytic enzymes (moulds and latex enolase), superoxide dismutase (latex, moulds and human manganese SOD), carbohydrate active enzymes (weed pollen pectate lyase, latex/fruit glucanase and chitinase, chicken egg lysozyme, insect venom hyaluronidase and milk alpha-lactalbumin), and esterases (insect venom phospholipase A1 and A2). Other groups of allergens are transport proteins (food nsLTP, Fagales pollen group 1, milk beta-lactoglobulin and casein), protease inhibitors (egg, ovomucoid and ovalbumin), regulatory proteins (pollen/food profilins and pollen calcium-binding proteins), structural proteins (arthropods tropomyosins and fish parvalbumins), and storage proteins (plant albumins and globulins). In case of some allergens, it has been suggested that their enzymatic activity might function as pro-allergic adjuvant. For example, the cysteine protease activity of Der p 1 enhances its own permeability in the bronchial epithelium, increases IgE production by cleaving the low-affinity IgE receptor (CD23) on B cells and monocytes, and decreases the proliferation of Th1 cells by cleaving the IL-2 receptor (CD25) (20, 21). However, it is still unclear to what extent enzymatic activities or other biochemical functions of allergens are involved in the process of sensitization and allergic reactions (22).

Below we give a short description of cross-reactive molecules grouped as in Tables 1–4, but with no intention of exhausting the published data on allergens. For additional information, the reader is referred to given specialized review articles and to specialized databases listed in Table 5.

#### Fagales pollen – group 1 (PR-10)

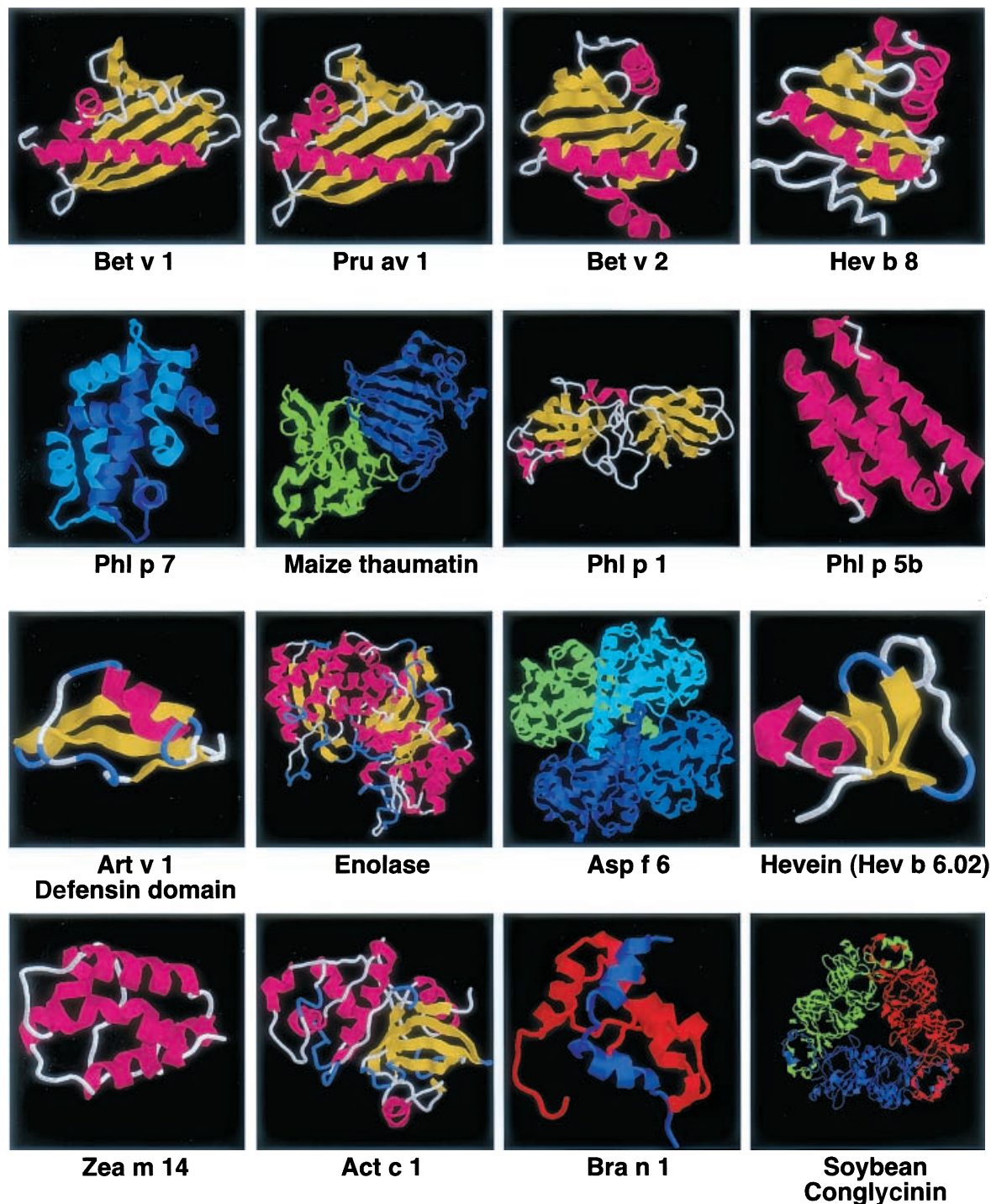
Bet v 1, Cor a 1, Aln g 1, Car b 1 and other major pollen allergens from Fagales trees belong to the PR-10 family

of proteins. These pollen allergens exist as multiple isoforms showing a high degree of sequence similarity. Sensitization by these isoallergens frequently leads to cross-reactions with homologous proteins in apple, cherry, apricot, pear, hazelnut, carrot, celery and other vegetables (Table 1). Bet v 1 is the best characterized allergen in this group. The crystal structure of Bet v 11, a naturally occurring hypoallergenic isoform, was recently determined in complex with deoxycholate (23). Furthermore, ligand binding studies with Bet v 11 (23), Bet v 1.2801 (24), and with Pru av 1 (25) showed interaction with various phytosteroids. Thus, it has been suggested that Bet v 1 and related PR-10 proteins might function as general plant-steroid carriers (23).

The IgE cross-reactivity of Bet v 1 and its homologous proteins is one of the main causes of PFS for patients allergic to pollen from trees of the Fagales order. The IgE binding to Bet v 1 and homologous proteins is conformation dependent and cross-reactivity is assumed to be due to very similar three-dimensional structures. Interestingly, the three-dimensional structure of Bet v 11, a low IgE binding isoform, does not show significant differences when compared with the structures of high IgE-binding Bet v 1.2801 and Pru av 1 molecules. Although no sequential epitopes have been identified for the Bet v 1 family, single amino acid residues/positions involved in epitope formation were successfully identified by site-directed mutagenesis. Amino acid positions 10, 30, 57, 112, 113 and 125 were shown to be crucial for IgE recognition of pollen Bet v 1 and food homologues Mal d 1 and Api g 1 (26, 27). Position 111/112 was also for Mal d 1 (28) and Pru av 1 (29). In addition, glutamic acid in position 45 was shown to be important for the IgE binding activity of Bet v 1 (30) and Pru av 1 (31).

#### Profilins

Profilin is involved in the regulation of actin polymerization and signal transduction of phosphatidylinositol pathway. Profilin is now considered as a ubiquitous cross-reactive plant allergen and sensitized patients typically react to a broad range of pollen and food sources (8, 32). Just to cite a few examples, profilin is responsible for cross-reactions between birch/mugwort pollen-celery-spices, grass pollen-celery-carrots and tree pollen-hazelnut (Table 1). It is believed that IgE cross-reactivity is mostly because of the highly conserved three-dimensional structure of profilins and not to similarities at the level of amino acid sequence (33). Three major epitope regions involved in IgE binding, including the amino and carboxy-terminal alpha-helices of birch profilin were identified, which are also highly conserved regions interacting with the physiologic ligands actin and proline-rich peptides (34). Despite extensive cross-reactivity among plant profilin and to the human homologue as well, it seems that a large proportion of IgE reactivities to profilins is clinically irrelevant (35, 36). The lack of



*Figure 1.* Cartoon representation of the three-dimensional structure of cross-reactive allergens. List of allergens with their PDB codes in parenthesis: birch pollen Bet v 1 (1BV1), cherry Pru av 1 (1EO9), birch pollen Bet v 2 (1CQA), latex Hev b 8 (1G5U), timothy grass pollen Phl p 7 (1K9U), maize thaumatin (1DU5), timothy grass pollen Phl p 1 (1N1O), timothy grass pollen Phl p 5 (1L3P), mugwort pollen Art v 1 (54), *Saccharomyces cerevisiae* enolase (3ENL), *Aspergillus fumigatus* Asp f 6 (1KKC), latex Hev b 6.02 (1HEV), maize Zea m 14 (1MZL), kiwi Act c 1 (2ACT), oilseed rape Bra n 1 (1PNB), soyabean conglycinin (1IPK), soyabean glycinin (1OD5), turkey egg ovomucoid (1OMU), chicken egg Gal d 2 (1OVA), chicken egg Gal d 3 (1OVT), chicken egg Gal d 4 (1E8L), bovine milk Bos d 4 (1F6S), bovine milk Bos d 5 (1GXA), house dust mite Der f 2 (1AHK), house dust mite Der p 2 (1KTJ), carp Cyp c 1 (1B8R), bee venom Api m 1 (1POC), bee venom Api m 2 (1FCV), yellow-jacket venom Ves v 5 (1QNX). For single chain allergen molecules, secondary structure elements are displayed in red (helices), yellow (beta sheets), blue/white (loops and turns), with the exception of Der f 2. Each chain of oligomeric allergens is displayed in a different colour.

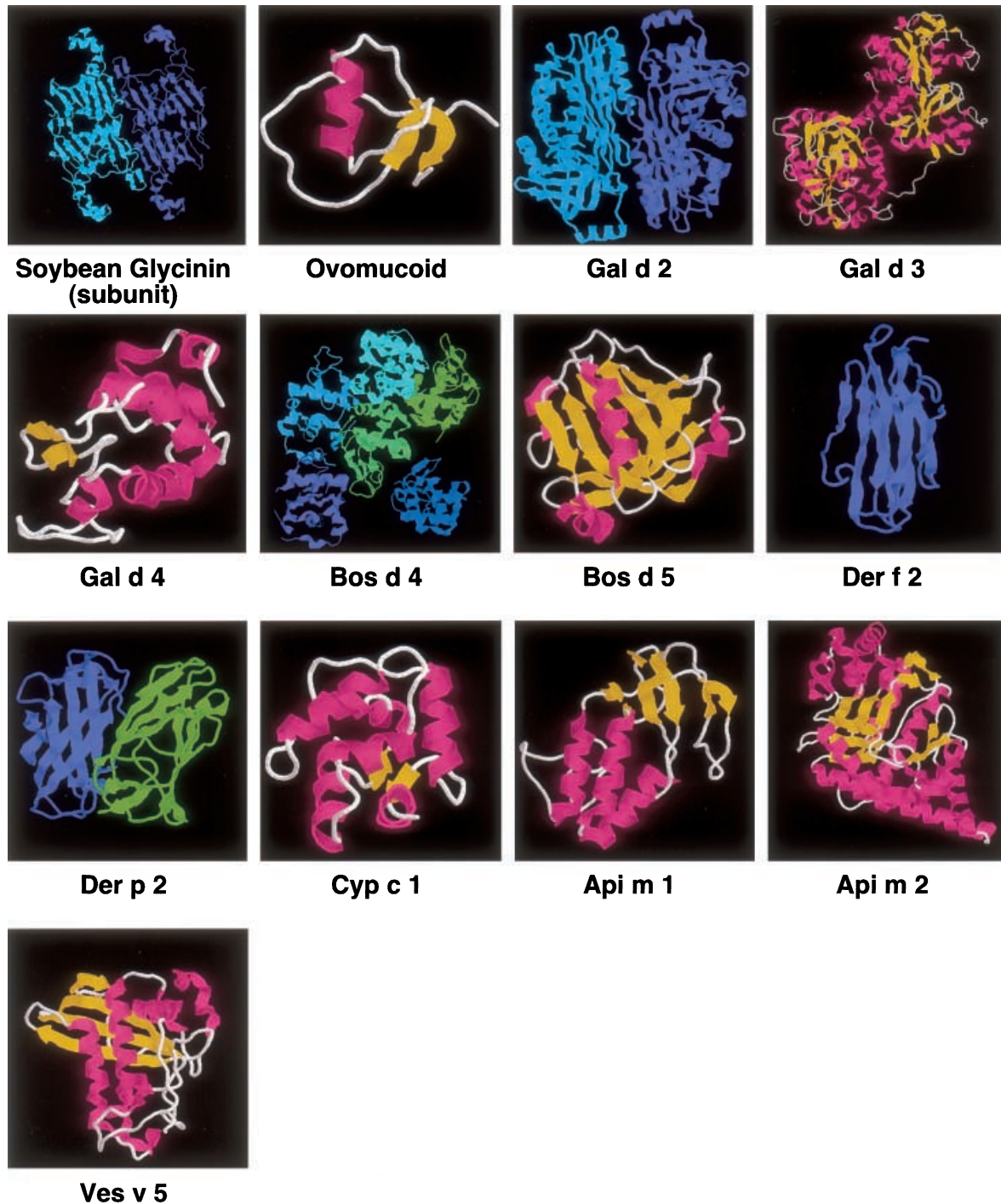


Figure 1. Continued.

correlation between profilin sensitization and clinical manifestation of allergic reactions or even autoimmune diseases might be partially explained by recent findings showing that mast cell exocytosed chymase cleaves human and birch pollen profilin causing a reduction in their IgE binding activity. The destruction of the IgE-binding epitopes of profilin by chymase might thus hinder further mast cell activation and limit

the allergic responses to profilin in sensitized individuals (37).

#### Pollen calcium-binding proteins – polcalcins

Calcium-binding allergens containing 2 EF-hands (Bet v 4, Aln g 4, Ole e 3, Cyn d 7, Phl p 7 and Bra r 1), 3 EF-hands (Bet v 3), and 4 EF-hands (Jun o 4, Ole e 8)

Table 1. Allergenic molecules grouped on the basis of their functions and sources

Allergen	Function	Pollens			Fruits and vegetables	Legumes, nuts and seeds	Latex	Human
		Trees	Grasses	Weeds				
<b>Fagales, group 1</b>	Plant steroid hormone transporter, PR-10	<b><i>Aln g 1*</i></b> <b><i>Bet v 1*</i></b> <b><i>Car b 1*</i></b> <b><i>Cas s 1*</i></b> <b><i>Cor a 1*</i></b> <b><i>Fag s 1</i></b> <b><i>Que a 1*</i></b>			<b><i>Api g 1*</i></b>  <b><i>Dau c 1*</i></b> <b><i>Mal d 1*</i></b> <b><i>Pru ar 1*</i></b> <b><i>Pru av 1*</i></b> <b><i>Pyr c 1*</i></b>	<b><i>Cor a 1.04*</i></b>  <b><i>Gly m 4*</i></b>		
<b>Profilins</b>	Actin-binding protein	<b><i>Bet v 2*</i></b> <b><i>Car b 2</i></b> <b><i>Cor a 2*</i></b> <b><i>Fra e 2</i></b> <b><i>Ole e 2*</i></b> <b><i>Pho d 2*</i></b> <b><i>Pla a ?</i></b>	<b><i>Cyn d 12*</i></b> <b><i>Lol p 12</i></b> <b><i>Ory s 12</i></b> <b><i>Phl p 12*</i></b> <b><i>Poa p 12</i></b> <b><i>Zea m 12</i></b>	<b><i>Amb a ?</i></b> <b><i>Art v 4*</i></b> <b><i>Che a ?</i></b> <b><i>Hel a 2*</i></b> <b><i>Mer a 1*</i></b> <b><i>Par j 3*</i></b> <b><i>Zyg f ?</i></b>	<b><i>Ana c 1*</i></b> <b><i>Api g 4*</i></b> <b><i>Aspa o ?</i></b> <b><i>Cap a 2*</i></b> <b><i>Cit l ?</i></b> <b><i>Cuc m ?</i></b> <b><i>Cuc p ?</i></b> <b><i>Cuc s ?</i></b> <b><i>Dau c 4*</i></b> <b><i>Gly m 3*</i></b> <b><i>Lit c 1*</i></b> <b><i>Lyc e 1*</i></b> <b><i>Mal d 4*</i></b> <b><i>Mus xp 1*</i></b> <b><i>Pru av 4*</i></b> <b><i>Pru p 4*</i></b> <b><i>Pyr c 4*</i></b>	<b><i>Ara h 5*</i></b> <b><i>Bra n ?</i></b> <b><i>Cor a 2*</i></b>	<b><i>Hev b 8*</i></b>	<b><i>Hom s ?</i></b>
<b>Polcalcins</b>	Calcium-binding protein	<b><i>Aln g 4</i></b> <b><i>Bet v 3*</i></b> <b><i>Bet v 4*</i></b> <b><i>Car b ?</i></b> <b><i>Fra e 3</i></b> <b><i>Jun o 4*</i></b> <b><i>Ole e 3*</i></b> <b><i>Ole e 8*</i></b> <b><i>Syr v 3</i></b>	<b><i>Cyn d 7</i></b> <b><i>Phl p 7</i></b>	<b><i>Amb a ?</i></b> <b><i>Art v ?</i></b> <b><i>Bra n ?</i></b> <b><i>Bra r ?</i></b> <b><i>Che a ?</i></b> <b><i>Par j ?</i></b>				
<b>Oleaceae, group 1</b>	Trypsin inhibitor	<b><i>Fra e 1*</i></b> <b><i>Lig v 1*</i></b> <b><i>Ole e 1*</i></b> <b><i>Syr v 1*</i></b>	<b><i>Lol p 11*</i></b> <b><i>Phl p 11*</i></b>	<b><i>Che a 1*</i></b> <b><i>Pla l 1*</i></b> <b><i>Sal k ?</i></b>				
<b>Thaumatin</b>	PR-5	<b><i>Jun a 3*</i></b>			<b><i>Act c 2*</i></b> <b><i>Cap a 1*</i></b> <b><i>Mal d 2*</i></b> <b><i>Pru av 2*</i></b> <b><i>Vit v ?</i></b>			

\* Allergenic molecules listed in the Official International Union of Immunological Societies Allergen Nomenclature website (<http://www.allergen.org>). In bolditalic are reported crossreactive molecules. In bold molecules with function and sequence homologies but lacking demonstrated crossreactivity. Act c, *Actinidia chinensis* (Kiwi); Aln g, *Alnus glutinosa* (Alder); Amb a, *Ambrosia artemisiifolia* (Short ragweed); Ana c, *Ananas comosus* (Pineapple); Api g, *Apium graveolens* (Celery); Ara h, *Arachis hypogaea* (Peanuts); Art v, *Artemisia vulgaris* (Mugwort); Aspa o, *Asparagus officinalis*; Bet v, *Betula verrucosa* (Birch); Bra n, *Brassica napus* (Rapeseed); Bra r, *Brassica rapa* (Turnip); Cap a, *Capsicum annuum* (Bell pepper); Car b, *Carpinus betulus* (Hornbeam); Cas s, *Castanea sativa* (Chestnut); Che a, *Chenopodium album* (Goosefoot); Cit l, *Citrullus lanatus* (Watermelon); Cor a, *Corylus avellana* (Hazel); Cuc m, *Cucumis melo* (Muskmelon); Cuc p, *Cucurbita pepo* (Zucchini); Cuc s, *Cucumis sativus* (Cucumber); Cyn d, *Cynodon dactylon* (Bermuda grass); Dau c, *Daucus carota* (Carrot); Fag s, *Fagus sylvatica* (Beech); Fra e, *Fraxinus excelsior* (Ash); Gly m, *Glycine max* (Soy); Hel a, *Helianthus annuus* (Sunflower); Hev b, *Hevea brasiliensis* (Latex); Hom s, *Homo sapiens*; Jun a, *Juniperus ashei* (Mountain cedar); Jun o, *Juniperus oxycedrus* (Prickly juniper); Lig v, *Ligustrum vulgare* (Common privet); Lit c, *Litchi chinensis*; Lol p, *Lolium perenne* (Rye grass); Lyc e, *Lycopersicon esculentum* (Tomato); Mal d, *Malus domestica* (Apple); Mer a, *Mercurialis annua* (Annual mercury); Mus xp, *Musa x paradisiaca* (Banana); Ole e, *Olea europaea* (Olive); Ory s, *Oryza sativa* (Rice); Par j, *Parietaria judaica* (Pellitory); Phl p, *Phleum pratense* (Timothy grass); Pho d, *Phoenix dactylifera* (Date palm); Pla a, *Platanus acerifolia* (London plane tree); Pla l, *Plantago lanceolata* (English plantain); Poa p, *Poa pratensis* (Kentucky blue grass); Pru ar, *Prunus armeniaca* (Apricot); Pru av, *Prunus avium* (Cherry); Pru p, *Prunus persica* (Peach); Pyr c, *Pyrus communis* (Pear); Que a, *Quercus alba* (White oak); Sal k, *Salsola kali* (Russian thistle); Syr v, *Syringa vulgaris* (Common lilac); Vit v, *Vitis vinifera* (Grape); Zea m, *Zea mays* (Corn); Zyg f, *Zygophyllum fabago* (Syrian bean-caper).

Table 2. Allergenic molecules grouped on the basis of functions and sources

Allergen	Function	Pollens			Fruits and vegetables	Legumes, nuts and seeds	Latex	Moulds	Human
		Trees	Grasses	Weeds					
<b>Grasses, group 1</b>	$\beta$ -Expansin		<b><i>Agr a 1</i></b> <b><i>Ant o 1</i></b> <b><i>Ave s 1</i></b> <b><i>Cyn d 1*</i></b> <b><i>Dac g 1*</i></b> <b><i>Fes e 1</i></b> <b><i>Fes p 1</i></b> <b><i>Hol l 1*</i></b> <b><i>Hor v 1</i></b> <b><i>Lol p 1*</i></b> <b><i>Ory s 1*</i></b> <b><i>Pha a 1*</i></b> <b><i>Phl p 1*</i></b> <b><i>Phr a 1</i></b> <b><i>Poa p 1*</i></b> <b><i>Sec c 1</i></b> <b><i>Sor h 1*</i></b> <b><i>Tri a 1</i></b> <b><i>Zea m 1*</i></b>						
<b>Grasses, group 5</b>	Unknown		<b><i>Ant o 5</i></b> <b><i>Ave s 5</i></b> <b><i>Cyn d 5</i></b> <b><i>Dac g 5*</i></b> <b><i>Fes e 5</i></b> <b><i>Fes p 5</i></b> <b><i>Fes r 5</i></b> <b><i>Hol l 5</i></b> <b><i>Hor v 5</i></b> <b><i>Imp c 5</i></b> <b><i>Lol p 5*</i></b> <b><i>Pha a 5</i></b> <b><i>Phl p 5*</i></b> <b><i>Phr a 5</i></b> <b><i>Poa p 5*</i></b> <b><i>Sec c 5</i></b>						
<b>Ragweed, group 1</b>	Pectate lyase	<b><i>Cha o 1</i></b> <b><i>Cry j 1*</i></b> <b><i>Cup a 1*</i></b> <b><i>Cup s 1*</i></b> <b><i>Jun a 1*</i></b>		<b><i>Amb a 1*</i></b> <b><i>Art v ?</i></b>					
<b>Compositae, group 1</b>	PR-12, defensin domain			<b><i>Art v 1*</i></b> <b><i>Hel a ? (SF18)</i></b> <b><i>Par h 1</i></b>					

\* Allergenic molecules listed in the Official International Union of Immunological Societies Allergen Nomenclature website (<http://www.allergen.org>).

In bolditalic are reported crossreactive molecules. In bold molecules with function and sequence homologies but lacking demonstrated crossreactivity.

Act c, *Actinidia chinensis* (Kiwi); Agr a, *Agrostis alba* (Redtop grass); Alt a, *Alternaria alternata*; Amb a, *Ambrosia artemisiifolia* (Short ragweed); Ant o, *Anthoxanthum odoratum* (Sweet vernal grass); Art v, *Artemisia vulgaris* (Mugwort); Asp f, *Aspergillus fumigatus*; Ave s, *Avena sativa* (Cultivated oat); Bra r, *Brassica rapa* (Turnip); Cand a, *Candida albicans*; Cas s, *Castanea sativa* (Chestnut); Cha o, *Chamaecyparis obtusa* (Japanese cypress); Cla h, *Cladosporium herbarum*; Cry j, *Cryptomeria japonica* (Japanese cedar); Cup a, *Cupressus arizonica* (Arizona cypress); Cup s, *Cupressus sempervirens* (Mediterranean cypress); Cyn d, *Cynodon dactylon* (Bermuda grass); Dac g, *Dactylis glomerata* (Orchard grass); Fes e, *Festuca elatior* (Reed fescue); Fes p, *Festuca pratensis* (Meadow fescue); Fes r, *Festuca rubra*; Hel a, *Helianthus annuus* (Sunflower); Hev b, *Hevea brasiliensis* (Latex); Hol l, *Holcus lanatus* (Velvet grass); Hom s, *Homo sapiens*; Hor v, *Hordeum vulgare* (Barley); Imp c, *Imperata cylindrica* (Cogon grass); Jun a, *Juniperus ashei* (Mountain cedar); Lol p, *Lolium perenne* (Rye grass); Mus xp, *Musa x paradisiaca* (Banana); Ory s, *Oryza sativa* (Rice); Par h, *Parthenium hysterophorus* (Feverfew); Pen c, *Penicillium citrinum*; Pers a, *Persea americana* (Avocado); Pha a, *Phalaris aquatica* (Canary grass); Phl p, *Phleum pratense* (Timothy grass); Phr a, *Phragmites australis* (Common reed); Poa p, *Poa pratensis* (Kentucky blue grass); Rho m, *Rhodotorula mucilaginosa*; Sac c, *Saccharomyces cerevisiae* (Baker's yeast); Sec c, *Secale cereale* (Rye); Sor h, *Sorghum halepense* (Johnson grass); Tri a, *Triticum aestivum* (Wheat); Vit v, *Vitis vinifera* (Grape); Zea m, *Zea mays* (Corn).

Table 2. (Continued)

Allergen	Function	Pollens			Fruits and vegetables	Legumes, nuts and seeds	Latex	Moulds	Human
		Trees	Grasses	Weeds					
<b>Enolases</b>	Glycolytic enzyme						<b>Hev b 9*</b>	<b>Alt a 11*</b> <b>Asp f 22*</b> <b>Cand a ?</b> <b>Cla h 6*</b> <b>Pen c 22*</b> <b>Rho m 1*</b> <b>Sac c ?</b>	
<b>SOD</b>	Manganese superoxide dismutase						<b>Hev b 10*</b>	<b>Asp f 6*</b> <b>Sac c ?</b>	<b>Hom s ?</b>
<b>Glucanase</b>	PR-2				<b>Mus xp ?</b>		<b>Hev b 2*</b>		
<b>Chitinase</b>	PR-3				<b>Act c ?</b> <b>Bra r 2</b> <b>Cas s 5*</b> <b>Mus xp ?</b> <b>Pers a 1*</b> <b>Vit v ?</b>		<b>Hev b 6.02*</b> <b>Hev b 11*</b>		

domains were identified as pollen-specific cross-reactive proteins (Table 1). This group of allergens may thus be used as markers for multiple pollen sensitization (8). The IgE recognition of calcium-binding allergens seems to be conformation dependent and influenced by bound calcium. A comparison between allergens with 2-, 3- and 4-EF hand domains showed that Phl p 7 is the most cross-reactive allergen among polcalcins (38).

Oleaceae pollen – group 1

Ole e 1, the major allergen of olive pollen, is a polymorphic glycoprotein with three disulphide bonds. Several homologues have been identified in other Oleaceae pollen including Lig v 1, Fra e 1 and Syr v 1, which are responsible for a high degree of IgE cross-reactivity among Oleaceae plants (39) (Table 1). The IgE recognition of Ole e 1 depends on the integrity of the disulphide bonds (40). Moreover, the glycan moiety is able to bind IgE and seems to induce the release of histamine from basophils (41). Although Ole e 1-homologous proteins have been characterized in pollen from non-Oleaceae plants (e.g. grasses, English plantain and Chenopodium), IgE cross-reactivity seems to be very low. This is probably because of the low sequence similarity (30–44%) between Ole e 1 and non-Oleaceae homologues.

Thaumatococcus-like proteins (PR-5)

The PR-5 homologous allergens have been characterized in fruits (cherry Pru av 2, apple Mal d 2, kiwi Act c 2, grape Vit v ?), bell pepper (Cap a 1), and in pollen from mountain cedar (Jun a 3) (Table 1). Because of sequence similarities to thaumatin, the sweet-tasting protein from the African shrub *Thaumatococcus daniellii*, PR-5 proteins are also referred to as thaumatin-like proteins. Recombinant Mal d 2 was produced in tobacco plants

and shown to exhibit antifungal activity against *Fusarium oxysporum* and *Penicillium expansum*, indicating a function in plant defense against fungal pathogens (42). Sequence similarities among thaumatin-like allergens indicate a potential for IgE cross-reactivity, although this has not yet been demonstrated.

Grass pollen – group 1 (β-expansin)

Group 1 allergens are the most prominent allergens in pollen from grasses and have been characterized in at least 19 grass species [reviewed by Andersson and Lidholm (43) (Table 2)]. They are polymorphic, N-glycosylated, and contain seven conserved cysteine residues in the N-terminal part of the protein. Group 1 allergens are homologous to expansins, a family of plant proteins involved in cell wall loosening and extension. The exact biochemical mechanism of action of expansins and the identity of their target site of action is still uncertain. Using purified natural and recombinant group 1 allergens (Phl p 1 and Lol p 1) extensive IgE cross-reactivity was demonstrated among different grass species (44, 45).

Five continuous IgE epitopes were identified for Phl p 1. These IgE epitopes seem to be conserved among group 1 allergens from other grass species. However, a considerable proportion of Phl p 1-specific IgE is also directed to conformational Phl p 1 epitopes (46).

Grass pollen – group 5

Group 5 allergens seem to be phylogenetically confined as they have been identified only in members of the Pooideae grass subfamily [reviewed by Andersson and Lidholm (43)]. Nevertheless, they are important cross-reactive allergens for the species where they are expressed (Table 2). Multiple sequence variants have

Table 3. Allergenic molecules grouped on the basis of functions and sources

Allergen	Function	Pollens			Fruits and vegetables	Legumes, nuts and seeds	Latex	Egg	Milk
		Trees	Grasses	Weeds					
<b><i>nsLTP</i></b>	Non-specific Lipid Transfer Protein, PR-14	<b><i>Ole e 7</i></b>		<b><i>Art v 3*</i></b> <b><i>Par j 1*</i></b> <b><i>Par j 2*</i></b> <b><i>Par o 1*</i></b>	<b><i>Aspa o 1*</i></b> <b><i>Dau c ?</i></b> <b><i>Hor v ?</i></b> <b><i>Lac s 1*</i></b> <b><i>Mal d 3*</i></b> <b><i>Pru ar 3*</i></b> <b><i>Pru av 3*</i></b> <b><i>Pru d 3*</i></b> <b><i>Pru du ?</i></b> <b><i>Pru p 3*</i></b> <b><i>Pyr c 3</i></b> <b><i>Tri a ?</i></b> <b><i>Tri s ?</i></b> <b><i>Vit v 1*</i></b> <b><i>Zea m 14*</i></b> <b><i>Act c 1*</i></b> <b><i>Ana c ? (Bromelain)</i></b> <b><i>Car p ? (Papain)</i></b> <b><i>Fic c ? (Ficin)</i></b>	<b><i>Ara h ?</i></b> <b><i>Bra o ?</i></b> <b><i>Bra r ?</i></b> <b><i>Cas s 8*</i></b> <b><i>Cor a 8*</i></b> <b><i>Jug r 3*</i></b>			
<b><i>Plant proteases</i></b>	Cystein protease					<b><i>Gly m 1</i></b>			
<b><i>Plant albumins</i></b>	2S albumin					<b><i>Ana o ?</i></b> <b><i>Ara h 2*</i></b> <b><i>Ara h 6*</i></b> <b><i>Ara h 7*</i></b> <b><i>Ber e 1*</i></b> <b><i>Bra j 1*</i></b> <b><i>Bra n 1*</i></b> <b><i>Jug n 1*</i></b> <b><i>Jug r 1*</i></b> <b><i>Pru du ?</i></b> <b><i>Ric c 1*</i></b> <b><i>Ric c 3</i></b> <b><i>Ses i 1*</i></b> <b><i>Ses i 2*</i></b> <b><i>Sin a 1*</i></b> <b><i>Ana o 1*</i></b> <b><i>Ara h 1*</i></b> <b><i>Cor a 11*</i></b> <b><i>Gly m ?</i></b> <b><i>Jug n 2*</i></b> <b><i>Jug r 2*</i></b> <b><i>Len c 1*</i></b> <b><i>Pis s 1</i></b> <b><i>Ses i 3*</i></b> <b><i>Ana o 2*</i></b> <b><i>Ara h 3*</i></b> <b><i>Ara h 4*</i></b>			
<b><i>Plant globulins (1)</i></b>	7S globulin								
<b><i>Plant globulins (2)</i></b>	11S globulin								

\* Allergenic molecules listed in the Official International Union of Immunological Societies Allergen Nomenclature website (<http://www.allergen.org>).

† Reported cross-reactivity with homologous proteins in other avian eggs.

‡ Reported cross-reactivity with homologous proteins in other mammal milk.

In bolditalic are reported crossreactive molecules. In bold molecules with function and sequence homologies but lacking demonstrated crossreactivity.

*Act c*, *Actinidia chinensis* (Kiwi); *Ana c*, *Ananas comosus* (Pineapple); *Ana o*, *Anacardium occidentale* (Cashew); *Ara h*, *Arachis hypogaea* (Peanuts); *Art v*, *Artemisia vulgaris* (Mugwort); *Aspa o*, *Asparagus officinalis*; *Ber e*, *Bertholletia excelsa* (Brazil Nut); *Bos d*, *Bos domesticus* (Cow); *Bra j*, *Brassica juncea* (Oriental Mustard); *Bra n*, *Brassica napus* (Rapeseed); *Bra o*, *Brassica oleracea* (Broccoli); *Bra r*, *Brassica rapa* (Turnip); *Car p*, *Carica papaya* (Papaya); *Cas s*, *Castanea sativa* (Chestnut); *Cor a*, *Corylus avellana* (Hazel); *Dau c*, *Daucus carota* (Carrot); *Fag e*, *Fagopyrum esculentum* (Buckwheat); *Fic c*, *Ficus carica* (Fig); *Gal d*, *Gallus domesticus* (Hen); *Gly m*, *Glycine max* (Soy); *Hev b*, *Hevea brasiliensis* (Latex); *Hor v*, *Hordium vulgare* (Barley); *Jug n*, *Juglans nigra* (Black walnut); *Jug r*, *Juglans regia* (Walnut); *Lac s*, *Lactuca sativa* (Garden lettuce); *Len c*, *Lens culinaris* (Lentils); *Mal d*, *Malus domestica* (Apple); *Ole e*, *Olea europaea* (Olive); *Par j*, *Parietaria judaica* (Pellitory); *Par o*, *Parietaria officinalis* (Pellitory); *Pis s*, *Pisum sativum* (Garden pea); *Pru ar*, *Prunus armeniaca* (Apricot); *Pru av*, *Prunus avium* (Cherry); *Pru d*, *Prunus domestica* (European plum); *Pru du*, *Prunus dulcis* (Almond); *Pru p*, *Prunus persica* (Peach); *Pyr c*, *Pyrus communis* (Pear); *Ric c*, *Ricinus communis* (Castor bean); *Ses i*, *Sesamum indicum* (Sesame); *Sin a*, *Sinapis alba* (White mustard); *Tri a*, *Triticum aestivum* (Wheat); *Tri s*, *Triticum spelta* (Spelt); *Vit v*, *Vitis vinifera* (Grape); *Zea m*, *Zea mays* (Corn).

Table 3. (Continued)

Allergen	Function	Pollens			Fruits and vegetables	Legumes, nuts and seeds	Latex	Egg	Milk
		Trees	Grasses	Weeds					
				<i>Ber e 2*</i> <i>Cor a 9*</i> <i>Fag e ?</i> <i>Gly m ?</i>					
<b>Avian Proteins</b> †	Ovomucoid Ovalbumin Transferrin Lysozyme α-Livetin						<i>Gal d 1*</i> <i>Gal d 2*</i> <i>Gal d 3*</i> <i>Gal d 4*</i> <i>Gal d 5*</i>		
<b>Mammal Proteins</b> ‡	Lactalbumin Lactoglobulin Casein							<i>Bos d 4*</i> <i>Bos d 5*</i> <i>Bos d 8*</i>	

been characterized in several species but no sequence similarities were found suggesting a possible functional and biologic role for group 5 allergens.

A major IgE-binding epitope was identified comprising the first alanine-rich motif (aa 56–165) of Phl p 5 (47, 48). In addition, synthetic peptides (49), site-directed mutagenesis and short deletions located critical amino acid residues or regions involved in IgE recognition of Lol p 5 (50) and Phl p 5 (51).

Ragweed pollen – group 1 (pectate lyase)

Group 1 allergens from ragweed pollen comprises a family of closely related proteins (52). Ragweed Amb a 1 and homologous allergens in cypress and cedar pollen display sequence similarities to pectate lyases. Japanese cedar Cry j 1 was shown to have pectate lyase enzyme activity (53). Because pectate lyase is a pectin-degrading enzyme involved in the formation of pollen tubes during germination and fruit ripening, it is widely distributed in the environment and could be considered a potential cross-reactive allergen (Table 2). However, studies demonstrating the role of Amb a 1 in IgE cross-reactions are lacking.

Compositae pollen – group 1 (PR-12)

The major allergen of mugwort pollen, Art v 1, is a secreted protein with an N-terminal cysteine-rich domain homologous to plant defensins and a C-terminal proline/hydroxyproline-rich region (54). Homologous allergens have been characterized in other *Compositae* pollen (55, 56), but no data is available concerning IgE cross-reactivity of this group of allergens (Table 2).

Enolases

The glycolytic enzyme enolase was first identified as an allergen in *Saccharomyces cerevisiae* (57). Subsequently, enolase was also shown to be an important allergen of the

mould *Cladosporium herbarum* (58). Extensive IgE cross-reactivity was detected between enolases from several moulds including *C. herbarum*, *Alternaria alternata*, *Candida albicans*, *Aspergillus fumigatus*, *Penicillium citrinum*, *Rhodotorula mucilaginosa*, *Fusarium solani* (59–62). Enolase was also described in natural rubber latex and shown to cross-react with *A. alternata* enolase (63) (Table 2). A major IgE-binding epitope (aa 120–189) was identified, which cross-reacts with other mould enolases (59). As for profilins and polcalcins causing multiple pollen sensitization (8), IgE co-recognition of enolases from unrelated sources could be the molecular basis for multiple sensitization to fungi (64).

Manganese-superoxide dismutase

The MnSOD is a ubiquitous enzyme in prokaryotes and eukaryotes involved in physiologic responses to oxygen toxicity. It has been detected as a major allergen in *A. fumigatus* and shown to cross-react with human and *S. cerevisiae* MnSOD (65). The natural rubber latex homologue, Hev b 10, also cross-reacts with the human and *A. fumigatus* MnSOD (66). Thus, MnSOD could be considered as a potential autoallergen of the mould-latex group (Table 2).

β-1,3-Glucanases (PR-2)

The majority of plant β-1,3-glucanases are endoglucanases hydrolyzing polymers of the β-1,3-glucans, essential components of most fungi. Hev b 2, a latex basic β-1,3-glucanase (67, 68), was shown to be involved in the latex-fruit syndrome (reviewed in (16, 18, 69, 70) and to cross react with homologous allergens from banana, potato and tomato (71) (Table 2).

Class I (basic) chitinases (PR-3)

In most cases plant chitinases are endochitinases that hydrolyze chitin polymers, which are major components

Table 4. Allergenic molecules grouped on the basis of functions and sources

Allergen	Function	Mites	Cockroaches and other Arthropods	Crustacean and Mollusks	Fishes and Amphibians	Nematodes	Insect venom
<b>Mite, group 1</b>	Cystein protease	<b>Blo t 1*</b> <b>Der f 1*</b> <b>Der m 1*</b> <b>Der p 1*</b> <b>Der s 1</b> <b>Eur m 1</b>					
<b>Mite, group 2</b>	Unknown	<b>Aca s 2</b> <b>Der f 2*</b> <b>Der p 2*</b> <b>Der s 2</b> <b>Eur m 2*</b> <b>Gly d 2*</b> <b>Lep d 2*</b> <b>Pso o 2</b> <b>Tyr p 2*</b>					
<b>Tropomyosins</b>	Muscle contraction control	<b>Blo t 10*</b> <b>Der f 10*</b> <b>Der p 10*</b> <b>Lep d 10*</b>	<b>Chi k 10*</b> <b>Per a 7*</b>	<b>Cha f 1</b> <b>Cra g 1</b> <b>Hal d 1</b> <b>Hal m 1</b> <b>Hel as 1*</b> <b>Hom a 1*</b> <b>Met e 1*</b> <b>Pan s 1</b> <b>Par f 1</b> <b>Pen a 1*</b> <b>Pen i 1*</b> <b>Pen m 1*</b> <b>Pena o 1</b> <b>Per v 1</b> <b>Tod p 1*</b> <b>Tur c 1*</b>		<b>Ani s 3*</b>	
<b>Parvalbumins</b>	Calcium-binding protein				<b>Cyp c 1</b> <b>Gad c 1*</b> <b>Gad m 1*</b> <b>Ran e ?</b> <b>Sal s 1*</b> <b>Sco a 1</b> <b>Sco j 1</b> <b>Sco s 1</b> <b>Sti l ?</b> <b>The c 1</b>		
<b>PLA1</b>	Phospholipase A1						<b>Dol m 1*</b> <b>Pol a 1*</b> <b>Pol e 1*</b> <b>Sol i 1</b> <b>Ves g 1</b> <b>Ves m 1*</b> <b>Ves s 1</b> <b>Ves v 1*</b> <b>Vesp c 1*</b> <b>Vesp m 1*</b>
<b>PLA2</b>	Phospholipase A2						<b>Api m 1*</b> <b>Bom t 1</b> <b>Bom p 1*</b> <b>Api m 2*</b> <b>Bom p ?</b> <b>Dol m 2*</b> <b>Pol a 2*</b>
<b>Hyaluronidases</b>	Hyaluronidase						

Table 4. (Continued)

Allergen	Function	Mites	Cockroaches and other Arthropods	Crustacean and Mollusks	Fishes and Amphibians	Nematodes	Insect venom
<b>Antigen 5</b>	Unknown						<b>Pol e 2</b> <b>Ves g 2</b> <b>Ves m 2*</b> <b>Ves s 2</b> <b>Ves v 2*</b> <b>Dol a 5*</b> <b>Dol m 5*</b> <b>Pol a 5*</b> <b>Pol d 5</b> <b>Pol e 5*</b> <b>Pol f 5*</b> <b>Pol g 5*</b> <b>Pol m 5*</b> <b>Pol s 5</b> <b>Sol i 3*</b> <b>Ves f 5*</b> <b>Ves g 5*</b> <b>Ves m 5*</b> <b>Ves p 5*</b> <b>Ves s 5*</b> <b>Ves v 5*</b> <b>Ves vi 5*</b> <b>Vesp c 5*</b> <b>Vesp m 5*</b>

\* Allergenic molecules listed in the Official International Union of Immunological Societies Allergen Nomenclature website (<http://www.allergen.org>). In bolditalic are reported crossreactive molecules. In bold molecules with function and sequence homologies but lacking demonstrated crossreactivity. Aca s, *Acarus siro*; Ani s, *Anisakis simplex*; Api m, *Apis mellifera* (Honey bee); Blo t, *Blomia tropicalis*; Bom p, *Bombus pennsylvanicus* (American bumble bee); Bom t, *Bombus terrestris* (Bumble bee); Cha f, *Charybdis feriatus* (Crab); Chi k, *Chironomus kiensis* (Midge); Cra g, *Crassostrea gigas* (Oyster); Cyp c, *Cyprinus carpio* (Carp); Der f, *Dermatophagoides farinae*; Der m, *Dermatophagoides microceras*; Der p, *Dermatophagoides pteronyssinus*; Der s, *Dermatophagoides siboney*; Dol a, *Dolichovespula arenaria* (Yellow hornet); Dol m, *Dolichovespula maculata* (White-faced hornet); Eur m, *Euroglyphus maynei*; Gad c, *Gadus callaris* (Codfish); Gad m, *Gadus morhua* (Atlantic cod); Gly d, *Glycyphagus domesticus*; Hal d, *Haliotis diversicolor* (Abalone); Hal m, *Haliotis midae* (Abalone); Hel as, *Helix aspersa* (Snail); Hom a, *Homarus americanus* (American lobster); Lep d, *Lepidoglyphus destructor*; Met e, *Metapenaeus ensis* (Greasyback shrimp); Pan s, *Panulirus stimpsoni* (Spiny Lobster); Par f, *Parapenaeus fissurus* (Shrimp); Pen a, *Penaeus aztecus* (Brown shrimp); Pen i, *Penaeus indicus* (Shrimp); Pen m, *Penaeus monodon* (Black tiger shrimp); Pena o, *Penaeus orientalis* (Shrimp); Per a, *Periplaneta americana* (American cockroach); Per v, *Perna viridis* (Mussel); Pol a, *Polistes annularis* (Paper wasp); Pol d, *Polistes dominulus* (Mediterranean paper wasp); Pol e, *Polistes exclamans* (Paper wasp); Pol f, *Polistes fuscatus* (Wasp); Pol g, *Polistes gallicus* (Wasp); Pol m, *Polistes metricus* (Wasp); Pol s, *Polybia scutellaris* (Wasp); Pso o, *Psoroptes ovis* (Sheep scab mites); Ran e, *Rana esculenta* (Frog); Sal s, *Salmo salar* (Atlantic salmon); Sco a, *Scomber australasicus* (Pacific mackerel); Sco j, *Scomber japonicus* (Spotted mackerel); Sco s, *Scomber scombrus* (Atlantic mackerel); Sol i, *Solenopsis invicta* (Fire ant); Sti l, *Stizostedion lucioperca* (Perch); The c, *Theragra chalcogramma* (Alaska pollack); Tod p, *Todarodes pacificus* (Japanese flying squid); Tur c, *Turbo cornutus*; Tyr p, *Tyrophagus putrescentiae*; Ves f, *Vespula flavopilosa* (Yellow jacket); Ves g, *Vespula germanica* (Yellow jacket); Ves m, *Vespula maculifrons* (Eastern yellow jacket); Ves p, *Vespula pensylvanica* (Yellow jacket); Ves s, *Vespula squamosa* (Southern yellow jacket); Ves v, *Vespula vulgaris* (Yellow jacket); Ves vi, *Vespula vidua* (Wasp); Vesp c, *Vespa crabro* (European hornet); Vesp m, *Vespa mandarinia* (Giant Asian hornet).

of the exoskeleton of insects and cell walls of most fungi. Hev b 6.01, a basic class I endochitinase has been identified as the major cross-reactive allergen in the latex-fruit syndrome [reviewed in (16, 18, 69, 70)]. Hev b 6.01 (prohevein) is post-translationally modified to yield an N-terminal fragment designated hevein (Hev b 6.02) with homology to PR-3 proteins and a C-terminal domain (Hev b 6.03) similar to PR-4 proteins. Hev b 6.02-homologous proteins were identified in banana, avocado, chestnut, kiwi, peaches, strawberries and citrus (Table 2). Recombinant endochitinase from avocado (rPers a 1) showed comparable enzymatic activity to the natural counterpart and inhibited fungal growth (72). Karisola et al. (73) showed that the IgE binding ability of hevein is essentially determined by its N-terminal and C-terminal

regions and that major IgE-binding epitopes of hevein are conformational.

Non-specific lipid transfer protein, nsLTP (PR-14)

Plant nsLTPs are involved in the transport of lipids and phospholipids across membranes. They also have potent antifungal and antibacterial activities. nsLTPs usually cause fruit allergy, particularly those of the Rosaceae family (apples, peach and apricot), without concomitant pollen hypersensitivity (Table 3). In addition, patients allergic to nsLTPs tend to have a higher rate of more severe symptoms, which can also reach multiple organs. This is in contrast to the food homologues of the Fagales group 1 allergens where pollen Bet v 1 seems to be the

Table 5. Major allergen databases and their most relevant features (updated July 2003)

Name	URL	Data source	Allergenic molecules	Allergen sequences	Biochemistry molecular biology	Clinical and epidemiological data	Internal search engine	Internal data cross-linking	Computational tools	User alert (newsletter)	References	Last update
Official Allergen Nomenclature (IUIS Subcommittee)	<a href="http://www.allergen.org">http://www.allergen.org</a>	Submission	All	Yes	Yes	No	No	No	No	No	++	July 3, 2003
All-Allergy	<a href="http://allallergy.net">http://allallergy.net</a>	Literature	All	No	No	Yes	Yes	No	No	Yes	++	Not supplied
Allergome	<a href="http://www.allergome.org">http://www.allergome.org</a>	Literature	All	Links	Yes	Yes	Yes	Yes	No	Yes	+++	25 July 2003
FARRP	<a href="http://www.allergenonline.com">http://www.allergenonline.com</a>	Protein databases and Medline	All	Links	Yes	No	Yes	No	Yes	Yes	None	8 April 2003
Food Allergy Information Page (BIFSD)	<a href="http://www.iit.edu/~gengel/fa.htm">http://www.iit.edu/~gengel/fa.htm</a>	Literature	All	Links	No	No	No	No	No	No	+	Not supplied
Protall	<a href="http://www.ifm.bbsrc.ac.uk/protall">http://www.ifm.bbsrc.ac.uk/protall</a>	Literature	Food	Links	Yes	Yes	Yes	No	No	No	+++	Not supplied
SDAP	<a href="http://fermi.utmb.edu/SDAP/sdap_src.html">http://fermi.utmb.edu/SDAP/sdap_src.html</a>	Protein databases	All	Links	Yes	No	Yes	No	Yes	No	None	Not supplied

IUIS, International Union of Immunological Societies; FARRP, Food Allergy and Resource Program; BIFSD, Biotechnology Information for Food Safety; SDAP, Structural Database of Allergenic Proteins.

sensitizing molecule and leads to more mild and localized cross-allergic reactions. These differences were attributed to the structural features of nsLTP, which has four disulphide bridges keeping four alpha helices packed together and results in extreme resistance to proteolysis, heat denaturation and pH changes. This enables them to survive the digestive tract environment, to cause IgE sensitization and to elicit severe symptoms. Therefore, they behave as complete food allergens (17, 19, 74). Interestingly, allergens showing limited sequence homology to fruit LTPs have also been described in *Parietaria* pollen (Par j 1) and soyabean (Gly m 1). The major IgE-binding epitope of Par j 1 was mapped to the first 30 amino terminal residues, with Cys14 and Cys29 being essential for maintaining the structure of the epitope (75).

#### Plant cysteine proteases

This class of proteases includes enzymes from fruits such as papain from papaya, ficin from fig, bromelain from pineapple and actinidin from kiwi (Table 3). The IgE cross-reactions were shown among these plant cysteine proteases (76–79), but not with group 1 cysteine proteases from house dust mites.

#### Plant albumins and globulins: seed storage proteins

Seed storage proteins have been traditionally characterized according to their solubility as albumins (soluble in low-salt buffers) and globulins (soluble in high-salt buffers), and by their sedimentation constants (e.g. 7S, 11S globulins and 2S albumins). Albumins and globulins are the major seed storage proteins of angiosperms and important cross-reactive food allergens (4, 17).

The 2S albumins are heterodimeric proteins with the two subunits linked by disulphide bonds. Allergenic 2S albumins were identified in mustard seeds (Sin a 1, Bra j 1), oilseed rape (Bra n 1), Brazil nut (Ber e 1), walnut (Jug r 1), peanut (Ara h 2, 6, 7) and others (see Table 3). Although one immunodominant linear epitope was identified in Jug r 1, strong evidence for the existence of conformational epitopes was also obtained (80).

The 7S globulins or vicilins are trimeric proteins and were identified as allergens in peanut (Ara h 1), cashew nut (Ana o 1), walnut (Jug r 2), soyabean (conglycinin) and several other nuts and seeds (Table 3). Overlapping peptides were used to identify the IgE-binding epitopes of Ara h 1. At least 23 different linear IgE-binding epitopes, located throughout the length of Ara h 1, were identified. Four of the peptides were immunodominant IgE-binding epitopes being recognized by more than 80% of the patients tested (81).

Legumins or 11S globulins are hexameric proteins. Each subunit is made up of an acidic and a basic chain linked by disulphide bonds. Among others, allergenic 11S globulins were characterized in peanut (Ara h 3, 4),

hazelnut (Cor a 9), cashew nut (Ana o 2), and soyabean (glycinin G1 and G2). The IgE-binding epitopes of glycinin G1 acidic chain were mapped to residues G217–V235 and G253–I265 and are similar to those identified for Ara h 3 (82).

#### Avian proteins

Allergens have been described in both egg white and yolk [reviewed by Poulsen et al. (83)]. The egg white proteins, ovomucoid, ovalbumin, ovotransferrin and lysozyme, were named in the allergen nomenclature as Gal d 1–d 4, respectively (Table 3). The egg yolk allergen, alpha-livetin (chicken serum albumin), was designated Gal d 5. Extensive cross-reactivity has been described among various avian eggs (84), but the clinical significance has not been extensively evaluated. Gal d 5 was identified as a cross-reactive allergen in the bird feather-egg-syndrome (85) and associated with reactions to chicken meat (86–88).

#### Mammalian proteins

Several milk proteins have been identified as allergens including alpha-lactalbumin (Bos d 4), beta-lactoglobulin (Bos d 5) and casein (Bos d 8) [reviewed by Wal (89); Table 3]. Both linear and conformational IgE-binding epitopes were identified in milk allergens. However, clear relationships between structure and allergenicity are not yet established. For casein, a highly conserved region corresponding to the major phosphorylation site was found to be an immunodominant IgE-binding epitope. Cross-reactivity among a variety of mammalian milk has been shown in *in vitro* and oral challenge studies (90–92). Interestingly, camel and mare's milk showed a low level of cross-reactivity with milk from cow, sheep, goat and others.

#### Mites – group 1 (cysteine protease)

Group 1 allergens from house dust mites are highly polymorphic cysteine proteases (93) that induce both species-specific and cross-reactive IgE antibodies. This causes a diversity of results for cross-reactivity tests (94). A recent study showed a lack of IgE cross-reactivity between Der p 1 and Blo t 1, very likely because the two allergens share only 35% sequence homology (95).

#### Mites – group 2

Mite group 2 allergens Der p 2, Der f 2 and Eur m 2 share 83–85% sequence identity (93) and are highly cross-reactive. However, Lep d 2 and Tyr p 2 did not react with sera from patients with IgE to *Dermatophagoides* species. The allergenic cross-reactivity between Der p 2, Der f 2, and Eur m 2 seems to be due to a conserved antigenic surface, whereas the lack of cross-reactivity with Lep d 2

and Tyr p 2 correlates with multiple substitutions across this surface (96).

#### Tropomyosin

The muscle protein tropomyosin is an important allergen in many invertebrates including shrimp (Pen a 1), cockroach (Per a 7), and house dust mites (Der p 10 and Der f 10). Because of a high degree of conservation and sequence identity, strong IgE cross-reactivity was reported among tropomyosins from various invertebrate species (94). Using synthetic peptides, Ayuso et al. (97) showed that Pen a 1-specific IgE antibodies recognize homologous amino acid sequences in Der p 10, Der f 10, Per a 7 and Hom a 1 allergens, thus providing the molecular basis of arthropod cross-reactivity. In this context, studies have shown that patients allergic to house dust mite and/or cockroach show IgE reactivity to shrimp Pen a 1 without previous exposure to shrimp (10) or that mite immunotherapy can induce allergic reactions to shrimp and snail (98).

#### Parvalbumin

Parvalbumin is the dominating fish allergen (83). Fish parvalbumin is a very stable calcium-binding protein: exposure to extremes in pH and temperature do not alter its IgE reactivity. Similarly to calcium-binding proteins from pollen, depletion of calcium drastically reduces IgE binding to fish parvalbumins (99). Recombinant carp parvalbumin was used to demonstrate IgE cross-reactivity with cod, tuna and salmon parvalbumins (100).

#### Phospholipase A1 and A2, hyaluronidase

Several major venom allergens from different insects of the Hymenoptera order have been characterized (101). Phospholipases A1 isolated from venom of three species of yellow jackets, white-faced hornets, European hornets and paper wasps showed variable IgE cross-reactivity, suggesting that there are multiple antigenic determinants and that individuals respond to different determinants. No general patterns of cross-reactivity could be observed (102–104). Vespid phospholipase A1 has no sequence similarity and no cross-reactivity with phospholipase A2 from bee venom. Cross-reactivity between hyaluronidases from *Vespula vulgaris* and *Dolichovespula maculata* has been demonstrated (103, 104).

#### Insect venom antigen 5

The antigen 5 (Ag5) proteins from various *Vespula* species share about 95% sequence identity and are highly cross-reactive. *Dolichovespula* and *Polistes* Ag5 allergens show 58–67% sequence homology and display only partial cross-reactivity within the Vespidae family (101). Conserved surface patches of the yellow-jacket Ves v 5

and homologous allergens in various yellow-jackets, hornets and paper wasps were suggested to be involved in their antigenic cross-reactivity (105).

#### Cross-reactive carbohydrate determinants

Carbohydrate side chains of allergenic glycoproteins contribute to IgE cross-reactivity. Therefore, characterization of postsynthetic modifications is highly relevant for the definition of the allergenic structure. The biochemical features and their diagnostic relevance have been recently reviewed by van Ree (106). Using allergenic extracts, IgE antibodies directed toward glycans seem to show the widest pattern of cross-reactivity among those presently known (107, 108). It mainly involves plant- and insect-derived glycoproteins. Fucose and xylose glycan residues are relevant for IgE cross-recognition (109). Among allergenic plants and insects, several native molecules have been reported carrying one or more IgE-binding glycan side-chains (Grass groups 1,4,11,13, Oleaceae group 1, Parietaria group 1, Api g 5, Api m 1, Ara h 1, Art v 1, Cry j 1, Cup a 1, Hev b 2, Lyc e 2, Par h 1, Pla l 1).

The IgE-binding carbohydrates were also described in other nonallergenic plant-derived molecules (e.g. pineapple bromelain, horseradish peroxidase, maize polyamine oxidase, *Cucurbita pepo* ascorbate oxidase, kidney bean phytohaemagglutinin) (108–111). The presence of nonallergenic IgE-reactive glycoproteins in unrelated sources may thus influence and extend the pattern of CCD reactivity when allergenic extracts are tested (108, 112). Moreover, the CCD-IgE co-recognition of similar carbohydrate structures on unrelated sources may lead to *in vitro* false positive results in diagnostic tests (14).

The clinical relevance of CCD is still questioned. Several reports demonstrating poor or absent biological activity of CCD (112, 113) were recently followed by studies showing *in vivo* (HRP) (108) or *in vitro* (Api g 5, HRP, Lyc e 2, Ole e 1) (41, 114, 115) histamine release activity of certain glycoproteins. Such biologic activity seems not to be shared by all CCD-bearing molecules and not present in all CCD-IgE reactive subjects (108). Differences in the glycan number or affinity of IgE antibodies could account for such differences (106).

#### **Bioinformatics applied to allergens: can cross-reactivity be predicted?**

An interesting approach to study relationships of allergenic molecule is to compare protein structures using computer algorithms (116). This approach is becoming increasingly relevant as genetically modified foods must undergo evaluation for their allergenicity (117–120). The sequence comparison approach is commonly used when the biological nature of a new allergenic protein must be identified. Dedicated algorithms (BLAST, FASTA, Clu-

stalW) available within protein and nucleotide sequence platforms (EMBL, SwissProt, Expasy, PIR) allow the comparison of a new given sequence with all the protein sequences submitted to the databases. This search verifies if any protein with a variable degree of identity, similarity or homology has ever been found before in other organisms. In the case the identified sequence belongs to an already known group of allergenic molecules the possible immunological relationship might be suspected (121).

As the number of identified allergenic molecules increase efforts are taken to create dedicated resources for allergenicity search (122). Search tools available within such databases allow the screening of linear amino acid sequences within known allergenic proteins (121, 122). This approach has been recently compared and implemented with the motif-based analysis resulting in a greater chance to identify allergenic proteins (123). A further improvement in the protein evaluation is the comparison considering their 3D-structure (124). This should overcome the difficulties of linear sequence comparisons, which does not disclose conformational epitopes of allergenic molecules.

A current limitation of computer-based approaches to predict allergenicity is the lack of general rules that can be applied to any molecule. The presence of 'unique allergens' (123), i.e. allergenic molecules without similar counterparts, suggest the existence of potential new allergens. This can be expected as the list of allergenic sources and allergenic molecules is still expanding and some of the available allergen sequences are only partial sequences (123).

The structural relationship between plant-derived proteases (papain, bromelain and chymopapain) was used to model the 3D structure of the major mite allergen, Der p 1 (125), although there is no *in vitro* IgE data or clinical evidences corroborating this relationship. The functional and structural similarities among proteins can be restricted to a portion of the molecule (e.g. enzymatic active site) and have no implications for allergic reactions. Similarly, the sequence similarity between some allergenic proteins (e.g. Ole 1 and Phl p 11, CBP from fish and plants) has never found an immunochemical, epidemiological, or clinical support. A future strategy should consider defining criteria to be applied in the identification of new allergenic molecules. This should lead to the most complete nonredundant catalogue of allergenic molecules. At the moment, an integrated approach using molecular- and clinical-based evidences is highly recommended.

#### **Clinical considerations of cross-reactivity in food allergies**

The following comments will focus on practical aspects of symptomatology, diagnosis and therapy of allergic cross-reactivity to foods.

## Pollen-associated food intolerance

Up to 80% of birch-pollen allergic patients suffer from immediate itching in the mouth and throat as well as local edema after eating a variety of fruit, nuts and vegetables, the so-called oral allergy syndrome (OAS). This condition is characterized by the symptoms mentioned because of cross-reactivity between aeroallergens, the initial source of sensitization and ingested allergens. Aeroallergens may be birch- (e.g. tree nuts, pomaceous fruit and stone-fruit), grass- (e.g. legumes, tomatoes), ragweed- (e.g. melon) or mugwort-pollen (e.g. celery, spices), the list of related foods is ever expanding. If one considers the continuous increase of pollen-allergic patients, this represents a growing problem. Most patients suffering from inhalant pollinosis react to two or more cross-allergic foods.

A significant proportion, namely 8.7% of patients with the OAS also reacts with systemic symptoms (126). Definition of allergens has led to clinically significant conclusions: the symptoms related to Bet v 1-related proteins tend to be mild (patients with correlated pollinosis, mainly in the northern parts of Europe), whereas the correlation with lipid-transfer-proteins (observed mainly in the southern parts of Europe) seems to be associated with more severe clinical symptoms.

Many patients tend to continue consumption of fruit or vegetables they react to ignoring mild oral symptoms, but their attention should be drawn to the principal possibility of anaphylactic reactions. This risk of systemic reactions increases with clinical allergy without sensitization to pollen, positive skin tests, systemic symptoms to another related food and history of reactions to cooked foods, the latter usually being tolerated. Regarding skin tests, patients reacting to commercial extracts are more likely to experience severe reactions than patients reacting to fresh food only (127).

A birch pollen specific T-cell response has been hold responsible for worsening atopic eczema in birch pollen-allergic patients after oral challenge with birch pollen-related foods (128).

## Latex-associated food allergy

Between 30 and 80% of patients with latex allergy report symptoms (anaphylaxis, asthma, eczema and OAS) to associated foods. An increasing number of mainly 'exotic' fruit and vegetables (e.g. banana, avocado, kiwi, fig, pineapple, papaya, passion fruit, peach, pear, walnut, hazelnut, almond, grapefruit, melon, strawberry, potato, tomato, spinach, lettuce, celery and many spices) has been associated with latex allergy since the first report in 1989 (129). These foods belong to different botanical families. Evaluation often gets complex because of multiple possible cross-reactions with different pollen and foods. Patients with concomitant pollinosis tended to react with celery and Rosaceae fruit. The sequence of sensitization is still not clear.

## Peanut, soyabean and other legumes

Peanut-allergic patients do not seem to react to other legumes like beans, peas, lupines, lentils, even if *in vitro* and skin tests show sensitization (130, 131). Thus elimination of all legumes in patients who react to only one legume seems to be unwarranted. Only soyabeans have been shown to cross-react and cause severe symptoms, but at this time there are not enough data to recommend soyabean avoidance in soya-tolerant, peanut-allergic patients (132). Cross-sensitization between peanut and tree nuts has been reported in up to 50% of atopic patients without significant clinical relevance.

Peanut is the most common food causing life-threatening reactions mainly in the American region, partly perhaps because of the cooking practice after one study (133): roasting seems to enhance the allergenicity of peanuts. Refined peanut oil does not contain considerable allergens (134) because of the use of very high temperatures, whereas other modes of processing seem to have little influence on allergenicity. A recent study reported loss of reactivity in about 20% of children, a good news relativized by the possibility of recurrence (135). Mothers should avoid peanuts during pregnancy and lactation, and peanut proteins should not be introduced to infants for the first 3 years (136). As peanut allergy is responsible for about 50% of deaths caused by food allergy and of an ever increasing incidence and prevalence not only in North America (137), intensified research has led to new therapeutic and prophylactic measures, namely anti-IgE therapy increasing the threshold of sensitivity (138) and long-term protection through vaccination with recombinant proteins in a mouse model (139).

## Tree nuts

As with peanuts, clinical reactions to tree nuts tend to be severe and potentially fatal. Cross-reactions with peanuts have been described, and tree nuts are important allergens in the birch-pollen-food association. Several studies have demonstrated multiple sensitivity to tree nuts, even if there is a lack of studies with oral food challenges (OFC) because of the frequency of severe anaphylaxis. The latter also justifies recommendations to avoid the whole family of nuts, even if this seems unnecessary in many cases. Contrary to the situation with peanuts, roasting of hazelnuts seems to reduce allergenicity (140).

## Milk and mammalian meat

Cow's milk allergy is a common disease mainly during childhood. Changing to milk of other animal species to avoid allergic reactions is seldom successful as extensive cross-allergies to goat's milk (92% cross-reactivity!) (141) and sheep's milk have been described. Only camel's milk in an *in vitro* - study (91) and mare's milk in a clinical study (92) seem to be useful in this respect. Cross-reactions of

milk-allergic children to beef have been observed in nearly 10% (142), cooking reducing the allergenicity of beef (143). The development of allergy to mare's milk after inhalation allergy to horse dander has been reported (144), as well as respiratory allergy to cow dander and food allergy to cow's milk, the so-called milk-dander syndrome (145). The porc (pork)–chat (cat) syndrome (146) has been described as cross-allergy between cat dander and pork meat, that is cross-reactivity between dander and meat of two different mammalian species.

#### Eggs and avian meat

A number of cross-reacting proteins between different avian eggs have been described (84), but there are still not enough data for clinical complications. A case of clinical reactivity to eggs from duck and goose without sensitization to hen egg proteins has been described (147).

Even if avian meat allergy is relatively rare (148), cross-reactions to different kinds of avian meat occur especially if the patient does not react to eggs (87, 88). We saw a patient who developed OAS and asthma to chicken-, duck-, goose-, turkey hen-, quail-, guinea fowl- and even fish eagle- and/or owl-meat (offered in the jungle of Sarawak) without reacting to eggs (T. Hawranek, unpublished data). Sensitization to  $\alpha$ -livetin found in feathers, avian meat and egg (Gal d 5) seems to be responsible for the so-called bird-egg syndrome (149), a syndrome combining allergy to egg yolk with pre-existing inhalation allergy to bird feathers (150). There also exists a so-called egg-bird syndrome (151), where allergy to birds follows that to eggs.

#### Cereal grains

Cross-reaction to multiple grains (wheat, oat, barley, rye, millet, sorghum, maize and rice) is possible, but uncommon. Although cross-sensitization in skin prick tests (SPT) is a frequent finding, only 21% of 145 children with positive SPT reacted clinically (152). The early introduction of cereals into children's diet was reported to be a risk factor for grass pollen asthma (153). In the diagnostic workup of anaphylactic reactions after consumption of flour one should also consider the possibility of anaphylaxis because of ingestion of mites in mite-contaminated food in mite-sensitized patients (154, 155).

#### Fish

Allergic reactions have to be distinguished from nonallergic (i.e. toxic or histamine-caused) symptoms. Cross-reaction between different fish is very common and may demand avoidance of the whole group, even if allergy to isolated species has been described. As fish represents an important food, oral challenge tests often are unavoidable. Processing such as cooking and canning leads to a reduction of allergenicity (156).

#### Crustaceans and other shellfish

Invertebrate tropomyosin is the panallergen linking crustaceans (crabs, lobster and shrimps) with mollusks (squids, scallops, clams and oysters) as well as parasites (e.g. anisakis) and insects (e.g. house dust mites). Cross-reaction between different crustaceans is common and often severe and may demand avoidance of the whole group, those between crustaceans and mollusks is reported, but not well defined. Oral challenge tests often are desired by the patients. The rate of cross-reactions with mollusks seems to be lower. Both in crustacean- and mollusk-allergic patients, specific immunotherapy (SIT) with house dust mites may represent a risk (see below).

#### House dust mites

There are multiple reports on cross-reactivity between house dust mites and snails, the symptomatology ranging from urticaria to asthma and anaphylaxis. Clinically less well documented are cross-reactive allergens of crustaceans and bivalves (94). As in most other cross-relations between inhalant allergens and food-allergens, the latter seems to be the consequence of the former.

#### Liliaceae

Bronchial asthma, rhinoconjunctivitis, contact dermatitis and anaphylactic reactions have been described for the subfamily of aliolideas (garlic, onion, chives and leek) (157–164), but despite their wide use their occurrence seems to be rare. Cross-reactivity has been demonstrated between aliolideas and asparagoidea (asparagus). Though there are common epitopes, there seems to be a much smaller amount of allergen in onion than in asparagus (165).

#### Moulds and mushrooms

Similar to cross-reactions between respiratory allergy to animal dander and to food derived from the same animals, the coincidence of respiratory allergy to moulds and food-allergy to mushrooms has been reported several times (166–168). In one such patient cross-allergy to spinach was described (169).

#### Diagnosis issues

Diagnostic tests for food allergy pose problems not yet solved, especially with regard to cross-reactive allergens. These tend to elicit positive *in vitro* and *in vivo* tests without clinical relevance, whereas commercially available food extracts often lead to false-negative results, partly because of a lack of standardization as well as enzymatic degrading processes. Prick-to-prick tests with fresh food show a high sensitivity and are used widely,

remaining the reference method of skin tests to diagnose food allergy, but are not standardized at all, bear the risk of systemic reactions and often give false-positive results. Determination of specific IgE by RIA (radio immuno assay) or by FEIA (fluorescence enzyme immuno assay) proves sensitization, but says little about clinical relevance even if the risk of a clinical reaction rises with increasing concentration of specific IgE (170). A negative test result makes clinical relevance unlikely. In infants under the age of 1 year a positive RAST-result suggests clinical relevance because tolerance has hardly developed yet. An essential test for research in cross-allergy is the so-called RAST (enzyme-linked immunosorbent assay)-inhibition test, performed to rule out coincidental cross-reactivity and to prove that there exist common epitopes between two foods for example. Patch tests with food may be a helpful tool mainly in the diagnosis of delayed-type reactions (171).

The definition and use of recombinant allergens promises to lead to an improvement of this situation, i.e. to be able to differentiate between clinically irrelevant and relevant sensitization and by this hopefully allow to predict which food may bear danger when eaten for the first time. The expected benefit of cooking may be predicted as well. After first successes with rApi g 1 from celery (172) a recent study (173) demonstrated that recombinant allergens may ameliorate the clinical meaningfulness of diagnostic tests by associating severe clinical symptoms of Spanish patients allergic to cherry with sensitization to recombinant Pru av 3, whereas Swiss patients with less severe symptoms mainly bound to Pru av 1 and Pru av 4, which are related to birch pollen Bet v 1 and Bet v 2, respectively.

As the clinician is left with positive and/or negative results of *in vitro* – and skin tests of uncertain clinical relevance, OFC, particularly the double-blind placebo-controlled food challenge (DBPCFC), after more than 50 years (174) still represent the current mainstay in the diagnosis of a food reaction to avoid extensive unnecessary diets. Clinical history may only be validated in < 50% by OFC (175). Numerous studies (170, 176–180) have demonstrated that exact evaluation of SPT and specific IgE may reduce the need to perform OFC by approximately 40%, but this is only of little help while clarifying an individual case. A minute clinical history of tolerance has to be executed before challenge tests. Most studies prove that the majority of cross-reactive foods are tolerated, even if positive *in vitro* or skin tests precede. Because of the lability of many cross-reactive proteins, special attention has to be paid to prepare the foods for oral provocation tests. Processing methods like heating (156), fermentation (181), treatment with acidic oxidative potential water (182), freezing or peeling (183) may reduce the allergenicity, but not always for every food (184–186). Because of the possibility of false-negative results because of processing, an open challenge with the ‘natural’ food has to

prove nonreactivity even after a negative blinded challenge test. The decision to perform oral challenge tests has to be discussed with the patient, depending on food preferences, dietary needs or other circumstances. Epidemiological evidence for a possible reaction may help. A table of the approximate risk of clinical reactivity to related foods has been drawn up recently (4). Many patients are content to abstain from foods they have reacted to in the past or foods that got suspicious because of positive *in vitro* or skin tests or known cross-reactivity.

### Therapeutic options

Avoidance of foods which have been proven to cause clinical symptoms is the logic most important step to escape new anaphylactic reactions. Patients have to check all food labels and to avoid high-risk situations, mainly eating out. Because of ‘hidden allergens’, i.e. the contamination of a safe food by utensils or equipment, misleading labels and ingredient switching (187) this often proves to be an impossible task.

As disodium cromoglycate has to be taken before exposition of the allergenic food, it always comes too late. If consumption has taken place, an interesting starting-point is the prevention of ongoing resorption of food allergens (e.g. peanuts) from the gastrointestinal tract by administering activated charcoal which forms insoluble complexes with peanut proteins no longer able to bind IgE (188). The same mechanism may work for other foods, too.

For birch pollen-associated food allergy SIT with the according pollen has shown to be successful in most studies and case reports (189–193) with symptom reduction rates of up to 84%. The positive effect in a subset of patients both negative clinically and in SPT by the end of SIT was still demonstrable after 30 months in 78% (194). Relapses of the OAS was preceded or associated with a relapse of skin reactivity in all cases. No effect by subcutaneous and oral SIT was observed in an early study (195). One paper reported success with mugwort/ragweed SIT in a patient with associated OAS to fennel, cucumber and melon (196). The SIT with house dust mite has been associated with the induction (98, 197, 198) or deterioration (199) of snail allergy – suggesting to avoid SIT to house dust mites in patients with snail allergy – as well as protection against possible sensitization to snails (200).

The idea of using sublingual/swallow immunotherapy (SLIT) at the location of the OAS seems to be promising, but no data are available until now to the best of our knowledge. The procedure seems to be safe (201).

Sublingual desensitization with the respective native food the patient is allergic to (202–206) represents an interesting alternative starting-point for the treatment of food-allergic patients and has met partial success, even if

the long-term effect of this treatment has yet to be assessed and some studies are poorly controlled. A well-controlled trial with subcutaneous desensitization in peanut-allergic patients (207) showed limited response rates and a high rate of adverse reactions.

One may speculate about future therapies (208) using SIT with panallergens, mutated allergen protein immunotherapy, antigen-immunostimulatory sequence-modulated immunotherapy, peptide immunotherapy, plasmid-DNA immunotherapy, cytokine-modulated immunotherapy and anti-IgE monoclonal antibody therapy. Recently, successful prophylaxis of peanut allergy with a monoclonal anti-IgE-antibody (TNX-901) has been described (138).

For patients with anaphylactic symptoms after food intake, an emergency kit comprising epinephrine, an antihistamine and a corticosteroid should be prescribed. Whether all patients should be provided with injectable epinephrine is widely discussed (209–213), mainly among paediatricians, even if it is regarded as the only medication that is active against collapse. Kemp (214) proposes to take into account several risk factors: age over 5 years, history of respiratory tract involvement in previous reactions, history of asthma requiring preventer medication, peanut or tree nut sensitivity, reactions induced by small amounts of the allergen (215, 216), and perhaps a strongly positive SPT. This issue has yet to be answered, and each case has to be handled individually. As asthma is the main cause of death because of food anaphylaxis and epinephrine is not always sufficient in severe asthma (217), the addition of a rapid-action  $\beta$ -agonist spray to the emergency kit has been suggested (218). Often, the application of epinephrine spray is recommended in case of laryngeal oedema. The use of this emergency kit should be trained with patients, parents of food allergic children, as well as teaching and caring staff of children, as the kits are used appropriately in only 29% of subsequent anaphylactic reactions (219), a number confirmed by most other reports.

## References

1. AALBERSE RC. Structural biology of allergens. *J Allergy Clin Immunol* 2000;**106**:228–238.
2. AALBERSE RC, AKKERDAAS J, van REE R. Cross-reactivity of IgE antibodies to allergens. *Allergy* 2001;**56**:478–490.
3. WEBER RW. Patterns of pollen cross-allergenicity. *J Allergy Clin Immunol* 2003;**112**:229–239.
4. SICHERER SH. Clinical implications of cross-reactive food allergens. *J Allergy Clin Immunol* 2001;**108**:881–890.
5. VALENTA R, DUCHENE M, PETTENBURGER K, SILLABER C, VALENT P, BETTELHEIM P et al. Identification of profilin as a novel pollen allergen; IgE autoreactivity in sensitized individuals. *Science* 1991;**253**:557–560.
6. CRAMERI R, FAITH A, HEMMANN S, JAUSSE R, ISMAIL C, MENZ G et al. Humoral and cell-mediated autoimmunity in allergy to *Aspergillus fumigatus*. *J Exp Med* 1996;**184**:265–270.
7. FERREIRA F, HIRTENLEHNER K, JILEK A, GODNIK-CVAR J, BREITENEDER H, GRIMM R et al. Dissection of immunoglobulin E and T lymphocyte reactivity of isoforms of the major birch pollen allergen Bet v 1: potential use of hypoallergenic isoforms for immunotherapy. *J Exp Med* 1996;**183**:599–609.
8. MARI A. Multiple pollen sensitization: a molecular approach to the diagnosis. *Int Arch Allergy Immunol* 2001;**125**:57–65.
9. FERREIRA F, WALLNER M, BREITENEDER H, HARTL A, THALHAMER J, EBNER C. Genetic engineering of allergens: future therapeutic products. *Int Arch Allergy Immunol* 2002;**128**:171–178.
10. FERNANDES J, RESHEF A, PATTON L, AYUSO R, REESE G, LEHRER SB. Immunoglobulin E antibody reactivity to the major shrimp allergen, tropomyosin, in unexposed Orthodox Jews. *Clin Exp Allergy* 2003;**33**:956–961.

## Conclusions and future perspectives

The impact of the huge number of studies on allergenic molecules and extracts and their relationships is highly relevant for the clinical allergologist. Of particular interest are those studies showing how the clustering of the allergenic source reactivity can be explained by structural relationships between allergens (8, 38). Before the knowledge about the molecular composition of allergenic extracts and their relationships became available, the general assumption was that patients might show reactivity from one to hundreds of allergenic sources. This view has quickly changed with the discovery of family-restricted homologous molecules [e.g. group 1 grasses (43)] or broad-reactive allergens (e.g. panallergens as plant profilins (36), plant calcium-binding proteins (8, 38), and arthropod/crustacean tropomyosin (97)). The analysis of reactivity clusters in diagnosis allows the interpretation of patient's reactivity as the main outcome of the sensitizing process, which often begins with exposure to a single source. A number of different clustering options can be defined within these two extremes. For instance, group 1 Fagales allergen sensitization might include reactivity to pollens belonging to different families as well as plant-derived food taxonomically distant from the Fagales order (36). By the extensive use of the molecule-based approach it is possible to reach the finest resolution of the reactivity spectrum. As for the bioinformatics approach to allergenicity of a molecule, a novel framework should be developed for a joined work of molecular biologists and clinical allergologists.

## Acknowledgments

This study was supported by the Joint Research Project S88-B01 (S8802-B01, S8816-B01) of the 'Fonds zur Förderung der Wissenschaftlichen Forschung, FWF', Austria.

11. de GROOT H, van SWIETEN P, AALBERSE RC. Evidence for a Fel d I-like molecule in the "big cats" (Felidae species). *J Allergy Clin Immunol* 1990;**86**: 107–116.
12. MARI A, WALLNER M, FERREIRA F. Fagales pollen sensitization in a birch-free area: a respiratory cohort survey using Fagales pollen extracts and birch recombinant allergens (rBet v 1, rBet v 2, rBet v 4). *Clin Exp Allergy* 2003;**33**:1419–1428.
13. LODRUP CARLSEN KC, CARLSEN KH, BUCHMANN MS, WIKSTROM J, MEHL R. Cockroach sensitivity in Norway: a previously unidentified problem? *Allergy* 2002;**57**:529–533.
14. MARI A. Skin test with a timothy grass (*Phleum pratense*) pollen extract vs IgE to a timothy extract vs IgE to rPhl p 1, rPhl p 2, nPhl p 4, rPhl p 5, rPhl p 6, rPhl p 7, rPhl p 11, and rPhl p 12: epidemiological and diagnostic data. *Clin Exp Allergy* 2003;**33**:43–51.
15. HANNINEN AR, MIKKOLA JH, KALKKINEN N, TURJANMAA K, YLITALO L, REUNALA T et al. Increased allergen production in turnip (*Brassica rapa*) by treatments activating defense mechanisms. *J Allergy Clin Immunol* 1999;**104**:194–201.
16. MIDORO-HORIUTI T, BROOKS EG, GOLDBLUM RM. Pathogenesis-related proteins of plants as allergens. *Ann Allergy Asthma Immunol* 2001;**87**: 261–271.
17. BREITENEDER H, EBNER C. Molecular and biochemical classification of plant-derived food allergens. *J Allergy Clin Immunol* 2000;**106**:27–36.
18. YAGAMI T. Allergies to cross-reactive plant proteins. Latex-fruit syndrome is comparable with pollen-food allergy syndrome. *Int Arch Allergy Immunol* 2002;**128**:271–279.
19. HOFFMANN-SOMMERGRUBER K. Pathogenesis-related (PR)-proteins identified as allergens. *Biochem Soc Trans* 2002;**30**:930–935.
20. GOUGH L, SCHULZ O, SEWELL HF, SHAKIB F. The cysteine protease activity of the major dust mite allergen Der p 1 selectively enhances the immunoglobulin E antibody response. *J Exp Med* 1999;**190**:1897–1902.
21. WAN H, WINTON HL, SOELLER C, TOVEY ER, GRUENERT DC, THOMPSON PJ et al. Der p 1 facilitates transepithelial allergen delivery by disruption of tight junctions. *J Clin Invest* 1999;**104**:123–133.
22. BREDEHORST R, DAVID K. What establishes a protein as an allergen? *J Chromatogr B Biomed Sci Appl* 2001;**756**:33–40.
23. MARKOVIC-HOUSLEY Z, DEGANO M, LAMBA D, ROEPENACK-LAHAYE E, CLEMENS S, SUSANI M et al. Crystal structure of a hypoallergenic isoform of the major birch pollen allergen Bet v 1 and its likely biological function as a plant steroid carrier. *J Mol Biol* 2003;**325**:123–133.
24. MOGENSEN JE, WIMMER R, LARSEN JN, SPANGFORT MD, OTZEN DE. The major birch allergen, Bet v 1, shows affinity for a broad spectrum of physiological ligands. *J Biol Chem* 2002;**277**: 23 684–23 692.
25. NEUDECKER P, SCHWEIMER K, NERKAMP J, SCHEURER S, VIETHS S, STICHT H et al. Allergic cross-reactivity made visible: the solution structure of the major cherry allergen Pru av 1. *J Biol Chem* 2001;**276**:22 756–22 763.
26. FERREIRA F, EBNER C, KRAMER B, CASARI G, BRIZA P, KUNGL AJ et al. Modulation of IgE reactivity of allergens by site-directed mutagenesis: potential use of hypoallergenic variants for immunotherapy. *FASEB J* 1998;**12**: 231–242.
27. FERREIRA F, HEBENSTREIT D, KRAMER B, HIMLY M, BREITENEDER H, SCHEINER O et al. Amino acid positions involved in the formation of IgE-binding epitopes of Api g 1 and Mal d 1 allergens. *J Allergy Clin Immunol* 2000;**105**:S137.
28. SON DY, SCHEURER S, HOFFMANN A, HAUSTEIN D, VIETHS S. Pollen-related food allergy: cloning and immunological analysis of isoforms and mutants of Mal d 1, the major apple allergen, and Bet v 1, the major birch pollen allergen. *Eur J Nutr* 1999;**38**:201–215.
29. SCHEURER S, SON DY, BOEHM M, KARAMLOO F, FRANKE S, HOFFMANN A et al. Cross-reactivity and epitope analysis of Pru a 1, the major cherry allergen. *Mol Immunol* 1999;**36**:155–167.
30. MIRZA O, HENRIKSEN A, IPSEN H, LARSEN JN, WISSENBACH M, SPANGFORT MD et al. Dominant epitopes and allergic cross-reactivity: complex formation between a Fab fragment of a monoclonal murine IgG antibody and the major allergen from birch pollen Bet v 1. *J Immunol* 2000;**165**:331–338.
31. VIETHS S, SCHEURER S, BALLMER-WEBER B. Current understanding of cross-reactivity of food allergens and pollen. *Ann NY Acad Sci* 2002;**964**: 47–68.
32. KAZEMI-SHIRAZI L, NIEDERBERGER V, LINHART B, LIDHOLM J, KRAFT D, VALENTA R. Recombinant marker allergens: diagnostic gatekeepers for the treatment of allergy. *Int Arch Allergy Immunol* 2002;**127**:259–268.
33. RIHS HP, CHEN Z, RUEFF F, PETERSEN A, ROZYNEK P, HEIMANN H et al. IgE binding of the recombinant allergen soybean profilin (rGly m 3) is mediated by conformational epitopes. *J Allergy Clin Immunol* 1999;**104**:1293–1301.
34. FEDOROV AA, BALL T, MAHONEY NM, VALENTA R, ALMO SC. The molecular basis for allergen cross-reactivity: crystal structure and IgE-epitope mapping of birch pollen profilin. *Structure* 1997;**5**:33–45.
35. SCHEURER S, WANGORSCH A, HAUSTEIN D, VIETHS S. Cloning of the minor allergen Api g 4 profilin from celery (*Apium graveolens*) and its cross-reactivity with birch pollen profilin Bet v 2. *Clin Exp Allergy* 2000;**30**:962–971.
36. WENSING M, AKKERDAAS JH, van LEEUWEN WA, STAPEL SO, BRUINZEEL-KOOMEN CA, AALBERSE RC et al. IgE to Bet v 1 and profilin: cross-reactivity patterns and clinical relevance. *J Allergy Clin Immunol* 2002;**110**:435–442.
37. MELLON MB, FRANK BT, FANG KC. Mast cell alpha-chymase reduces IgE recognition of birch pollen profilin by cleaving antibody-binding epitopes. *J Immunol* 2002;**168**:290–297.
38. TINGHINO R, TWARDOSZ A, BARLETTA B, PUGGIONI EM, IACOVACCI P, BUTTERONI C et al. Molecular, structural, and immunologic relationships between different families of recombinant calcium-binding pollen allergens. *J Allergy Clin Immunol* 2002;**109**: 314–320.
39. LOMBARDO M, OBISPO T, CALABOZO B, LEZAUN A, POLO F, BARBER D. Cross-reactivity between olive and other species. Role of Ole e 1-related proteins. *Allergy* 2002;**57**:29–34.
40. GONZALEZ E, VILLALBA M, LOMBARDO M, AALBERS M, van REE R, RODRIGUEZ R. Influence of the 3D-conformation, glycan component and microheterogeneity on the epitope structure of Ole e 1, the major olive allergen. Use of recombinant isoforms and specific monoclonal antibodies as immunological tools. *Mol Immunol* 2002;**39**:93–101.
41. BATANERO E, CRESPO JF, MONSALVE RI, MARTIN-ESTEBAN M, VILLALBA M, RODRIGUEZ R. IgE-binding and histamine-release capabilities of the main carbohydrate component isolated from the major allergen of olive tree pollen, Ole e 1. *J Allergy Clin Immunol* 1999;**103**:147–153.

42. KREBITZ M, WAGNER B, FERREIRA F, PETERBAUER C, CAMPILLO N, WITTY M et al. Plant-based heterologous expression of Mal d 2, a thaumatin-like protein and allergen of apple (*Malus domestica*), and its characterization as an antifungal protein. *J Mol Biol* 2003;**329**:721–730.
43. ANDERSSON K, LIDHOLM J. Characteristics and immunobiology of grass pollen allergens. *Int Arch Allergy Immunol* 2003;**130**:87–107.
44. NIEDERBERGER V, LAFFER S, FROSCHL R, KRAFT D, RUMPOLD H, KAPIOTIS S et al. IgE antibodies to recombinant pollen allergens (Phl p 1, Phl p 2, Phl p 5, and Bet v 2) account for a high percentage of grass pollen-specific IgE. *J Allergy Clin Immunol* 1998;**101**:258–264.
45. van REE R, van LEEUWEN WA, AALBERSE RC. How far can we simplify in vitro diagnostics for grass pollen allergy?: a study with 17 whole pollen extracts and purified natural and recombinant major allergens. *J Allergy Clin Immunol* 1998;**102**:184–190.
46. BALL T, FUCHS T, KRAFT D, VALENTA R. Lessons from the antibody recognition of the major timothy grass pollen allergen Phl p 1. *Int Arch Allergy Immunol* 1999;**118**:208–209.
47. FLICKER S, VRTALA S, STEINBERGER P, VANGELISTA L, BUFE A, PETERSEN A et al. A human monoclonal IgE antibody defines a highly allergenic fragment of the major timothy grass pollen allergen, Phl p 5: molecular, immunological, and structural characterization of the epitope-containing domain. *J Immunol* 2000;**165**:3849–3859.
48. MAGLIO O, SALDANHA JW, VRTALA S, SPITZAUER S, VALENTA R, PASTORE A. A major IgE epitope-containing grass pollen allergen domain from Phl p 5 folds as a four-helix bundle. *Protein Eng* 2002;**15**:635–642.
49. SUPHIOGLU C, BLAHER B, ROLLAND JM, MCCCLUSKEY J, SCHAPPI G, KENRICK J et al. Molecular basis of IgE-recognition of Lol p 5, a major allergen of rye-grass pollen. *Mol Immunol* 1998;**35**:293–305.
50. SWOBODA I, de WEERD N, BHALLA PL, NIEDERBERGER V, SPERR WR, VALENT P et al. Mutants of the major ryegrass pollen allergen, Lol p 5, with reduced IgE-binding capacity: candidates for grass pollen-specific immunotherapy. *Eur J Immunol* 2002;**32**:270–280.
51. SCHRAMM G, KAHLERT H, SUCK R, WEBER B, STUWE HT, MULLER WD et al. “Allergen engineering”: variants of the timothy grass pollen allergen Phl p 5b with reduced IgE-binding capacity but conserved T cell reactivity. *J Immunol* 1999;**162**:2406–2414.
52. RAFNAR T, GRIFFITH IJ, KUO MC, BOND JF, ROGERS BL, KLAPPER DG. Cloning of Amb a I (antigen E), the major allergen family of short ragweed pollen. *J Biol Chem* 1991;**266**:1229–1236.
53. TANIGUCHI Y, ONO A, SAWATANI M, NANBA M, KOHNO K, USUI M et al. Cry j I, a major allergen of Japanese cedar pollen, has pectate lyase enzyme activity. *Allergy* 1995;**50**:90–93.
54. HIMLY M, JAHN-SCHMID B, DEDIC A, KELEMEN P, WOPFNER N, ALTMANN F et al. Art v 1, the major allergen of mugwort pollen, is a modular glycoprotein with a defensin-like and a hydroxyproline-rich domain. *FASEB J* 2002;**17**:106–108.
55. GUPTA N, MARTIN BM, METCALFE DD, RAO PV. Identification of a novel hydroxyproline-rich glycoprotein as the major allergen in *Parthenium* pollen. *J Allergy Clin Immunol* 1996;**98**:903–912.
56. DOMON C, EVRARD JL, HERDENBERGER F, PILLAY DT, STEINMETZ A. Nucleotide sequence of two anther-specific cDNAs from sunflower (*Helianthus annuus* L.). *Plant Mol Biol* 1990;**15**:643–646.
57. BALDO BA, BAKER RS. Inhalant allergies to fungi: reactions to bakers’ yeast (*Saccharomyces cerevisiae*) and identification of bakers’ yeast enolase as an important allergen. *Int Arch Allergy Appl Immunol* 1988;**86**:201–208.
58. ACHATZ G, OBERKOFER H, LECHENAUER E, SIMON B, UNGER A, KANDLER D et al. Molecular cloning of major and minor allergens of *Alternaria alternata* and *Cladosporium herbarum*. *Mol Immunol* 1995;**32**:213–227.
59. SIMON-NOBBE B, PROBST G, KAJAVA AV, OBERKOFER H, SUSANI M, CRAMERI R et al. IgE-binding epitopes of enolases, a class of highly conserved fungal allergens. *J Allergy Clin Immunol* 2000;**106**:887–895.
60. LAI HY, TAM MF, TANG RB, CHOU H, CHANG CY, TSAI JJ et al. cDNA cloning and immunological characterization of a newly identified enolase allergen from *Penicillium citrinum* and *Aspergillus fumigatus*. *Int Arch Allergy Immunol* 2002;**127**:181–190.
61. CHANG CY, CHOU H, TAM MF, TANG RB, LAI HY, SHEN HD. Characterization of enolase allergen from *Rhodotorula mucilaginosa*. *J Biomed Sci* 2002;**9**:645–655.
62. VERMA J, SINGH BP, SRIDHARA S, GAUR SN, ARORA N. Purification and characterization of a cross-reactive 45-kD major allergen of *Fusarium solani*. *Int Arch Allergy Immunol* 2003;**130**:193–199.
63. WAGNER S, BREITENEDER H, SIMON-NOBBE B, SUSANI M, KREBITZ M, NIGGEMANN B et al. Hev b 9, an enolase and a new cross-reactive allergen from *Hevea latex* and molds purification, characterization, cloning and expression. *Eur J Biochem* 2000;**267**:7006–7014.
64. MARI A, SCHNEIDER P, WALLY V, BREITENBACH M, SIMON-NOBBE B. Sensitisation to fungi: epidemiology, comparative skin tests and IgE reactivity of fungal extracts. *Clin Exp Allergy* 2003;**33**:1429–1438.
65. FLUCKIGER S, SCAPOZZA L, MAYER C, BLASER K, FOLKERS G, CRAMERI R. Immunological and structural analysis of IgE-mediated cross-reactivity between manganese superoxide dismutases. *Int Arch Allergy Immunol* 2002;**128**:292–303.
66. WAGNER S, SOWKA S, MAYER C, CRAMERI R, FOCKE M, KURUP VP et al. Identification of a *Hevea brasiliensis* latex manganese superoxide dismutase (Hev b 10) as a cross-reactive allergen. *Int Arch Allergy Immunol* 2001;**125**:120–127.
67. CHYE ML, CHEUNG KY.  $\beta$ -1,3-Glucanase is highly-expressed in laticifers of *Hevea brasiliensis*. *Plant Mol Biol* 1995;**29**:397–402.
68. SUNDERASAN E, HAMZAH S, HAMID S, WARD MA, YEANG HY, CARDOSA MJ et al. Latex B-serum  $\beta$ -1,3-glucanase (Hev b II) and a component of the microhelix (Hev b IV) are major latex allergens. *J Nat Rubber Res* 1995;**10**:82–99.
69. WAGNER S, BREITENEDER H. The latex-fruit syndrome. *Biochem Soc Trans* 2002;**30**:935–940.
70. SUSSMAN GL, BEEZHOLD DH, KURUP VP. Allergens and natural rubber proteins. *J Allergy Clin Immunol* 2002;**110**:S033-S039.
71. YAGAMI T, SATO M, NAKAMURA A, KOMIYAMA T, KITAGAWA K, AKASAWA A et al. Plant defense-related enzymes as latex antigens. *J Allergy Clin Immunol* 1998;**101**:379–385.

72. SOWKA S, HSIEH LS, KREBITZ M, AKASAWA A, MARTIN BM, STARRETT D et al. Identification and cloning of Prs a 1, a 32-kDa endochitinase and major allergen of avocado, and its expression in the yeast *Pichia pastoris*. *J Biol Chem* 1998;**273**:28 091–28 097.
73. KARISOLA P, ALENIUS H, MIKKOLA J, KALKKINEN N, HELIN J, PENTIKAINEN OT et al. The major conformational IgE-binding epitopes of hevein (Hev b 6.02) are identified by a novel chimera-based allergen epitope mapping strategy. *J Biol Chem* 2002;**277**: 22 656–22 661.
74. van REE R. Clinical importance of non-specific lipid transfer proteins as food allergens. *Biochem Soc Trans* 2002;**30**:910–913.
75. COLOMBO P, KENNEDY D, RAMSDALE T, COSTA MA, DURO G, IZZO V et al. Identification of an immunodominant IgE epitope of the *Parietaria judaica* major allergen. *J Immunol* 1998;**160**:2780–2785.
76. GALL H, KALVERAM KJ, FORCK G, STERRY W. Kiwi fruit allergy: a new birch pollen-associated food allergy. *J Allergy Clin Immunol* 1994;**94**:70–76.
77. DIEZ-GOMEZ ML, QUIRCE S, ARAGON-ESSES E, CUEVAS M. Asthma caused by *Ficus benjamina* latex: evidence of cross-reactivity with fig fruit and papain. *Ann Allergy Asthma Immunol* 1998;**80**: 24–30.
78. PASTORELLO EA, CONTI A, PRAVETTONI V, FARIOLI L, RIVOLTA F, ANSALONI R et al. Identification of actinidin as the major allergen of kiwi fruit. *J Allergy Clin Immunol* 1998;**101**:531–537.
79. CAMBRA O, BERRENS L. Monoclonal antibodies against *Dermatophagoides* group I allergens as pseudo-cystatins blocking the catalytic site of cysteine proteinases. *Immunol Lett* 1996;**50**: 173–177.
80. ROBOTHAM JM, TEUBER SS, SATHE SK, ROUX KH. Linear IgE epitope mapping of the English walnut (*Juglans regia*) major food allergen, Jug r 1. *J Allergy Clin Immunol* 2002;**109**:143–149.
81. BURKS AW, SHIN D, COCKRELL G, STANLEY JS, HELM RM, BANNON 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**:334–339.
82. BEARDSLEE TA, ZEEBE MG, SARATH G, MARKWELL JP. Soybean glycinin G1 acidic chain shares IgE epitopes with peanut allergen Ara h 3. *Int Arch Allergy Immunol* 2000;**123**:299–307.
83. POULSEN LK, HANSEN TK, NORGAARD A, VESTERGAARD H, STAHL SP, BINDSLEV-JENSEN C. Allergens from fish and egg. *Allergy* 2001;**56**:39–42.
84. LANGELAND T. A clinical and immunological study of allergy to hen's egg white. VI. Occurrence of proteins cross-reacting with allergens in hen's egg white as studied in egg white from turkey, duck, goose, seagull, and in hen egg yolk, and hen and chicken sera and flesh. *Allergy* 1983;**38**:399–412.
85. SZEPPALUSI Z, EBNER C, PANDJAITAN R, ORLICEK F, SCHEINER O, BOLTZ-NITULESCU G et al. Egg yolk alpha-livetin (chicken serum albumin) is a cross-reactive allergen in the bird-egg syndrome. *J Allergy Clin Immunol* 1994;**93**:932–942.
86. BAUSELA BA, GARCIA-ARA MC, MARTIN EM, BOYANO MARTINEZ TB, DIAZ PENA JM, OJEDA CASAS JA. Peculiarities of egg allergy in children with bird protein sensitization. *Ann Allergy Asthma Immunol* 1997;**78**: 213–216.
87. KELSO JM, COCKRELL GE, HELM RM, BURKS AW. Common allergens in avian meats. *J Allergy Clin Immunol* 1999;**104**:202–204.
88. CAHEN YD, FRITSCH R, WUTHRICH B. Food allergy with monovalent sensitivity to poultry meat. *Clin Exp Allergy* 1998;**28**:1026–1030.
89. WAL JM. Cow's milk proteins/allergens. *Ann Allergy Asthma Immunol* 2002;**89**:3–10.
90. SPUERGIN P, WALTER M, SCHILTZ E, DEICHMANN K, FORSTER J, MUELLER H. Allergenicity of  $\alpha$ -caseins from cow, sheep, and goat. *Allergy* 1997;**52**:293–298.
91. RESTANI P, GAIASCHI A, PLEBANI A, BERETTA B, CAVAGNI G, FIOCCHI A et al. Cross-reactivity between milk proteins from different animal species. *Clin Exp Allergy* 1999;**29**:997–1004.
92. BUSINCO L, GIAMPIETRO PG, LUCENTI P, LUCARONI F, PINI C, DI FELICE G et al. Allergenicity of mare's milk in children with cow's milk allergy. *J Allergy Clin Immunol* 2000;**105**:1031–1034.
93. THOMAS WR, SMITH WA, HALES BJ, MILLS KL, O'BRIEN RM. Characterization and immunobiology of house dust mite allergens. *Int Arch Allergy Immunol* 2002;**129**:1–18.
94. SIDENIUS KE, HALLAS TE, POULSEN LK, MOSBECH H. Allergen cross-reactivity between house-dust mites and other invertebrates. *Allergy* 2001;**56**:723–733.
95. CHEONG N, YANG L, LEE BW, CHUA KY. Cloning of a group 3 allergen from *Blomia tropicalis* mites. *Allergy* 2003;**58**:352–356.
96. SMITH WA, HALES BJ, JARNICKI AG, THOMAS WR. Allergens of wild house dust mites: environmental Der p 1 and Der p 2 sequence polymorphisms. *J Allergy Clin Immunol* 2001;**107**: 985–992.
97. AYUSO R, REESE G, LEONG-KEE S, PLANTE M, LEHRER SB. Molecular basis of arthropod cross-reactivity: IgE-binding cross-reactive epitopes of shrimp, house dust mite and cockroach tropomyosins. *Int Arch Allergy Immunol* 2002;**129**:38–48.
98. van REE R, ANTONICELLI L, AKKERDAAS JH, GARRITANI MS, AALBERSE RC, BONIFAZI F. Possible induction of food allergy during mite immunotherapy. *Allergy* 1996;**51**:108–113.
99. BUGAJSKA-SCHRETTER A, ELFMAN L, FUCHS T, KAPIOTIS S, RUMPOLD H, VALENTA R et al. Parvalbumin, a cross-reactive fish allergen, contains IgE-binding epitopes sensitive to periodate treatment and Ca<sup>2+</sup> depletion. *J Allergy Clin Immunol* 1998;**101**:67–74.
100. SWOBODA I, BUGAJSKA-SCHRETTER A, VERDINO P, KELLER W, SPERR WR, VALENT P et al. Recombinant carp parvalbumin, the major cross-reactive fish allergen: a tool for diagnosis and therapy of fish allergy. *J Immunol* 2002;**168**:4576–4584.
101. MULLER UR. Recombinant *Hymenoptera venom* allergens. *Allergy* 2002;**57**:570–576.
102. HOFFMAN DR. Allergens in *Hymenoptera venom*. XVI: Studies of the structures and cross-reactivities of vespid venom phospholipases. *J Allergy Clin Immunol* 1986;**78**:337–343.
103. LU G, KOCHOUMIAN L, KING TP. Sequence identity and antigenic cross-reactivity of white face hornet venom allergen, also a hyaluronidase, with other proteins. *J Biol Chem* 1995;**270**:4457–4465.
104. KING TP, LU G, GONZALEZ M, QIAN N, SOLDATOVA L. Yellow jacket venom allergens, hyaluronidase and phospholipase: sequence similarity and antigenic cross-reactivity with their hornet and wasp homologs and possible implications for clinical allergy. *J Allergy Clin Immunol* 1996;**98**:588–600.
105. HENRIKSEN A, KING TP, MIRZA O, MONSALVE RI, MENO K, IPSEN H et al. Major venom allergen of yellow jackets, Ves v 5: Structural characterization of a pathogenesis-related protein superfamily. *Proteins* 2001;**45**:438–448.
106. van REE R. Carbohydrate epitopes and their relevance for the diagnosis and treatment of allergic diseases. *Int Arch Allergy Immunol* 2002;**129**:189–197.

107. WILSON IB, HARTHILL JE, MULLIN NP, ASHFORD DA, ALTMANN F. Core  $\alpha$ 1,3-fucose is a key part of the epitope recognized by antibodies reacting against plant N-linked oligosaccharides and is present in a wide variety of plant extracts. *Glycobiology* 1998;**8**:651–661.
108. MARI A. IgE to cross-reactive carbohydrate determinants: analysis of the distribution and appraisal of the in vivo and in vitro reactivity. *Int Arch Allergy Immunol* 2002;**129**:286–295.
109. van REE R, CABANES-MACHETEAU M, AKKERDAAS J, MILAZZO JP, LOUVELIER-BOURHIS C, RAYON C et al.  $\beta$ (1,2)-xylose and  $\alpha$ (1,3)-fucose residues have a strong contribution in IgE binding to plant glycoallergens. *J Biol Chem* 2000;**275**:11 451–11 458.
110. BATANERO E, VILLALBA M, MONSALVE RI, RODRIGUEZ R. Cross-reactivity between the major allergen from olive pollen and unrelated glycoproteins: evidence of an epitope in the glycan moiety of the allergen. *J Allergy Clin Immunol* 1996;**97**:1264–1271.
111. IACOVACCI P, PINI C, AFFERNI C, BARLETTA B, TINGHINO R, SCHININA E et al. A monoclonal antibody specific for a carbohydrate epitope recognizes an IgE-binding determinant shared by taxonomically unrelated allergenic pollens. *Clin Exp Allergy* 2001;**31**:458–465.
112. MARI A, IACOVACCI P, AFFERNI C, BARLETTA B, TINGHINO R, DI FELICE G et al. Specific IgE to cross-reactive carbohydrate determinants strongly affect the in vitro diagnosis of allergic diseases. *J Allergy Clin Immunol* 1999;**103**:1005–1011.
113. VAN DER VEEN MJ, van REE R, AALBERSE RC, AKKERDAAS J, KOPPELMAN SJ, JANSEN HM et al. Poor biologic activity of cross-reactive IgE directed to carbohydrate determinants of glycoproteins. *J Allergy Clin Immunol* 1997;**100**:327–334.
114. BUBLIN M, RADAUER C, WILSON IBH, KRAFT D, SCHEINER O, BREITENEDER H et al. Cross-reactive N-glycans of Api g 5, a high molecular weight glycoprotein allergen from celery, are required for immunoglobulin E binding and activation of effector cells from allergic patients. *FASEB J* 2003.
115. FOETISCH K, WESTPHAL S, LAUER I, RETZEK M, ALTMANN F, KOLARICH D et al. Biological activity of IgE specific for cross-reactive carbohydrate determinants. *J Allergy Clin Immunol* 2003;**111**:889–896.
116. BRUSIC V, PETROVSKY N. Bioinformatics for characterisation of allergens, allergenicity and allergic crossreactivity. *Trends Immunol* 2003;**24**:225–228.
117. GENDEL SM. Sequence databases for assessing the potential allergenicity of proteins used in transgenic foods. *Adv Food Nutr Res* 1998;**42**:63–92.
118. KLETER GA, PEIJNENBURG AA. Screening of transgenic proteins expressed in genetically modified food crops for the presence of short amino acid sequences identical to potential, IgE-binding linear epitopes of allergens. *BMC Struct Biol* 2002;**2**:8.
119. GENDEL SM. Sequence analysis for assessing potential allergenicity. *Ann NY Acad Sci* 2002;**964**:87–98.
120. ZORZET A, GUSTAFSSON M, HAMMERLING U. Prediction of food protein allergenicity: a bioinformatic learning systems approach. *In Silico Biol* 2002;**2**.
121. HILEMAN RE, SILVANOVICH A, GOODMAN RE, RICE EA, HOLLESCHAK G, ASTWOOD JD et al. Bioinformatic methods for allergenicity assessment using a comprehensive allergen database. *Int Arch Allergy Immunol* 2002;**128**:280–291.
122. IVANCIUC O, SCHEIN CH, BRAUN W. SDAP: database and computational tools for allergenic proteins. *Nucleic Acids Res* 2003;**31**:359–362.
123. STADLER MB, STADLER BM. Allergenicity prediction by protein sequence. *FASEB J* 2003;**17**:1141–1143.
124. IVANCIUC O, SCHEIN CH, BRAUN W. Data mining of sequences and 3D structures of allergenic proteins. *Bioinformatics* 2002;**18**:1358–1364.
125. FURMONAVICIENE R, SHAKIB F. The molecular basis of allergenicity: comparative analysis of the three dimensional structures of diverse allergens reveals a common structural motif. *Mol Pathol* 2001;**54**:155–159.
126. ORTOLANI C, PASTORELLO EA, FARIOLI L, ISPANO M, PRAVETTONI V, BERTI C et al. IgE-mediated allergy from vegetable allergens. *Ann Allergy* 1993;**71**:470–476.
127. ASERO R. Detection and clinical characterization of patients with oral allergy syndrome caused by stable allergens in Rosaceae and nuts. *Ann Allergy Asthma Immunol* 1999;**83**:377–383.
128. REEKERS R, BUSCHE M, WITTMANN M, KAPP A, WERFEL T. Birch pollen-related foods trigger atopic dermatitis in patients with specific cutaneous T-cell responses to birch pollen antigens. *J Allergy Clin Immunol* 1999;**104**:466–472.
129. M'RAIHI L, CHARPIN D, PONS A, BONGRAND P, VERVLOET D. Allergie croisée entre latex et banane. *Rev Fr Allergol* 1989;**29**:187–189.
130. BARNETT D, BONHAM B, HOWDEN ME. Allergenic cross-reactions among legume foods – an in vitro study. *J Allergy Clin Immunol* 1987;**79**:433–438.
131. BERNHISEL-BROADBENT J, SAMPSON HA. Cross-allergenicity in the legume botanical family in children with food hypersensitivity. *J Allergy Clin Immunol* 1989;**83**:435–440.
132. SICHERER SH, SAMPSON HA, BURKS AW. Peanut and soy allergy: a clinical and therapeutic dilemma. *Allergy* 2000;**55**:515–521.
133. MALEKI S, VIQUEZ O, JACKS T, DODO H, CHAMPAGNE ET, CHUNG SY et al. The major peanut allergen, Ara h 2, functions as a trypsin inhibitor, and roasting enhances this function. *J Allergy Clin Immunol* 2003;**112**:190–195.
134. BOUSQUET J, BJORKSTEN B, BRUIJNZEEL-KOOMEN CA, HUGGETT A, ORTOLANI C, WARNER JO et al. Scientific criteria and the selection of allergenic foods for product labelling. *Allergy* 1998;**53**:3–21.
135. FLEISCHER DM, CONOVER-WALKER MK, CHRISTIE L, BURKS AW, WOOD RA. The natural progression of peanut allergy: resolution and the possibility of recurrence. *J Allergy Clin Immunol* 2003;**112**:183–189.
136. SAMPSON HA. Peanut allergy. *N Engl J Med* 2002;**346**:1294–1299.
137. SICHERER SH, MUNOZ-FURLONG A, BURKS AW, SAMPSON HA. Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey. *J Allergy Clin Immunol* 1999;**103**:559–562.
138. LEUNG DY, SAMPSON HA, YUNGINGER JW, BURKS AW Jr, SCHNEIDER LC, WORTEL CH et al. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 2003;**348**:986–993.
139. LI XM, SRIVASTAVA K, GRISHIN A, HUANG CK, SCHOFIELD B, BURKS W et al. Persistent protective effect of heat-killed *Escherichia coli* producing “engineered,” recombinant peanut proteins in a murine model of peanut allergy. *J Allergy Clin Immunol* 2003;**112**:159–167.
140. HANSEN KS, BALLMER-WEBER BK, LUTTKOPF D, SKOV PS, WUTHRICH B, BINDSLEV-JENSEN C et al. Roasted hazelnuts – allergenic activity evaluated by double-blind, placebo-controlled food challenge. *Allergy* 2003;**58**:132–138.
141. BELLIONI-BUSINCO B, PAGANELLI R, LUCENTI P, GIAMPIETRO PG, PERBORN H, BUSINCO L. Allergenicity of goat's milk in children with cow's milk allergy. *J Allergy Clin Immunol* 1999;**103**:1191–1194.

142. WERFEL SJ, COOKE SK, SAMPSON HA. Clinical reactivity to beef in children allergic to cow's milk. *J Allergy Clin Immunol* 1997;**99**:293–300.
143. FIOCCHI A, RESTANI P, RIVA E, MIRRI GP, SANTINI I, BERNARDO L et al. Heat treatment modifies the allergenicity of beef and bovine serum albumin. *Allergy* 1998;**53**:798–802.
144. FANTA C, EBNER C. Allergy to mare's milk. *Allergy* 1998;**53**:539–540.
145. SZEPELALUSI Z, EBNER C, URBANEK R, EBNER H, SCHEINER O, BOLTZ-NITULESCU G et al. Detection of IgE antibodies specific for allergens in cow milk and cow dander: milk-dander syndrome. *Int Arch Allergy Immunol* 1993;**102**:288–294.
146. DROUET M, SABBAAH A. The pork/cat syndrome or crossed reactivity between cat epithelia and pork meat. *Monogr Allergy* 1996;**32**:164–173.
147. ANIBARRO B, SEANE FJ, VILA C, LOMBARDEO M. Allergy to eggs from duck and goose without sensitization to hen egg proteins. *J Allergy Clin Immunol* 2000;**105**:834–836.
148. BOCK SA, SAMPSON HA, ATKINS FM, ZEIGER RS, LEHRER S, SACHS M et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J Allergy Clin Immunol* 1988;**82**:986–997.
149. MANDALLAZ MM, DE WECK AL, DAHINDEN CA. Bird-egg syndrome. Cross-reactivity between bird antigens and egg-yolk livetins in IgE-mediated hypersensitivity. *Int Arch Allergy Appl Immunol* 1988;**87**:143–150.
150. de MAAT-BLEEKER F, van DIJK AG, BERRENS L. Allergy to egg yolk possibly induced by sensitization to bird serum antigens. *Ann Allergy* 1985;**54**:245–248.
151. WYSS M, HUWYLER T, WÜTHRICH B. „Bird-egg“ und „egg-bird syndrome“. Kreuzsensibilisierung zwischen inhalativen und ingestiven Vogelproteinen. In WÜTHRICH B, editor. *Nahrungsmittel und Allergie*. München: Dustri 1996;218–225.
152. JONES SM, MAGNOLFI CF, COOKE SK, SAMPSON HA. Immunologic cross-reactivity among cereal grains and grasses in children with food hypersensitivity. *J Allergy Clin Immunol* 1995;**96**:341–351.
153. ARMENTIA A, BANUELOS C, ARRANZ ML, DEL V, MARTIN-SANTOS JM, GIL FJ et al. Early introduction of cereals into children's diets as a risk-factor for grass pollen asthma. *Clin Exp Allergy* 2001;**31**:1250–1255.
154. ERBEN AM, RODRIGUEZ JL, MCCULLOUGH J, OWNBY DR. Anaphylaxis after ingestion of beignets contaminated with *Dermatophagoides farinae*. *J Allergy Clin Immunol* 1993;**92**:846–849.
155. MATSUMOTO T, GOTO Y, MIKE T. Anaphylaxis to mite-contaminated flour. *Allergy* 2001;**56**:247.
156. BERNHISEL-BROADBENT J, STRAUSE D, SAMPSON HA. Fish hypersensitivity. II: Clinical relevance of altered fish allergenicity caused by various preparation methods. *J Allergy Clin Immunol* 1992;**90**:622–629.
157. VALDIVIESO R, SUBIZA J, VARELA-LOSADA S, SUBIZA JL, NARGANES MJ, MARTINEZ-COCERA C et al. Bronchial asthma, rhinoconjunctivitis, and contact dermatitis caused by onion. *J Allergy Clin Immunol* 1994;**94**:928–930.
158. ANIBARRO B, FONTELA JL, DE LA HF. Occupational asthma induced by garlic dust. *J Allergy Clin Immunol* 1997;**100**:734–738.
159. PEREZ-PIMIENTO AJ, MONEO I, SANTAOLALLA M, de PAZ S, FERNANDEZ-PARRA B, DOMINGUEZ-LAZARO AR. Anaphylactic reaction to young garlic. *Allergy* 1999;**54**:626–629.
160. ARENA A, CISLAGHI C, FALAGIANI P. Anaphylactic reaction to the ingestion of raw onion. A case report. *Allergol Immunopathol (Madr)* 2000;**28**:287–289.
161. CADOT P, TITS G, BUSSELS L, CEUPPENS JL. Asthma and hand dermatitis to leek. *Allergy* 2001;**56**:192–193.
162. ASERO R, MISTRELLO G, RONCAROLO D, AMATO S. A case of onion allergy. *J Allergy Clin Immunol* 2001;**108**:309–310.
163. PEREZ-CALDERON R, GONZALO-GARIJO MA, FERNANDEZ DS. Exercise-induced anaphylaxis to onion. *Allergy* 2002;**57**:752–753.
164. PIRES G, PARGANA E, LOUREIRO V, ALMEIDA MM, PINTO JR. Allergy to garlic. *Allergy* 2002;**57**:957–958.
165. SANCHEZ-HERNANDEZ MC, HERNANDEZ M, DELGADO J, GUARDIA P, MONTESEIRIN J, BARTOLOME B et al. Allergenic cross-reactivity in the Liliaceae family. *Allergy* 2000;**55**:297–299.
166. TEE RD, GORDON DJ, WELCH JA, Newman Taylor AJ. Investigation of possible adverse allergic reactions to mycoprotein ('Quorn'). *Clin Exp Allergy* 1993;**23**:257–260.
167. DAUBY PA, WHISMAN BA, HAGAN L. Cross-reactivity between raw mushroom and molds in a patient with oral allergy syndrome. *Ann Allergy Asthma Immunol* 2002;**89**:319–321.
168. VAN DURME P, CEUPPENS JL, CADOT P. Allergy to ingested mycoprotein in a patient with mold spore inhalant allergy. *J Allergy Clin Immunol* 2003;**112**:452–454.
169. HERRERA I, MONEO I, CABALLERO ML, de PAZ S, PEREZ PA, REBOLLO S. Food allergy to spinach and mushroom. *Allergy* 2002;**57**:261–262.
170. SAMPSON HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;**107**:891–896.
171. NIGGEMANN B, REIBEL S, WAHN U. The atopy patch test (APT) – a useful tool for the diagnosis of food allergy in children with atopic dermatitis. *Allergy* 2000;**55**:281–285.
172. HOFFMANN-SOMMERGRUBER K, DEMOLY P, CRAMER R, BREITENEDER H, EBNER C, LAIMER DA CAMARA MM et al. IgE reactivity to Api g 1, a major celery allergen, in a Central European population is based on primary sensitization by Bet v1. *J Allergy Clin Immunol* 1999;**104**:478–484.
173. BALLMER-WEBER BK, SCHEURER S, FRITSCHKE P, ENRIQUE E, CISTERO-BAHIMA A, HAASE T et al. Component-resolved diagnosis with recombinant allergens in patients with cherry allergy. *J Allergy Clin Immunol* 2002;**110**:167–173.
174. LOVELESS MH. Milk allergy: a survey of its incidence; experiments with a masked ingestion test for its diagnosis. *J Allergy* 1950;**21**:500–509.
175. SAMPSON HA. Food allergy. Part 2: diagnosis and management. *J Allergy Clin Immunol* 1999;**103**:981–989.
176. SAMPSON HA, HO DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;**100**:444–451.
177. SPORIK R, HILL DJ, HOSKING CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Allergy* 2000;**30**:1540–1546.
178. RANCE F, ABBAL M, LAUWERS-CANCES V. Improved screening for peanut allergy by the combined use of skin prick tests and specific IgE assays. *J Allergy Clin Immunol* 2002;**109**:1027–1033.
179. MONTI G, MURATORE MC, PELTRAN A, BONFANTE G, SILVESTRO L, OGGERO R et al. High incidence of adverse reactions to egg challenge on first known exposure in young atopic dermatitis children: predictive value of skin prick test and radioallergosorbent test to egg proteins. *Clin Exp Allergy* 2002;**32**:1515–1519.

180. BOYANO-MARTINEZ T, GARCIA-ARA C, DIAZ-PENA JM, MUNOZ FM, GARCIA SG, ESTEBAN MM. Validity of specific IgE antibodies in children with egg allergy. *Clin Exp Allergy* 2001;**31**:1464–1469.
181. BARKHOLT V, JORGENSEN PB, SORENSEN D, BAHRENSCHEER J, HAIKARA A, LEMOLA E et al. Protein modification by fermentation: effect of fermentation on the potential allergenicity of pea. *Allergy* 1998;**53**:106–108.
182. MATSUMOTO T. Mitigation of the action of wheat allergen by acidic oxidative potential water. *Allergy* 2002;**57**:926–930.
183. FERNANDEZ-RIVAS M, CUEVAS M. Peels of Rosaceae fruits have a higher allergenicity than pulps. *Clin Exp Allergy* 1999;**29**:1239–1247.
184. BALLMER-WEBER BK, HOFFMANN A, WUTHRICH B, LUTTKOPF D, POMPEI C, WANGORSCH A et al. Influence of food processing on the allergenicity of celery: DBPCFC with celery spice and cooked celery in patients with celery allergy. *Allergy* 2002;**57**:228–235.
185. DE SWERT LF, CADOT P, CEUPPENS JL. Allergy to cooked white potatoes in infants and young children: a cause of severe, chronic allergic disease. *J Allergy Clin Immunol* 2002;**110**:524–529.
186. IBANEZ SD, MARTINEZ SI, MARANON LF, FERNANDEZ-CALDAS E, ALONSO LE, LASO BT. Specific IgE determinations to crude and boiled lentil (*Lens culinaris*) extracts in lentil-sensitive children and controls. *Allergy* 1999;**54**:1209–1214.
187. STEINMAN HA. “Hidden” allergens in foods. *J Allergy Clin Immunol* 1996;**98**:241–250.
188. VADAS P, PERELMAN B. Activated charcoal forms non-IgE binding complexes with peanut proteins. *J Allergy Clin Immunol* 2003;**112**:175–179.
189. ASERO R. Effects of birch pollen-specific immunotherapy on apple allergy in birch pollen-hypersensitive patients. *Clin Exp Allergy* 1998;**28**:1368–1373.
190. KELSO JM, JONES RT, TELLEZ R, YUNGINGER JW. Oral allergy syndrome successfully treated with pollen immunotherapy. *Ann Allergy Asthma Immunol* 1995;**74**:391–396.
191. HERRMANN D, HENZGEN M, FRANK E, RUDESCHKO O, JAGER L. Effect of hyposensitization for tree pollinosis on associated apple allergy. *J Investig Allergol Clin Immunol* 1995;**5**:259–267.
192. MODRZYNSKI M, ZAWISZA E, RAPIEJKO P, PRZYBYLSKI G. Specific-pollen immunotherapy in the treatment of oral allergy syndrome in patients with tree pollen hypersensitivity. *Przegl Lek* 2002;**59**:1007–1010.
193. HENZGEN M, SCHLENVOIGT G, DIENER C, JAGER L. Nahrungsmittelallergie bei Frühblüherpollinosis und deren Beeinflussung mittels Hyposensibilisierung. *Allergologie* 1991;**14**:90–94.
194. ASERO R. How long does the effect of birch pollen injection SIT on apple allergy last? *Allergy* 2003;**58**:435–438.
195. MOLLER C. Effect of pollen immunotherapy on food hypersensitivity in children with birch pollinosis. *Ann Allergy* 1989;**62**:343–345.
196. ASERO R. Fennel, cucumber, and melon allergy successfully treated with pollen-specific injection immunotherapy. *Ann Allergy Asthma Immunol* 2000;**84**:460–462.
197. de MAAT-BLEEKER F, AKKERDAAS JH, van REE R, AALBERSE RC. Vineyard snail allergy possibly induced by sensitization to house-dust mite (*Dermatophagoides pteronyssinus*). *Allergy* 1995;**50**:438–440.
198. PERONI DG, PIACENTINI GL, BODINI A, BONER AL. Snail anaphylaxis during house dust mite immunotherapy. *Pediatr Allergy Immunol* 2000;**11**:260–261.
199. PAJNO GB, LA GRUTTA S, BARBERIO G, CANONICA GW, PASSALACQUA G. Harmful effect of immunotherapy in children with combined snail and mite allergy. *J Allergy Clin Immunol* 2002;**109**:627–629.
200. MEGLIO P, PLANTAMURA M, ARABITO E, FALAGIANI P, TORRE A, ROSSI P. Does SIT to Der p protect from snail sensitization? *Allergy* 2002;**57**:868–869.
201. LOMBARDI C, CANONICA GW, PASSALACQUA G. Sublingual IT in OAS. *Allergy* 2000;**55**:677–678.
202. MEMPEL M, RAKOSKI J, RING J, OLLERT M. Severe anaphylaxis to kiwi fruit: immunologic changes related to successful sublingual allergen immunotherapy. *J Allergy Clin Immunol* 2003;**111**:1406–1409.
203. RUEFF F, EBERLEIN-KONIG B, PRZYBILLA B. Oral hyposensitization with celery juice. *Allergy* 2001;**56**:82–83.
204. PATRIARCA G, SCHIAVINO D, NUCERA E, SCHINCO G, MILANI A, GASBARRINI G. Food allergy in children: results of a standardized protocol for oral desensitization. *Hepatogastroenterology* 1998;**45**:52–58.
205. WUTHRICH B, HOFER T. Food allergies. III. Therapy: elimination diet, symptomatic drug prophylaxis and specific hyposensitization. *Schweiz Med Wochenschr* 1986;**116**:1401–1410.
206. BAUER A, EKANAYAKE MS, WIGGER-ALBERTI W, ELSNER P. Oral rush desensitization to milk. *Allergy* 1999;**54**:894–895.
207. NELSON HS, LAHR J, RULE R, BOCK A, LEUNG D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J Allergy Clin Immunol* 1997;**99**:744–751.
208. SAMPSON HA. Immunological approaches to the treatment of food allergy. *Pediatr Allergy Immunol* 2001;**12**(Suppl. 14):91–96.
209. MACDOUGALL CF, CANT AJ, COLVER AF. How dangerous is food allergy in childhood? The incidence of severe and fatal allergic reactions across the UK and Ireland. *Arch Dis Child* 2002;**86**:236–239.
210. WARNER JO. How dangerous is food allergy in childhood? *Pediatr Allergy Immunol* 2002;**13**:149–150.
211. GOLD MS. EpiPen epidemic or good clinical practice? *J Paediatr Child Health* 2003;**39**:376–377.
212. UNSWORTH DJ. Adrenaline syringes are vastly over prescribed. *Arch Dis Child* 2001;**84**:410–411.
213. HOURIHANE J. Controversies in paediatrics? *Arch Dis Child* 2001;**85**:510.
214. KEMP A. EpiPen epidemic: suggestions for rational prescribing in childhood food allergy. *J Paediatr Child Health* 2003;**39**:372–375.
215. HALLETT R, HAAPANEN LA, TEUBER SS. Food allergies and kissing. *N Engl J Med* 2002;**346**:1833–1834.
216. LEPP U, ZABEL P, SCHOCKER F. Playing cards as a carrier for peanut allergens. *Allergy* 2002;**57**:864.
217. PUMPHREY RS, NICHOLLS JM. Epinephrine-resistant food anaphylaxis. *Lancet* 2000;**355**:1099.
218. MONERET-VAUTRIN DA, KANNY G, MORISSET M, FLABBE J, GUENARD L, BEAUDOUIN E et al. Food anaphylaxis in schools: evaluation of the management plan and the efficiency of the emergency kit. *Allergy* 2001;**56**:1071–1076.
219. GOLD MS, SAINSBURY R. First aid anaphylaxis management in children who were prescribed an epinephrine autoinjector device (EpiPen). *J Allergy Clin Immunol* 2000;**106**:171–176.