REVIEWS

Cross-reactivity Syndromes in Food Allergy

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■ Abstract

The immunological phenomenon of cross-reactivity has consequences for the diagnosis and treatment of certain food allergies. Once allergy to a particular food has been confirmed, positive test results are often obtained against other foods and, although less frequently, true clinical cross-reactivity is determined. This article reviews the relevant clinical aspects of food allergies in which the underlying mechanism is cross-reactivity between foods that are both related and unrelated taxonomically.

Key words: Food allergy. Food hypersensitivity. Allergens. Allergenic components. Cross-reactivity.

■ Resumen

El fenómeno inmunológico de la reactividad cruzada tiene consecuencias tanto en el diagnóstico como en el tratamiento de algunas alergias alimentarias. Una vez se confirma alergia frente a un determinado alimento, con frecuencia se obtienen test positivos y menos frecuentemente verdadera reactividad cruzada clínica con otros alimentos. En este artículo se revisan aspectos clínicos de interés en la alergia alimentaria, en los que el mecanismo subyacente es la reactividad cruzada entre alimentos relacionados y no relacionados taxonómicamente.

Palabras clave: Alergia alimentaria. Hipersensibilidad a alimentos. Alérgenos. Componentes alergénicos. Reactividad cruzada.

Introduction

Cross-reactivity (CR) occurs when an adaptive immune response to a particular antigen causes reactivity to other antigens that are structurally related to the inducer [1]. CR represents an advantage in defense against infections, but has negative effects in some immune disorders, the most notable of which are autoimmune diseases and allergic disorders, in which both diagnosis and treatment can be affected.

The antigen–antibody reaction is based on the spatial complementarity of the epitope with the idiotope. Epitopes, which are made up of fragments of 5-7 amino acids, may be linear or conformational, although the latter are more frequent and variable. The concept of homology is based on the fact that the similarity in the sequences observed between molecules arises from their common origin. They therefore share the same function, and so must conserve the same overall folding. Consequently, aspects that are essential for the stability of the core (double-stranded ß helices, α helices, ß-pleated sheets, and disulphide bridges) must be conserved, and this is possible with 35% sequence similarity. In contrast, the external loops that are more exposed and house most immunoglobulin (Ig) E epitopes are more open to evolutionary changes.

The World Health Organization guidelines for the prediction of allergenicity specify that a protein can be considered to cross-react with an allergen if they share at least 35% sequence similarity in a fragment of 80 amino acids or complete identity with a peptide of 6-8 amino acids from an allergen [2]. However, given that for mastocytes and basophils to become activated it is necessary for IgE antibodies bound to the receptors of these cells to recognize more than 2 epitopes with high affinity, CR between IgE and effector cells is unlikely if sequential similarity is less than 70%.

Therefore, CR is an immunological phenomenon whose clinical manifestation—when this occurs—is the association of 2 or more allergies. The clinical and epidemiologic observations on which the descriptions of the different syndromes reviewed below are based make it possible to establish CR between species. Thus, CR syndromes have been described between phylogenetically close species, in which it seems that the shorter the taxonomic distance, the greater the likelihood of CR. However, CR has also been described between phylogenetically distant species. In these cases, the allergens responsible are usually homologous proteins belonging to specific families of molecules. Frequently, the reaction is caused by proteins that are highly conserved from an evolutionary point of view and that, given their widespread presence, have been termed panallergens. Thus, we must take into account not only the taxonomic classification of organisms, but also the molecular classification of the allergens, as both play a key role in CR syndromes.

Allergy to Milk

CR Between Milk Proteins From Different Mammals

CR between milk proteins (α-lactalbumins, ß-lactoglobulins, and caseins) from cow, buffalo, sheep, and goat is widespread, as has been demonstrated in in vitro studies [3] and challenge tests. Thus, 92% of patients with allergy to cow milk proteins showed a reaction to goat milk [4]. In contrast, only 4% of children with allergy to cow milk showed clinical reactivity to mare milk [5]. Donkey milk [6] and camel milk [7] also seem to be less allergenic than cow milk. However, from a practical point of view, once a diagnosis of allergy to milk from one mammal has been established, milk from other mammals should be avoided at least until tolerance can be tested under controlled conditions, with good tolerance being more common for milk from Equidae [8]. Nevertheless, there have been reports of allergy to sheep and goat milk without allergy to cow milk proteins [9].

CR Between Cow Milk and Veal

Between 10% and 20% of children allergic to cow milk are also allergic to veal; conversely, 93% of children allergic to veal are also allergic to milk [10,11]. The molecular basis for this syndrome is allergy to bovine serum albumin [11], which is at least partially thermolabile. Given that allergenicity to bovine serum albumin is reduced by heating [12], the likelihood of clinical reactions is lower if the meat is well cooked. In practice, the consumption of cow meat should only be restricted in cow milk–allergic patients with previous clinical symptoms by veal.

Allergy to Eggs

CR Between Eggs From Different Birds

CR between proteins from different birds is frequent [13], although the clinical implications have not been studied systematically. Allergy to duck and goose eggs without allergy to chicken eggs has been described as exceptional [13]. Therefore, once a diagnosis of allergy to eggs from one bird has been made, other eggs should be avoided, at least until tolerance has been tested under controlled conditions.

Bird–Egg Syndrome

Bird–egg syndrome is the association between respiratory allergy to bird antigens and food allergy to egg yolk [15,16], and in some cases, meat from the same or different bird species. It is more common in adults than in children. Clinically, the respiratory allergy usually precedes the food allergy [17], in which digestive and respiratory symptoms predominate. Patients frequently tolerate ingestion of well-cooked eggs and poultry.

The main molecular basis of this syndrome lies in allergy to α-livetins or avian serum albumins such as Gal d 5 from chicken [18], which are found in feather, meat, and egg yolk and which are at least partially thermolabile. CR between conalbumin (ovotransferrin) and its serum homolog, transferrin, could also be involved in bird–egg syndrome.

Allergy to Fish

The normal molecular substrate of fish allergy is allergy to parvalbumins, which are muscular sarcoplasm proteins that control the flow of calcium and cause extensive CR between fish from different families [19,20], although not with the same intensity [21] or likelihood of clinical reactivity. Approximately 50% of patients allergic to one fish species will react to at least one other [22]; however, up to 40% of patients sensitized to 1 or more fish species show no symptoms after ingesting other species [20], even after positive results in diagnostic tests (skin prick tests or specific IgE). The best-tolerated fish belong to the Escombrideae (tuna, bonito, mackerel), Xiphidae (swordfish), and Salmonidae (salmon, trout) families [23].

There have also been reports of sensitization to just 1 species. In Spain, this phenotype of fish allergy has been described mainly with megrim [20].

In general, once a diagnosis of fish allergy has been established, all fish should be avoided, at least in patients sensitized to several species, until tolerance has been demonstrated under controlled conditions. This occurs most frequently in the case of tuna and swordfish.

A parvalbumin is also responsible for the infrequent allergy to frog meat [24].

Allergy to Shellfish

Shellfish are a nontaxonomic and heterogeneous group of marine invertebrates including crustaceans and molluscs. The allergens most commonly implicated in allergies to the 2 taxonomic classes are the tropomyosins [25,26], which are structural proteins in eukaryotic cells. Tropomysins present in the muscle cells of invertebrates are key to understanding the CR existing between species of the same class of shellfish (crustaceans, bivalves, gastropods, and cephalopods), between crustaceans and mollusks [27], and in such diverse invertebrates as crustaceans, mollusks, mites, insects, and nematodes [28,29]. Tropomyosin is therefore a panallergen capable of sensitization both by ingestion and inhalation. CR between tropomyosins of species of the same class of shellfish is the norm. The risk of reaction with a second species is 75% in patients allergic to 1 species of crustacean [22]. The CR observed between mites (Der p 10) and shellfish is also frequent, mainly with crustaceans and, to a lesser extent, with mollusks [26] and insects. Furthermore, other as yet unidentified allergens could be implicated in the CR between mites and crustaceans [30] and snails [31].

There have also been reports of selective allergies to species of shellfish in which the triggers are allergens other than tropomyosins [32,33].

Allergy to Meats

The best-characterized allergens in meats are the albumins (from cow and chicken) and the immunoglobulins, although there have been occasional reports involving other allergens (actin, myosin, tropomyosin, and α-parvalbumin) [34]. On the basis of sensitization to these allergens, it is possible to establish 3 models of CR or cosensitization:

a) CR between meats from related species. Patients with allergies to meat from a mammal may show reactions to meat from other mammals and those with allergy to poultry meat may show reactions to meat from other birds [35,36].

b) CR between meats and other foods of animal origin (milk and egg). As mentioned above, between 10% and 20% of children allergic to milk are also allergic to meat of bovine origin and 93% of patients allergic to meat of bovine origin are also allergic to milk [10,11]. Patients allergic to poultry meat frequently exhibit bird–egg syndrome (see above).

c) CR between meat and animal dander. Albumins from mammals are found in several animal tissues and secretions including meat, skin, and milk and are fairly well conserved in different species of mammal. The co-occurrence of both circumstances leads to CR phenomena such as cat–pig syndrome [37] (allergy to pork in patients with respiratory allergy to the cat albumin Fel d 2), allergy to lamb meat with sensitization to cat, or allergy to horsemeat associated with respiratory allergy to hamster or cat [38].

A fourth pattern of CR with meats does not have sensitization against a protein allergen as its molecular substrate, but rather a glucide determinant, galactose-α-1,3-galactose [39], which is present in proteins from nonprimate mammals. These carbohydrates have also been considered responsible for anaphylaxis induced by cetuximab, a chimeric (mouse/human) monoclonal antibody used to treat metastatic colorectal cancer and head and neck cancer. This agent also contains galactose-α-1,3-galactose and has been proposed as a reagent for the detection of this type of sensitization [40], since skin tests with meat extracts are often negative. The most notable clinical characteristic is the late onset of symptoms, which are often severe. Furthermore, the geographical distribution of anaphylaxis by meat overlaps with that of the more frequent anaphylactic reactions to cetuximab. A study of reactions to cetuximab found that, in some areas, up to 18% of untreated

Table. Allergens in Nuts, Legumes, and Other Seeds

Source	2S Albumins	7S Globulins	11S Globulins	LTP	Profilin	PR-10	Oleosins
Cashew nut	Ana o 3	Ana o 1	Ana o 2				
Pistachio nut	Pis v 1	Pis v 3	Pis v 2				
Hazelnut	Cor a 14	Cor a 11	Cor a 9	Cor a 8	Cor a 2	Cor a 1	Cor a 12 Cor a 13
Almond	Pru du 2S Albumin		Pru du 6	Pru du 3	Pru du 4		
Walnut	Jug r 1	Jug r 2	Jug r 4	Jug r 3			
Pecan nut	Ber e 1		Ber e 2				
Chestnut				Cas s 8		Cas s 1	
Sunflower seed				Hel a 3	Hela 2		
Sesame	Ses i 1 Ses i 2	Ses i 3	Ses i 7 Ses i 6				Ses i 4 Ses i 5
Mustard	Sin a 1		Sin a 2	Sin a 3	Sin a 4		
Peanut	Ara h 2 Ara h 6 Ara h 7	Ara h 1	Ara h 3 Ara h 4	Ara h 9	Ara h 5	Ara h 8	Ara h 10 Ara h 11 Ara h 18 kDa
Soy	Gly m 2S Albumin	Gly m 5 Gly m conglycin	Gly m 6 Gly m glycinin		Gly m 3	Gly m 4	
Lentil		Len c 1		Len c 3			
Chickpea	Cic a 2S Albumin						
Pea		Pis s 1					
Lupin		Lup an 1	Lup an-α conglutin				

Abbreviation: LTP, lipid transfer protein.

patients had IgE to galactose-α-1,3-galactose [41], which was suspected to have been induced by tick bites [39].

Allergy to Legumes

CR between different species of legumes is very frequent in patients allergic to one type of legume, but its clinical relevance seems to vary greatly depending on dietary habits and the culprit legume. In a population from the United States, clinical reactivity to a second species in patients allergic to one species (peanut or soy) did not exceed 5% [42]. In Spain, where the most frequent cause of childhood allergies to legumes is lentil (followed by chickpea), 82% of patients reacted to 2 or more legumes [43,44]. The most frequent associations were lentil and pea (73%), lentil and chickpea (69%), chickpea and pea (60%), pea and peanut (57%), and lentil and peanut (50%). More than 90% of children tolerated green bean.

The molecular bases of this CR are not yet fully understood, although the homologous storage proteins present in the seeds of legumes and other plant families (nuts, sesame, and mustard) are firm candidates (Table). Storage proteins are classified into albumins (2S albumins or conglutins) and globulins, which are in turn divided into 7S globulins (vicilins) and 11S globulins (glycines and legumins). Furthermore, lipid transfer protein (LTP) has been described in lentil (Len c 3) and peanuts (Ara h 9), its allergenic relevance being more important in Mediterranean populations.

Allergy to Nuts

Although nuts are a nontaxonomic group of foods, CR between different nuts is frequent. Between 28% and 49% of peanut-allergic patients have been shown to react to another nut. Clinical reactivity to more than 1 species of hard-shelled nut is seen in one-third of patients [45] and is most frequent between nuts of the same taxonomic family, eg, pistachio and cashew nuts and walnut and pecan nuts [46-48].

Although the responsibility of each allergen in CR has not been defined, the allergens potentially responsible for the CR between different seeds are storage proteins, LTPs, profilins, homologs of Bet v 1, and the oleosins. The Table shows the proteins of the families described as allergens in nuts, legumes, and seeds in general.

Furthermore, in the Mediterranean region, a frequent clinical association has been observed between allergy to Rosaceae fruits and allergy to nuts [49-51]. In these cases, the probable immunological basis is sensitization to LTPs.

Latex–Fruit Syndrome

Latex–fruit syndrome is the association of latex allergy and allergy to plant foods, which affects up to 50% of latex-allergic patients [52]. The foods most frequently involved are banana (28%), avocado (28%), chestnut (24%), and kiwi (20%). With these foods, clinical symptoms are often severe, as is the case

with other foods less frequently related to latex (fig, papaya, and tomato), whilst with potato the reactions described are usually local and of low intensity. Allergy to latex usually precedes food allergy, although this is not always the case. Frequently, the spectrum of food allergies increases with time.

The most important molecular basis of the latex–fruit syndrome is the homology between the hevein (Hev b 6.02) of the latex with the hevein-like N-terminal domain of the class I chitinases of plants [53] (70% identity), although some determinants of the catalytic portion of these chitinases may also contribute to CR with latex (possibly with the class I chitinase Hev b 11) [54]. Other allergens which have homologs in plant foods and thus are potential causes of CR are Hev b 1 (homolog of papain), Hev b 2 (plant glucanases), Hev b 4 (plant glycosidase), Hev b 5 (kiwi acid protein), Hev b 6 (radish prohevein) Hev b 6.03 (win potato and tomato proteins and plant lectins), Hev b 7 (potato patatin), Hev b 8 (profilins), Hev b 9 (enolases), Hev b 10 (Mn superoxide dismutases), Hev b 12 (plant LTPs), and hevamine (class III plant chitinases).

Pollen–Plant Food Syndromes

Foods From the Apiaceae Family

Allergy to Apiaceae (umbellifers), mainly celery and carrot (but also including dill, fennel, parsley, coriander, and aniseed), has been described in 3 types of patients according to their sensitization to pollens (reviewed in [55]), as follows:

• Patients sensitized only to birch: Birch–Apiaceae syndrome. This is seen principally in central Europe. The typical clinical picture is oral allergy syndrome (OAS), which occurs when raw foods are ingested. The allergy to Apiaceae is secondary to pollinosis and is due to the presence in these foods of proteins that are homologous to Bet v 1 (Api g 1 and Dau c 1) and less frequently to profilins [56-59].

• Patients sensitized to *Artemisia*: Celery-*Artemisia*-spices syndrome. In the same geographic areas, patients who are allergic to *Artemisia* with no concomitant allergy to birch frequently present systemic reactions following the ingestion of these vegetables, both when raw and when cooked. Homologous proteins of Art v 60 kDa are suspected of being responsible for this CR [59,60].

• Patients sensitized to birch and *Artemisia*: Celery-birch-*Artemisia*-spices syndrome. The clinical profile of the allergens involved is intermediate, with homologs of Bet v 1, profilins, cross-reactive carbohydrate determinants, and allergens of 40-60 kDa being recognized [60].

Artemisia–Vegetables in Spain (Reviewed in [55])

In place of the celery-*Artemisia*-spices syndrome described in central European populations, in Spain there is a statistically significant association between sensitization to *Artemisia* pollen and to foods from the Compositae family (lettuce and sunflower seed), honey, peanuts, nuts, *Rosaceae*, tomato, and Brassica [61,62], that is, to a series of foods that are taxonomically unrelated. Clinical symptoms following ingestion vary from OAS to anaphylaxis, and sensitization

to *Artemisia* may be subclinical; therefore, the source of sensitization could be foods. LTPs appear to be the main allergens involved. CR has been observed between Art v 3, Pru p 3, Mal d 3, and Bra o 3 [63].

Birch–Plant Foods Syndrome

Up to 70% of patients allergic to pollen from birch and other Fagales show symptoms of allergy to plant foods. Although the list of foods described is considerably long, those most frequently involved are the Rosaceae (especially apple), nuts (mainly hazel nut), and vegetables from the Apiaceae family (mainly celery and carrot). Pollinosis precedes the symptoms induced by the foods. These tend to be slight, characteristically OAS, and occur following ingestion of the raw food.

The main culprit allergen, which is involved in more than 90% of patients with allergy to plant foods associated with allergy to birch pollen, is Bet v 1 [56], a PR-10, which gives rise to CR with its homologs in these foods. Less than 25% of patients with this syndrome are sensitized to Bet v 2 (birch profilin), although its contribution to symptoms remains unclear [56-58].

CR Syndrome Due to Allergy to Profilins [64]

Profilins are structural proteins that are both ubiquitous and very well conserved from an evolutionary point of view (Figure 1). As for their allergenic potential, they are considered to be incomplete allergens, capable of inducing sensitization by inhalation, but not by ingestion, due to their lability against peptic digestion. Therefore, this syndrome presents with variable frequency in patients with pollinosis depending on the primary pollinosis and, probably, allergenic pressure. Thus, whilst in the north of Europe it is associated with allergy to birch pollen [65], in Spain it is more frequent and associated mainly with pollinoses due to grasses [66]. The clinical manifestation of this food allergy is OAS induced by the raw food. Several foods could be involved, given that many allergenic profilins have been described in plant foods that are eaten raw. Nevertheless, OAS has been proposed as a clinical marker of sensitization to profilins for banana, tomato, melon (100% of patients with OAS due to melon are sensitized to profilins [67]), watermelon, or citrus fruits [68]. In the Mediterranean region, in patients allergic to Rosaceae the frequency of sensitization to profilins is approximately 40%, although this rises to 75% in patients with allergy to Rosaceae and associated pollinosis [55].
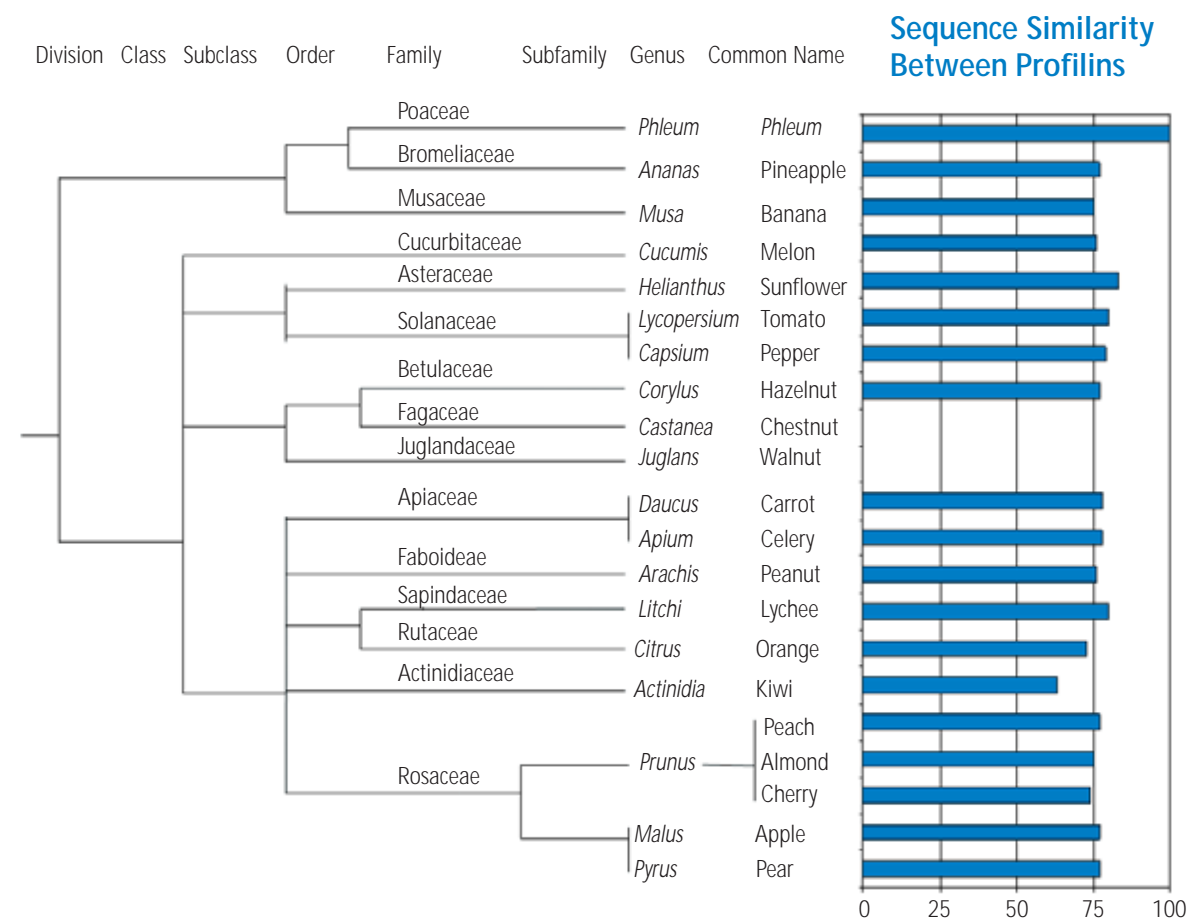

Figure 1. Sequence similarity between profilins from different sources in relation to that of *Phleum pretense*, Phl p 12, according to alignments made by FASTA 3.45 from the SDAP web (The University of Texas Medical Branch), http://fermi.utmb.edu/SDAP/index.html

Syndromes due to LTPs

LTPs are plant defense proteins that are highly conserved and present in all plant organs [69], including fruits in whose epidermal tissue they are found in high concentrations. LTPs are thermally stable and resistant to peptic digestion, as a result of which they behave as full allergens, sensitizing by ingestion and often causing systemic reactions. They are the major allergens of fruits the Rosaceae family [70]. According to the Allergome database [71], together with the Rosaceae LTPs (Pru p 3 from peaches, Pru ar 3 from apricot, Pru av 3 from cherry, Pru d 3 from plum, Pru du 3 from almond, Fra a 3 from strawberry, Mal d 3 from apple, Pyr c 3 from pear and Rub i 3 from raspberry), allergenic LTPs have been identified in other fruits (Act c 10 from kiwi, Vit v 1 from grape, Cit s 3 from orange, Cit r 3 from mandarin, Cit l 3 from lemon, Mus a 3 from banana, Mor n 3 from blackberry, Pun g 3 from pomegranate), nuts (Jug r 3 from walnut, Cor a 8 from hazelnut, Cas s 8 from chestnut, Hel a 3 from sunflower seed), legumes (Ara h 9 from peanut, Len c 3 from lentil, Pha v 3 from haricot bean), other seeds (Sin a 3 from mustard), vegetables (Lyc e 3 from tomato, Lac s 1 from lettuce, Aspa o 1 from asparagus, Api g 2 from celery, All c 3 from onion, Dau c 3 from carrot, Pet c 3 from parsley, Cro s 3 from saffron, Bra o 3 from broccoli, Bra r 3 from turnip), and cereals (Hor v 14 from barley, Tri a 14 from wheat, Tri s 14 from spelt, Zea m 14 from corn, and Ory s 14 from rice), as well as pollens (Ole e 7, Par j 1 and 2, Par o 1, Art v 3, Amb a 6, Pla a 3) and latex (Hev b 12). CR has been observed with several of these allergens, although frequently with no clinical manifestations.

The main trigger for sensitization for most patients allergic to LTPs seems to be peach, as it is usually the first food to produce symptoms, it is rarely tolerated normally, and IgE levels are usually higher for Pru p 3 than for other LTPs [72].

Nevertheless, we can distinguish different types of patients with regard to the number of LTPs recognized by their IgE. On the one hand, we have those that only recognize LTPs from the Rosaceae family, frequently only of the Prunoideae subfamily or even just that from peaches. At the other extreme, we find many patients whose IgE recognizes a wide range of the LTPs mentioned above, not all with clinical significance beyond numerous positive results in diagnostic tests. However, patients in this category report clinical symptoms in relation to many foods other than peach, among which the most common are walnut and other nuts [73]. These patients also recognize
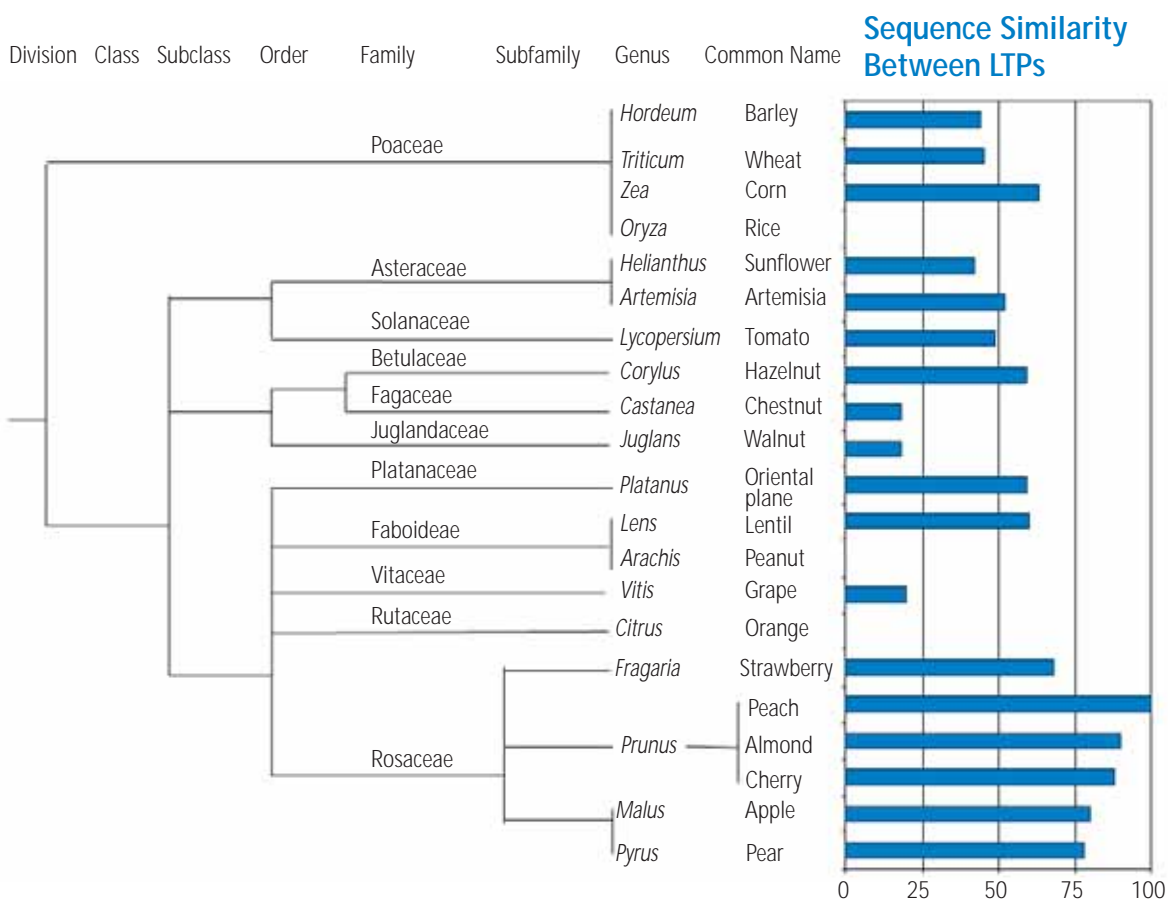

Figure 2. Sequence similarity between lipid transfer proteins (LTPs) from different sources in relation to that of *Prunus persica*, Pru p 3, according to alignments made by FASTA 3.45 from the SDAP web (The University of Texas Medical Branch), http://fermi.utmb.edu/SDAP/index.html.

LTPs from the pollen of *Artemisia* and *Platanus* (Art v 3 and Pla a 3), so that, in patients who are allergic to peach with sensitization to Pru p 3, those who are also sensitized to Art v 3 seem to recognize a wider range of food LTPs [74]. Similarly, patients with allergy to chestnut and sensitization to Cas s 8 are sensitized to *Artemisia* [63]. In the same way, patients allergic to lettuce with sensitization to Lac s 1 are sensitized to *Platanus* pollen [38]. Although the exact route of sensitization in these cases is not clear [75], sensitization to LTPs from *Artemisia* and *Platanus* probably should be considered as a marker rather than as an inducer [55]. Patients sensitized to multiple LTPs experience reactions that are often severe with a larger number of foods and, very frequently, the number of foods involved increases progressively. The future risk regarding the foods to which they are sensitized but still tolerate is not predictable on the basis of the similarity of sequences in the LTPs, since, while in patients allergic to peach the concomitant allergy to walnuts is much more frequent than allergy to pear, the percentage of similarity in their LTP sequences is 80% between peach and pear and 18% between peach and walnut (Figure 2). Consequently, these patients constitute a high-risk group that is difficult to manage. It is therefore essential that they be instructed about the factors that can alleviate or aggravate the clinical manifestations of a latent food allergy and about self-administration of adrenaline to treat anaphylaxis.

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