Cross-Reactive Aeroallergens: Which Need to Cross Our Mind in Food Allergy Diagnosis?

Margaretha A. Faber, MD, PhD[a], Athina L. Van Gasse, MD[a,b], Ine I. Decuyper, MD[a,b], Vito Sabato, MD, PhD[a], Margo M. Hagendorens, MD, PhD[a,b], Christel Mertens, MLT[a], Chris H. Bridts, MLT[a], Luc S. De Clerck, MD, PhD[a], and Didier G. Ebo, MD, PhD[a] *Antwerp, Belgium*

INFORMATION FOR CATEGORY 1 CME CREDIT

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the following instructions.

Method of Physician Participation in Learning Process: The core material for these activities can be read in this issue of the Journal or online at the *JACI: In Practice* Web site: www.jaci-inpractice.org/. The accompanying tests may only be submitted online at www.jaci-inpractice.org/. Fax or other copies will not be accepted.

Date of Original Release: November 1, 2018. Credit may be obtained for these courses until October 31, 2019.

Copyright Statement: Copyright © 2018-2020. All rights reserved.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for 1.00 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Margaretha A. Faber, MD, PhD, Athina L. Van Gasse, MD, Ine I. Decuyper, MD, Vito Sabato, MD, PhD, Margo M. Hagendorens, MD, PhD, Christel Mertens, MLT, Chris H. Bridts, MLT, Luc S. De Clerck, MD, PhD, and Didier G. Ebo, MD, PhD (authors); Michael Schatz, MD, MS (editor)

Learning objectives:

1. To evaluate patients with possible food allergy based upon aero-allergen cross-reactive food proteins.

2. To describe proteins responsible for food-aeroallergen cross reactivity.

3. To recognize the potential severity of aeroallergen-food allergen cross-reactivity.

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Relevant Financial Relationships with Commercial Interests: The author declares that there are no relevant conflicts of interest. M. Schatz declares no relevant conflicts of interest.

Secondary food allergies due to cross-reactivity between inhalant and food allergens are a significant and increasing global health issue. Cross-reactive food allergies predominantly involve plant-derived foods resulting from a prior sensitization to cross-reactive components present in pollen (grass, tree, weeds) and natural rubber latex. Also, primary sensitization to allergens present in fungi, insects, and both nonmammalian and mammalian meat might induce cross-reactive food allergic syndromes. Correct diagnosis of these associated food allergies is not always straightforward and can pose a difficult challenge. As a matter of fact, cross-reactive allergens might hamper food allergy diagnosis, as they can cause clinically irrelevant positive tests to cross-reacting foods that are safely consumed. This review summarizes the most relevant cross-reactivity syndromes between inhalant and food allergens. Particular focus is paid to the potential and limitations of confirmatory testing such as skin testing, specific IgE assays, molecular diagnosis, and basophil activation test. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1813-23)

Key words: *Cross-reactivity; Inhalant allergens; Food allergy; Diagnosis; IgE; Skin tests; CRD; BAT*

Respiratory allergies are a significant and increasing global health issue that affects children as well as adults.[1-3] Over the last decades it has emerged that in many patients the clinical phenotype of an inhalant allergy extends beyond their respiratory symptoms (eg, rhinoconjunctivitis and bronchospasms) and also comprises heterogeneous symptoms on food consumption

[a]Faculty of Medicine and Health Science, Department of Immunology, Allergology, Rheumatology, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium
[b]Faculty of Medicine and Health Science, Department of Pediatrics, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium
No funding was received for this work.
Conflicts of interest: The authors declare that they have no relevant conflicts of interest.
Received for publication April 19, 2018; revised August 2, 2018; accepted for publication August 20, 2018.
Available online August 29, 2018.
Corresponding author: Didier G. Ebo, MD, PhD, Faculty of Medicine and Health Science, Department of Immunology, Allergology, Rheumatology, University of Antwerp, Campus Drie Eiken T.595, Universiteitsplein 1, 2610 Antwerp, Belgium. E-mail: immuno@uantwerpen.be.
2213-2198
© 2018 American Academy of Allergy, Asthma & Immunology
https://doi.org/10.1016/j.jaip.2018.08.010

Abbreviations used

BAT- Basophil activation tests
CCD- Cross-reactive carbohydrate determinant
CRD- Component resolved diagnosis
GRP- Gibberellin-regulated protein
HDM- House dust mite
NRL- Natural rubber latex
ns-LTP- Nonspecific lipid transfer protein
OAS- Oral allergy syndrome
PFS- Pollen-related food syndrome
PR-proteins- Pathogenesis-related proteins
sIgE- specific IgE
SPT- Skin prick test
TLP- Thaumatin-like protein

adding to a significant reduced quality of life, morbidity, and eventually also mortality.[4-7] These food allergic symptoms result from a cross-reactivity between inhalant and food allergens due to the production of cross-reactive specific IgE (sIgE) antibodies that are directed against structural homologous allergens from a taxonomically more or less related allergenic source. In these so-called secondary food allergies, allergic symptoms might vary from localized reactions restricted to the oropharynx to severe generalized and potentially life-threatening reactions. However, cross-reactive sIgE antibodies do not necessarily cause clinical symptoms and can go completely asymptomatic. The best known example of such a cross-reactivity syndrome is the pollen-related food syndrome (PFS), formerly called the "oral allergy syndrome (OAS)" as in most patients food-induced symptoms are confined to the oral cavity. However, the term OAS is misleading, as cross-reactive allergic symptoms on plant food are not necessarily limited to the oral cavity and, vice versa, allergic symptoms restricted to the oropharynx might also occur in patients without pollinosis. Therefore, in this review article, for clarity we decided to avoid the term OAS and we will literally describe symptoms involved in the PFS.

Severity of clinical symptoms is believed to mainly depend on the physical properties of the sensitizing component. In (older) children, adolescents, and adults, secondary food allergies predominantly involve plant-derived foods resulting from a prior sensitization to cross-reactive components present in pollen, latex, other plant-derived foods, and *Cannabis sativa*.[6-9] Other cross-reactivity syndromes rest on a primary sensitization to allergens present in fungi, insects, and both nonmammalian and mammalian meat.[10-12]

Unfortunately, unlike diagnosis of inhalant allergy that can generally easily be documented applying skin and sIgE tests, correct diagnosis of these associated food allergies is not always straightforward. Actually, cross-reactivity can have a significant deleterious effect on the outcome of diagnostics, as many subjects with an inhalant allergy produce cross-reactive sIgE antibodies to food allergens without any clinical significance, in other words demonstrating no allergic symptoms on exposure. Therefore, a positive skin prick test (SPT) or sIgE result should always be interpreted extremely cautiously as it might merely reflect (cross) sensitization rather than a genuine clinically relevant allergy.[13,14] To discriminate between genuine allergy and sensitization, it has been shown that to some extent component resolved diagnosis (CRD) and/or basophil activation tests (BAT) can be helpful. In contrast to conventional sIgE antibody assays, CRD does not rely on crude extract preparations obtained from native allergens (generally poorly defined mixtures containing both allergenic and nonallergenic components) but on sIgE antibodies directed towards single components purified from natural sources or produced by recombinant techniques.[15] Therefore, this technique makes it possible to establish personalized sensitization profiles and recognize cross-reactivity patterns. The principles and applications of BAT are beyond the scope of this review but are detailed elsewhere.[16,17] It appears that this technique that awaits entrance in mainstream clinical practice, to some extent, also allows us to discriminate between clinically relevant and irrelevant sIgE results and more closely mirrors the clinical situation than simple sIgE binding assays.[18-20]

This review summarizes the most relevant cross-reactivity syndromes between inhalant and food allergens with a particular focus on potential and limitations of confirmatory testing such as skin testing, sIgE assays, and molecular diagnosis (CRD).

CROSS-REACTIVE AEROALLERGENS OF PLANT ORIGIN

As summarized in Figure 1, the majority of allergen components involved in cross-reactivity between aeroallergens and plant food belong to the group of pathogenesis-related proteins (PR-proteins), structural proteins (eg, profilins and oleosins), or seed storage proteins.[21]

Grasses

Grass pollen is currently regarded as the main cause of pollen allergy worldwide with sensitization rates varying between 10% and 30%.[22,23] Exposure to grass pollen is dependent on geographical location, and therefore it is plausible that the prevalence and clinical characteristics of food allergies due to grass pollen sensitization also exhibit geographical variations. In general, studies focusing on cross-reactive food allergies linked to 1 specific inhalant allergen are scarce, most probably because the majority of our pollen allergic patients are sensitized to multiple aeroallergens. Hitherto, most data with a specific focus on food allergies linked to grass pollen are coming from northern Europe.[4,24] Out of these studies, in which patients with a monosensitization to grass pollen were included, it appears that only 4% of patients develop a grass-pollen—related PFS.[4] However, more studies in different geographical areas are needed to obtain better insights into the prevalence and clinical features of secondary food allergies linked to grass pollen.

The other way around, grass pollen sensitization can profoundly hamper correct diagnosis of food allergy diagnosis because pollen contain various IgE-binding components or epitopes, such as profilins and cross-reactive carbohydrate determinants (CCDs), which most frequently fail to trigger effector cell degranulation *in vivo*.[13,25,26] The influence of grass pollen sensitization on food allergy diagnosis is nicely demonstrated in the study of Venter et al.[27] In this study, respectively up to 78% and 40.5% of the patients with a grass pollen allergy demonstrated a positive SPT and sIgE to wheat, whereas only 0.48% of the patients had a genuine IgE-mediated wheat allergy as proved by the challenge test. Similarly, in a study of Martens et al,[28] it was estimated that in the general population, because of grass pollen sensitization, 9% and 4.7% of the people would

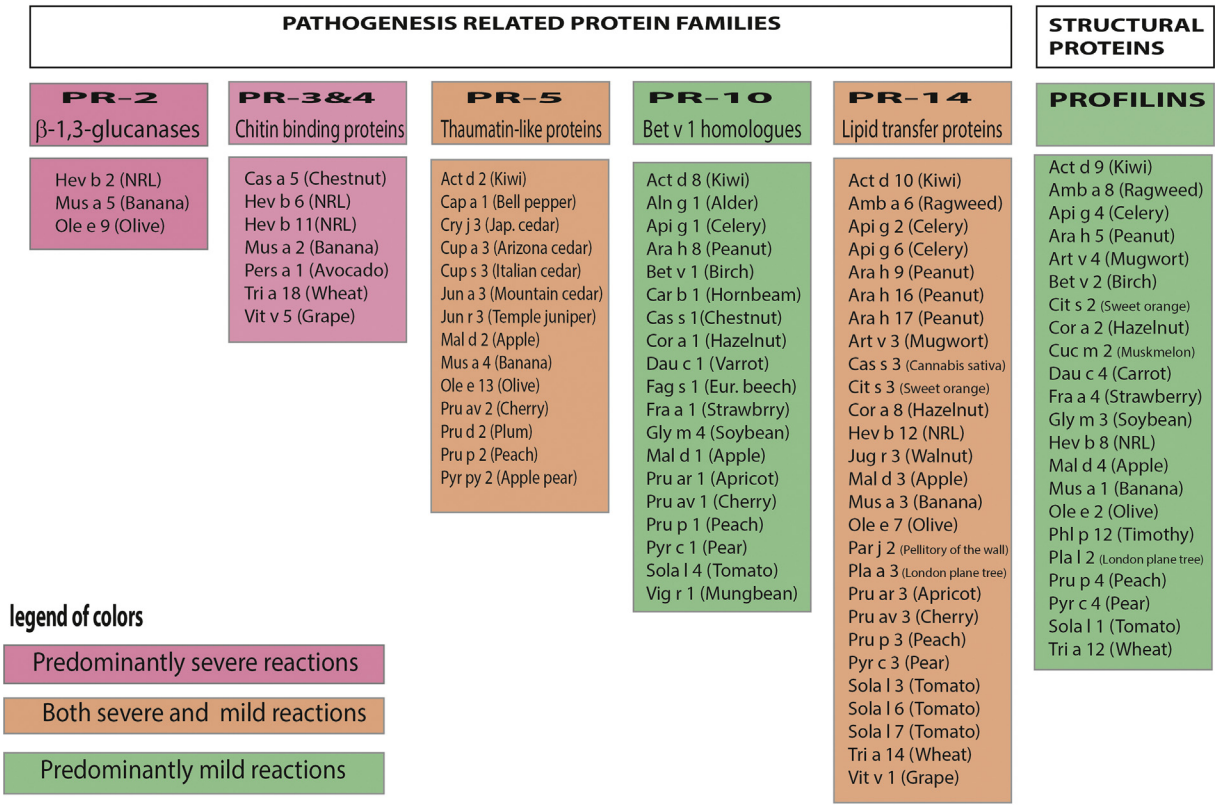


FIGURE 1. Overview of pathogenesis-related (PR) proteins and structural proteins (profilins) involved in cross-reactivity between aero-allergens and food (not exhaustive). *NRL*, Natural rubber latex.

have been erroneously diagnosed as allergic to cereals if diagnosis was only based on SPT and sIgE results, respectively.

As described above, sensitization to (grass) pollen profilins is a source for plant-derived cross-reactive food allergies only in a minority of patients.[29,30] Profilin is a structural protein present in all eukaryotic cells and does not resist thermal processing and pepsin digestion; therefore, sensitization is in general associated with symptoms restricted to the oropharynx, but severe allergic reactions to this structural protein have been rarely reported.[29,31-34] Theoretically, profilin can induce allergic symptoms to every plant-derived food, but as displayed in Figure 2, reactions predominantly involve melon, watermelon, tomato, banana, pineapple, and orange.[35] In children, kiwi, apricot, and cucumber seem also to be involved in profilin-related allergies.[36] A biomarker for profilin is Phl p 12 from timothy grass (*Phleum pratensis*).[37]

Trees

Birch. The best-known representative of the pollen-related food allergies is the "birch-fruit-vegetable syndrome" that results from a cross-reaction between the major allergen Bet v 1 from birch pollen (*Betula verrucosa*) and its labile homologues in many fruits, vegetables, and nuts. Sensitization to Bet v 1 is commonly described in the temperate climate zone of the northern hemisphere. Up to 70% of patients with birch pollen allergy can experience a "birch-fruit-vegetable syndrome"[38] mainly for Rosacea fruit (eg, apple, cherry, peach, pear), nuts (eg, hazelnut), and vegetables belonging to the *Apiacea* family (eg, celery, carrot).[4,38] Noticeably, some patients experience food allergic symptoms after typical Bet v 1 homologue—containing plant foods without suffering from inhalant symptoms during the tree pollen season. As shown in Figure 1, Bet v 1 belongs to the group of PR-proteins (PR-10). The PR-proteins are proteins that are induced in response to infections by pathogens such as fungi, bacteria, or viruses, or by noxious environmental factors.[39] The Bet v 1 homologues in plant foods are present in the peel and pulp and poorly resist both heating and gastric digestion.[40] These physiologic characteristics clarify why patients with the "birch-fruit-vegetable syndrome" generally experience localized symptoms restricted to the oropharynx when eating raw fruits, vegetables, and nuts. However, more generalized reactions are not excluded, particularly to Gly m 4 from soy (*Glycine max*).[41,42] Hitherto, the exact mechanism(s) for generalized reactions against labile Bet v 1 homologues are poorly understood, but it has been hypothesized that impairment of gastric digestion (eg, due to proton-pump inhibitors or bariatric surgery) might represent risk factors for more generalized allergic reactions in patients with a Bet v 1-related food allergy.[43-45] Like sensitization to profilins, sensitization to Bet v 1 does not necessarily trigger a birch-related food allergy and can also profoundly affect the outcome of traditional tests.[14,46,47]

Bet v 2, the birch pollen profilin, is another component able to induce cross-reactive sIgE antibodies. As exemplified in the grass pollen paragraph, the clinical relevance of sensitization to Bet v 2 is unpredictable.

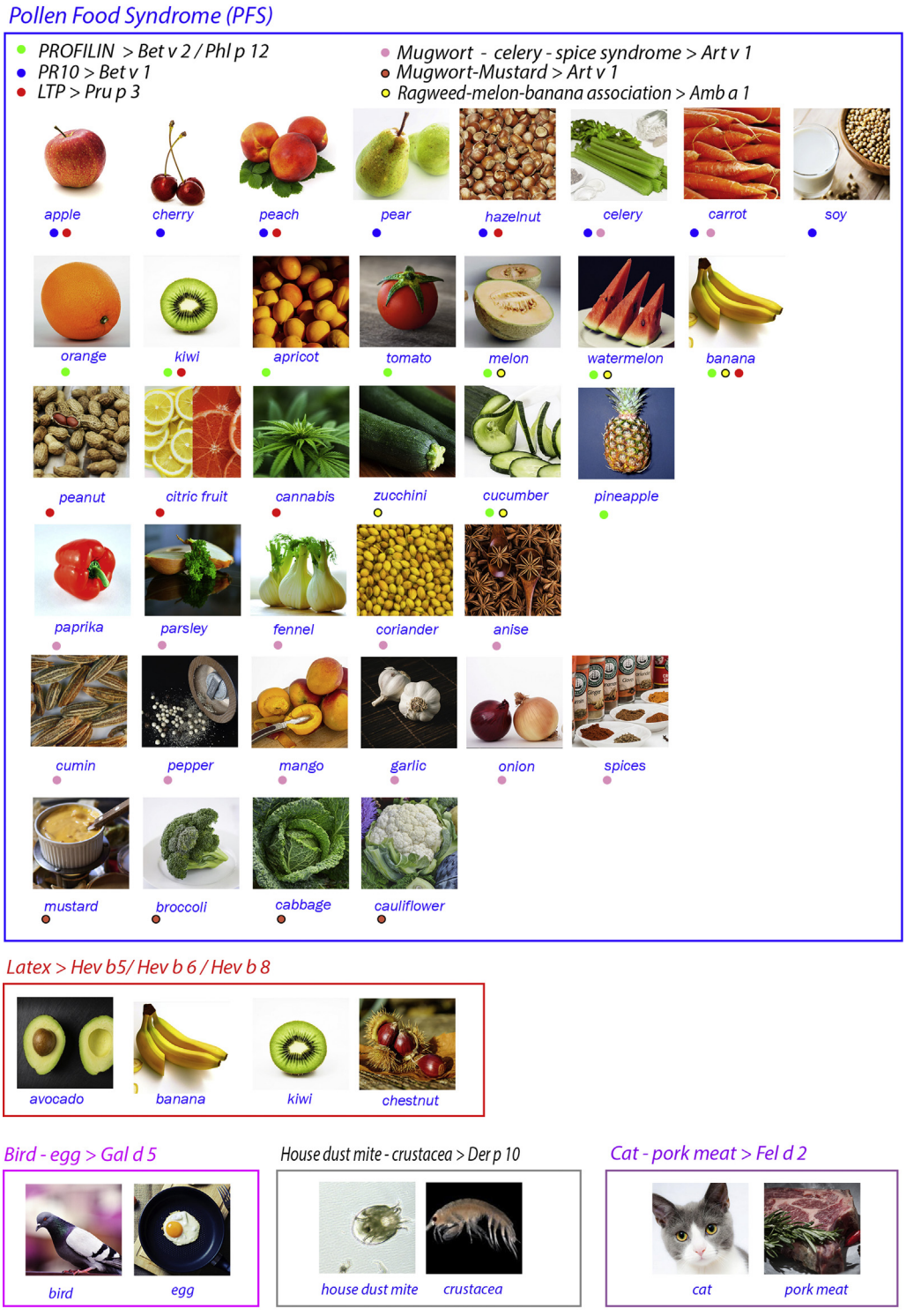


FIGURE 2. Overview of different cross-reactivity syndromes and their biomarkers (screening allergens). Colored dots in the figure display the plant foods (not exhaustive) most frequently involved in cross-reactivity between profilins (green), pathogenesis-related 10 proteins (PR-10) (blue), nonspecific lipid transfer proteins (ns-LTPs) (red), and plant foods most frequently involved in the celery-mugwort-spice syndrome (pink), mugwort-mustard allergy syndrome (orange), and ragweed-melon-banana association (white).

IgE antibodies specific for the minor allergen Bet v 6, an isoflavonoid reductase—homologous protein, have been shown to cross-react with proteins of comparable size in apple, pear, peach, orange, lychee fruit, strawberry, persimmon, zucchini, and carrot.[48]

Homologues of Bet v 7 and Bet v 8, a cyclophilin and a glutathione-S-transferase, respectively, are described in various plant foods, although cross-reactivity and clinical importance seem to be limited.[49,50]

Olive tree. Olive (*Olea europaea*) pollen are important aeroallergens, mainly in the Mediterranean area and California. Ole e 1 is repeatedly described as the major allergen in patients with olive pollinosis,[51-53] but is also recognized as a confounder in allergy diagnosis as it is highly glycosylated.[54]

Clinically relevant cross-reactions in patients sensitized to olive pollen have been described on several plant foods.[51,55] In a study of Florido Lopez et al,[55] approximately 30% of olive allergic patients experienced food allergic reactions. Peach, pear, melon, kiwi, and nuts have been reported as the predominant elicitors of secondary food allergies in patients with preexistent olive pollinosis. In a later study, the olive allergens Ole e 2, a profilin, and Ole e 7, a nonspecific lipid transfer protein (ns-LTP), are considered to be involved in the cross-reactivity with plant foods, and severity of the olive pollen—related food allergies seems to be dependent on the allergen involved in the cross-reactivity.[51] In this Spanish study, sensitization to olive profilin was detected in 90% of the patients experiencing symptoms restricted to the oropharynx, whereas severe allergic reactions were significantly associated with sensitization to Ole e 7 (ns-LTP).

Ns-LTPs belong to the PR-14 group and are recognized as important food allergens, especially in the Mediterranean basin.[56,57] Historically, sensitization towards ns-LTPs has mainly been associated with severe allergic reactions and attributed to a primary sensitization to Pru p 3, the ns-LTP from peach (*Prunus persica*).[58] However, paradigms about the ns-LTP syndrome are shifting as it appears that the ns-LPT syndrome is not necessarily governed by peach but might also be triggered by pollen.[59,60] Furthermore, patients do not necessarily exhibit severe reactions[20] but can be asymptomatic or only present a mild phenotype,[20,61] and finally the ns-LTP syndrome is certainly not restricted to the Mediterranean basin.[20,62]

Cross-reactivity between olive pollen and *Hevea* latex is also reported, and the glucanase in olive pollen (Ole e 9) might theoretically play a role in this "latex-fruit syndrome" as it demonstrates structural homology with the glucanase from natural rubber (*Hevea brasiliensis*, Hev b 2). Finally, recently a patient with olive pollinosis was reported, who developed olive fruit allergy, without having allergic symptoms to fruits other than olive, the name of "olive-olive syndrome" was proposed.[63]

Cypress. Pollen from cypresses (*Cupressus sp.pl*) are relevant inhalant allergens in the winter period, mainly for southern Europe, the coastal Mediterranean area, and Japan.[64]

The "cypress/peach syndrome" has received most attention, with symptoms ranging from mild to generalized allergic symptoms. The exact cross-reactive allergen has not yet been unraveled, although up to now 3 allergens have been proposed to be involved in the "cypress/peach syndrome."[65]

First, it has been repeatedly described that the ns-LTP of cypress pollen does cross-react with Pru p 3, the ns-LTP of peach,[60,65] and therefore could theoretically act as a trigger for the ns-LTP syndrome, although this has not yet been proven. Secondly, proteins belonging to the Snakin/gibberellin-regulated protein (GRP) family are thought to be causative allergens of the "cypress/peach syndrome."[64,66,67] Proteins of the Snakin/GRP family are widely distributed among plant species. Besides peach (Peamaclein, Pru p 7), they are also found in citrus, apples, oranges, grapes, castor beans, potatoes, and soybeans although detailed information about their allergenicity in these plant foods is still scarce.[68,69]

Finally, another allergen present in cypress pollen that might cross-react with plant foods, is Cup a 3 (*Cupressus arazonica*) belonging to the family of thaumatin-like proteins (TLPs). TLPs are identified in the pollen of cypress, birch, mugwort, olive, and plane trees.[70,71] Cross-reactivity between TLPs has been evaluated in a limited number of studies,[70,72] and only 1 study included TLPs from pollen.[70] This study of Palacin et al[70] included patients from different Spanish regions and showed evidence for cross-reactive allergy between TLPs from pollen and plant food. Because of the limited available clinical data, larger studies in different geographical areas are mandatory to evaluate the cross-reactive properties of TLPs.

Plane tree. Plane trees (*Platanus acerifolia*) are important inhalant allergens worldwide, mostly in urban regions.[73] In patients with plane tree pollinosis, hazelnuts, fruits (peach, apple, melon, and kiwi), peanuts, maize, chickpea, lettuce, and green beans are described as the most frequent causes of food allergic reactions.[74] These cross-reactive reactions cannot be explained by sensitization to the major inhalant allergens Pla 1 (invertase inhibitor) and Pla a 2 (polygalacturonase) nor by sensitization to profilins (Pla a 8).[75] Actually, the ns-LTP (Pla a 3) is assumed to be the most important allergen causing cross-reactivity to plant-derived food in plane tree allergic patients.[76,77] In a study of Scala et al,[78] a significant association was demonstrated between sensitization to Pla a 3 and having both mild symptoms restricted to the oropharynx and systemic reactions on plant food, and sensitization to Pla a 3 was inversely related to the presence of rhinoconjunctivitis or bronchial asthma.

Ficus tree. Sensitization to weeping fig (*Ficus benjamina*), a common indoor ornamental plant, can cause respiratory allergies in atopic as in otherwise nonatopic individuals.[79,80] It has been demonstrated that allergens are mainly present in the milky fluid ("latex") of the plant, and once transported to the leaf surfaces, they can accumulate in house dust, which explains the airborne sensitization route. Next to respiratory symptoms, cross-reactive allergic reactions on fresh and dried fig and other tropical fruits (eg, kiwi fruit, papaya, avocado, pineapple, and banana) are described in the so-called ficus-fruit syndrome. Figs are also involved in the "latex-fruit syndrome" as described later, but cross-reactivity in the "ficus-fruit syndrome" seems to be independent from sensitization to natural rubber latex (NRL).[79,81] Thiol proteases are assumed to be important cross-reactive allergens in this syndrome, as many patients with fig fruit allergy do show sIgE against papain, a thiol protease from papaya.[79,81,82]

Latex. NRL is obtained from the *H. brasiliensis* tree and has gained a lot of attention as allergen since the 1980s. A so-called latex-fruit syndrome has been described in 21% to 58% of individuals with an NRL allergy.[83,84] Clinical symptoms might be life threatening, and plant foods typically involved in the syndrome are avocado, banana, kiwifruit, and chestnut.[85] Among the NRL allergens, it has been demonstrated that class 1 chitinases (Hev b 6) do play a major role in the "latex-fruit syndrome." Class 1 chitinases have a defensive function, and Hev b 6 does show high sequence homology with chitinases present in fruits such as banana, avocado, and chestnut. Next to Hev b 6, many other NRL allergens (eg, profilin, glucanases, ns-LTPs) can add to the "latex-fruit syndrome." Furthermore, recently cassava (*Manihot esculenta*) and curry spice have been reported to cross-react with latex foods, and these reactions are thought to be due

to sensitization to Hev b 5 (protein with an unknown function) and Hev b 8 (profilin), respectively.[86-88] In a study of Beezhold et al,[83] cross-reactive reactions on potato and tomato were reported in NRL allergic patients; later these reactions were assigned to sensitization to Hev b 7, a patatin-like protein.[89-91] Also cross-reactive allergic symptoms on bell pepper have been described, which are thought to be due to cross-reactivity between Hev b 2, a beta-1,3-glucanase, and the bell pepper l-ascorbate peroxidase.[92] Finally, the ns-LTP of NRL (Hev b 12) has also been shown to be clinically relevant in a small number of NRL allergic patients.[93,94]

Like for other aeroallergens, sensitization to profilin (Hev b 8) might be clinically irrelevant and hamper diagnosis of NRL-related allergies, although some evidence for Hev b 8 sensitization with clinical relevancy does exist.[95-97] Finally, case reports mainly coming from France report cross-reactivity between NRL and spinach, although little is known about the eliciting allergen.[98,99]

Weeds

Mugwort. Mugwort (*Artemisia vulgaris*) is the most important allergenic weed in temperate and humid zones, and sensitization gives rise to late summer pollinosis.[100] Historically, several cross-reactive syndromes involving mugwort pollen have been described,[101-104] but on molecular level, these syndromes do not seem to rely on individual mugwort allergens but mainly ground on sensitization to panallergens such as profilins, Bet v 1 homologues, and ns-LTPs.[105]

One of the first syndromes described was the "celery-mugwort-spice syndrome," attributed to the cross-reactivity between mugwort pollen and members of the *Apiacea* family (celery, carrot, parsley, caraway seeds, fennel seeds, coriander seeds, and aniseeds).[101] But it appeared that also other botanical families such as the *Solanaceae* family (paprika), *Piperaceae* (pepper), *Anacardiaceae* family (mango), and the *Liliaceae* family (garlic, onion, leek) were involved in this cross-reactivity syndrome.[101,106,107] Currently, to the best of our knowledge, no epidemiologic data are available on the proportion of patients with an isolated mugwort allergy experiencing a mugwort-related PFS. It seems that this syndrome is caused by a mix of allergenic proteins, with a major role for profilins (Art v 4).[108,109] It has been assumed that also Bet v 1 homologues, which are not present in mugwort, play a role in this cross-reactive syndrome, and therefore it was proposed to extend the name to "celery-birch-mugwort-spice syndrome."[110] Next to profilins and Bet v 1 homologues, also high-molecular-weight allergens are described as relevant allergens in the "celery-birch-mugwort-spice syndrome" (eg, Api g 5 in celery).[111]

Another cross-reactive association with mugwort pollen is the "mugwort-mustard allergy syndrome," which most frequently presents as mild OAS on ingestion of mustard.[112] Within this syndrome, also vegetables from the Brassicaceae family (eg, broccoli, cabbage, and cauliflower) might cause allergic symptoms. Exact numbers on the prevalence of mustard allergy and/or allergic reactions on vegetable of the Brassicaceae family are lacking. However, it has been demonstrated that 37 of 38 patients with mustard allergy were sensitized to mugwort pollen and that all of these patients were allergic to other foods belonging to the Brassicaceae family.[112] The causative allergens are still a matter of intense research, but profilins, ns-LTPs, and high-molecular-weight allergens are assumed as candidates.[105,112]

Finally, also a mugwort-peach association has been proposed with the description of cross-reactivity between mugwort pollen, peach, and related Rosacea fruits. These cross-reactivities have been attributed to sensitization to ns-LTPs.[104,113,114]

Ragweed. *Ambrosia artemisiifolia* (ragweed) is a major inhalant allergen in the United States, but sensitization to ragweed is also increasing in Europe, Australia, and Asia.[115] Cross-reactivity between ragweed pollen and food was described for the first time almost 50 years ago.[116] At that time, it was given the name of "ragweed-melon-banana association," involving members of the gourd family (melon, watermelon, zucchini, and cucumber) and banana.[108,116] It has been thought that this "ragweed-melon-banana association" is mainly due to sensitization to profilin, but involvement of ns-LTPs and glycoallergens cannot be completely ruled out.[105,108]

CROSS-REACTIVE AEROALLERGENS OF FUNGAL ORIGIN

Sensitization rates for fungal species depend on geographic location and range from 6% to 24% in the general population.[117] Herrera et al[118] described the association between airborne mold allergy in asthmatics and allergic reactions to spinach and mushroom.[12,118] This phenomenon is supposed to be rare and is also referred to as "Alternaria-spinach syndrome." It has been thought to be based on cross-reactivity between a protein present in spinach and mushroom, with a molecular weight similar to the major allergens of *Alternaria alternata* (Alt a 1) and *Cladosporium herbarum* (Cla h 1).[12] Furthermore, a few case reports have been published describing patients with sensitization to inhalant fungal allergen(s), having severe IgE-mediated allergic reactions on food containing molds or yeasts.[119,120] Finally, patients sensitized to airborne mold allergens might rarely experience immediate allergic reactions on ingesting Quorn, which contains mycoprotein originating from the mold *Fusarium venenatum*.[121] It has been hypothesized that a 60S acidic ribosomal protein P2 present in *F. venenatum* is the responsible allergen for this mold-Quorn association.[122]

CROSS-REACTIVE AEROALLERGENS OF INVERTEBRATE ANIMAL ORIGIN

House dust mite

House dust mite (HDM) is an important perennial allergen source and a significant cause of allergic rhinitis and asthma. Cross-reactivity between allergens present in HDM and invertebrates, such as shellfish and edible insects, is frequently described.[123,124]

Most cross-reactive reactions are believed to result from sensitization to tropomyosin.[10] Tropomyosin is a minor allergen in HDM (*Dermatophagoides pteronyssinus*, Der p 10), although often described as a major allergen in shellfish particularly in crustaceans (shrimp, lobster, crab), molluscs (mussels, oysters, scallops, octopus, squids, snails, abalones, clams, razor shell), and cockroaches.[125-136] Whether HDM immunotherapy can rarely induce shellfish allergy remains controversial with pros[137-139] and cons,[140] and might be related to differences in particular components (eg, tropomyosin) present in the immunotherapy preparations. Next to tropomyosin, also other allergenic components present in HDM and shellfish are able to cause cross-reactive reactions. Amongst them arginine kinase, myosin

light chain, sarcoplasmic calcium-binding protein, and hemocyanin are the most relevant.[123,141,142] Because of the extensive *in vitro* and *in vivo* cross-reactivity, allergy tests for the diagnosis of shellfish allergy should always be interpreted with caution, especially in HDM allergic patients. In a study of Thalayasingam et al,[143] it was demonstrated that 26.3% of HDM allergic patients tolerating shrimp showed false-positive sIgE antibodies to a shrimp extract. As a matter of fact, the clinical relevance of positive sIgE and/or SPT to shrimp varies from 13% to 67% depending on the inclusion criteria.[144-146] These numbers underline that a food challenge is essential in patients with an unclear history of allergic symptoms to shellfish, particularly in those patients with an HDM sensitization. Besides that, the literature does not support the recommendation to (preventively) avoid crustaceans, molluscs, or edible insects in HDM allergic patients.

Finally, patients with HDM allergy might also react directly to mite allergens in food. In the so-called pancake syndrome, patients might develop (severe) allergic reactions after ingestion of food containing mite-contaminated flour.[147,148]

CROSS-REACTIVE AEROALLERGENS OFF VERTEBRATE ANIMAL ORIGIN

The most relevant cross-reactions between food and aeroallergens from mammalian and avian origin are the "pork-cat syndrome" and the "bird-egg syndrome."

The "pork-cat syndrome" was reported for the first time in France and is an IgE-mediated reaction on porcine meat triggered by a primary sensitization to the serum albumin present in cat dander (*Felis domesticus,* Fel d 2). Overall, it has been estimated that 1% to 3% of patients sensitized to cat, mainly older children or adults, are at risk to develop allergic symptoms on ingestion of mainly raw pork.[149] In general, allergic symptoms occur immediately after consumption of pork meat and can range from mild allergic symptoms restricted to the oropharynx to severe generalized symptoms. The fact that symptoms appear soon after ingestion of the meat might be helpful in differentiating "pork-cat syndrome" from delayed anaphylaxis to red meat due to sensitization to alpha-gal. Serum albumins are heat labile, and therefore allergic reactions do most frequently occur on fresh meat or dried and smoked pork. Next to allergic symptoms on pork meat, some patients with the cat/pork syndrome do experience allergic symptoms on consumption of beef meat, chicken meat, and fresh milk.[150-152] Furthermore, also horse, dog, and hamster dander have been described as primary sensitizers for serum albumin—related meat allergy.[150,153,154]

In the "bird-egg syndrome," respiratory sensitization to bird allergens causes cross-reactive allergy symptoms on the ingestion of egg.[155] This syndrome is due to cross-reactivity between airborne bird serum proteins and serum albumins present in egg yolk (eg, *Gallus domesticus*, Gal d 5). Clinical symptoms reported on raw or soft boiled egg yolk are varying from oral and/or gastrointestinal symptoms to systemic reactions.[156] Typically, egg allergy starts in early childhood and is likely to be outgrown; however, egg allergy within the "bird-egg syndrome" oftentimes occurs at later age and is persisting.[157] Although cross-sensitization to poultry meat is common in patients with "bird-egg syndrome," true clinical reactions after meat ingestion are reported, but appear to be rare, probably because chicken meat is consumed well cooked and serum albumins are heat labile.[158] Actually, sensitization to egg-yolk proteins could also predispose some patients to respiratory symptoms from birds (egg-bird syndrome).[157] Finally, also reported is an "egg-egg syndrome," in which airborne egg proteins used in the occupational setting (bakery and confectionery industry) induced cross-reactivity to ingested eggs.[159]

DIAGNOSIS

Like for all IgE-mediated diseases, a diagnostic approach of (secondary) food allergy starts with a thorough clinical history with a main focus on the inhalant allergy and potential related cross-reactivities and should further be pieced together using different *in vitro* and *in vivo* tests. In general, clinical suspicion of the underlying inhalant allergy is easily documented using traditional extract-based skin tests and sIgE antibody assays. In contrast, correct diagnosis of the related food allergies is oftentimes more challenging and poses significant difficulties, mainly because of the poor specificity of the available tests. As described above, a positive skin test and/or sIgE results do not necessarily reflect genuine allergy but merely clinically irrelevant sensitization. Currently available diagnostic methods have only a limited predictive value for the outcome of oral provocation testing or the severity of a clinical reaction. The reason why some sensitizations do result in allergic symptoms and other sensitizations are clinically irrelevant is currently unknown; however, it has been hypothesized that this might depend on inhibitory mechanisms,[160] specific IgG4 response,[161] the affinity of IgE antibodies, and the valency of allergens.[162,163] Furthermore, the clinical outcome also depends on the amount of allergen and/or allergenicity of the allergen ingested, which has been described to depend on different factors such as the cultivation conditions, ripeness of the fruit, and postharvest storage.[164,165]

In many occasions, additional tests such as molecular diagnosis, BAT, and eventually food challenges might be required for correct diagnosis and also to avoid unnecessarily restrictive diets. However, it should be emphasized that even these diagnostics do not display absolute predictive values and not all are easily accessible for mainstream use. For example, molecular diagnostics have been demonstrated to be of little value to diagnose Bet v 1-related food allergies, as the technique fails to discriminate between patients sensitized to birch with and without cross-reactive food allergy.[14,46] Therefore, in a patient with allergic reactions to related plant foods containing cross-reactive allergens out of the same protein family, it is commonly sufficient to test a gatekeeper/only 1 member of this cross-reactive allergen family. Additional tests would only demonstrate more cross-reactions with questionable clinical relevance. Furthermore, CCD-free recombinant proteins can benefit the identification of clinically irrelevant sIgE originating from a sensitization to plant and invertebrate CCDs as frequently observed in sensitization to grass and weed pollen.[13]

BATs might, to some extent, be helpful in discriminating between patients with a clinically significant sensitization and patients who are merely sensitized, as it reflects a functional response rather than sensitization.[18,20] More studies are needed to validate BAT and to allow its entrance in mainstream use.

Finally, in cases of an unclear history or inconclusive tests, oral provocations are mandatory to correctly diagnose food allergic patients and give correct dietary advices.

TREATMENT

If the diagnosis of a food allergy due to cross-reactions is confirmed, elimination diets should be recommended. In this review, it has been repeatedly shown that inhalant allergens might cause positive tests to cross-reacting foods that might not have any clinical implication. Therefore, elimination diets should never be based on sensitization profiles only, and besides that, it is not recommended to preventively avoid potential cross-reactive food sources.

The acute management of a food allergy and treatment of the different inhalant allergies potentially responsible for a secondary food allergy are beyond the scope of this review. The decision to prescribe an epinephrine autoinjector should be based on risk stratification for the individual patient (eg, likelihood of a systemic reaction, comorbidities, sensitization profile, foods involved, ease of access to emergency treatment).[166]

Hitherto, the evidence for immunotherapy modifying the underlying inhalant allergy to be efficacious to treat the associated cross-reactivities is contradictory. Beneficial effects of allergen immunotherapy on pollen-related food allergies have been described.[167,168] However, these results could not be reproduced in other studies.[169-171] Therefore, at present secondary food allergies do not justify immunotherapy to cross-reactive inhalants.

GENERAL CONCLUSIONS

A significant part of all IgE-mediated food allergies results from sensitization to cross-reactive structures present in food and inhalant allergens. The clinical presentation of secondary food allergies can be very heterogeneous and vary between mild symptoms restricted to the oropharynx and severe generalized reactions, including life-threatening anaphylaxis. Correct diagnosis of these cross-reactive food allergies is not always straightforward, mainly because the available diagnostic tests do not have an absolute predictive value. As a matter of fact, cross-reactivity might severely hinder food allergy diagnosis, as positive tests to cross-reacting foods might not correctly predict safe consumption. Therefore, recognition of cross-reactive patterns and associated allergic symptoms is the cornerstone of correct diagnosis and is needed for correct interpretation of diagnostic tests. In cases of vague histories or inconclusive tests, oral provocations are indicated. If the diagnosis of a cross-reactive food allergy is confirmed, elimination diets should be recommended and an epinephrine autoinjector should be prescribed in severe cases.

REFERENCES

1. Nathan RA, Meltzer EO, Derebery J, Campbell UB, Stang PE, Corrao MA, et al. The prevalence of nasal symptoms attributed to allergies in the United States: findings from the burden of rhinitis in an America survey. Allergy Asthma Proc 2008;29:600-8.
2. Linneberg A, Dam Petersen K, Hahn-Pedersen J, Hammerby E, Serup-Hansen N, Boxall N. Burden of allergic respiratory disease: a systematic review. Clin Mol Allergy 2016;14:12.
3. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J 2004;24:758-64.
4. Osterballe M, Hansen TK, Mortz CG, Bindslev-Jensen C. The clinical relevance of sensitization to pollen-related fruits and vegetables in unselected pollen-sensitized adults. Allergy 2005;60:218-25.
5. Turner PJ, Jerschow E, Umasunthar T, Lin R, Campbell DE, Boyle RJ. Fatal anaphylaxis: mortality rate and risk factors. J Allergy Clin Immunol Pract 2017;5:1169-78.
6. Werfel T, Asero R, Ballmer-Weber BK, Beyer K, Enrique E, Knulst AC, et al. Position paper of the EAACI: food allergy due to immunological cross-reactions with common inhalant allergens. Allergy 2015;70:1079-90.
7. Popescu FD. Cross-reactivity between aeroallergens and food allergens. World J Methodol 2015;5:31-50.
8. Hofmann A, Burks AW. Pollen food syndrome: update on the allergens. Curr Allergy Asthma Rep 2008;8:413-7.
9. Ebo DG, Swerts S, Sabato V, Hagendorens MM, Bridts CH, Jorens PG, et al. New food allergies in a European non-Mediterranean region: is *Cannabis sativa* to blame? Int Arch Allergy Immunol 2013;161:220-8.
10. Wong L, Huang CH, Lee BW. Shellfish and house dust mite allergies: is the link tropomyosin? Allergy Asthma Immunol Res 2016;8:101-6.
11. Hilger C, van Hage M, Kuehn A. Diagnosis of allergy to mammals and fish: cross-reactive vs. specific markers. Curr Allergy Asthma Rep 2017;17:64.
12. Herrera-Mozo I, Ferrer B, Luis Rodriguez-Sanchez J, Juarez C. Description of a novel panallergen of cross-reactivity between moulds and foods. Immunol Invest 2006;35:181-97.
13. Ebo DG, Hagendorens MM, Bridts CH, De Clerck LS, Stevens WJ. Sensitization to cross-reactive carbohydrate determinants and the ubiquitous protein profilin: mimickers of allergy. Clin Exp Allergy 2004;34:137-44.
14. Ebo DG, Bridts CH, Verweij MM, De Knop KJ, Hagendorens MM, De Clerck LS, et al. Sensitization profiles in birch pollen-allergic patients with and without oral allergy syndrome to apple: lessons from multiplexed component-resolved allergy diagnosis. Clin Exp Allergy 2010;40:339-47.
15. Van Gasse AL, Mangodt EA, Faber M, Sabato V, Bridts CH, Ebo DG. Molecular allergy diagnosis: status anno 2015. Clin Chim Acta 2015;444:54-61.
16. Santos AF, Shreffler WG. Road map for the clinical application of the basophil activation test in food allergy. Clin Exp Allergy 2017;47:1115-24.
17. Faber M, Sabato V, De Witte L, Van Gasse A, Hagendorens MM, Leysen J, et al. State of the art and perspectives in food allergy (part I): diagnosis. Curr Pharm Des 2014;20:954-63.
18. Santos AF, Douiri A, Becares N, Wu SY, Stephens A, Radulovic S, et al. Basophil activation test discriminates between allergy and tolerance in peanut-sensitized children. J Allergy Clin Immunol 2014;134:645-52.
19. Ebo DG, Hagendorens MM, Bridts CH, Schuerwegh AJ, De Clerck LS, Stevens WJ. Flow cytometric analysis of in vitro activated basophils, specific IgE and skin tests in the diagnosis of pollen-associated food allergy. Cytometry B Clin Cytom 2005;64:28-33.
20. Faber MA, Van Gasse AL, Decuyper II, Uyttebroek A, Sabato V, Hagendorens MM, et al. IgE-reactivity profiles to nonspecific lipid transfer proteins in a northwestern European country. J Allergy Clin Immunol 2017;139:679-682.e5.
21. Breiteneder H, Radauer C. A classification of plant food allergens. J Allergy Clin Immunol 2004;113:821-30. quiz 31.
22. Garcia-Mozo H. Poaceae pollen as the leading aeroallergen worldwide: a review. Allergy 2017;72:1849-58.
23. Newson RB, van Ree R, Forsberg B, Janson C, Lotvall J, Dahlen SE, et al. Geographical variation in the prevalence of sensitization to common aeroallergens in adults: the GA(2) LEN survey. Allergy 2014;69:643-51.
24. Ghunaim N, Gronlund H, Kronqvist M, Gronneberg R, Soderstrom L, Ahlstedt S, et al. Antibody profiles and self-reported symptoms to pollen-related food allergens in grass pollen-allergic patients from northern Europe. Allergy 2005;60:185-91.
25. 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;103:1005-11.
26. Mari A, Ooievaar-de Heer P, Scala E, Giani M, Pirrotta L, Zuidmeer L, et al. Evaluation by double-blind placebo-controlled oral challenge of the clinical relevance of IgE antibodies against plant glycans. Allergy 2008;63:891-6.
27. Venter C, Maslin K, Arshad SH, Patil V, Grundy J, Glasbey G, et al. Very low prevalence of IgE mediated wheat allergy and high levels of cross-sensitisation between grass and wheat in a UK birth cohort. Clin Transl Allergy 2016;6:22.
28. Martens M, Schnoor HJ, Malling HJ, Poulsen LK. Sensitization to cereals and peanut evidenced by skin prick test and specific IgE in food-tolerant, grass pollen allergic patients. Clin Transl Allergy 2011;1:15.
29. Santos A, Van Ree R. Profilins: mimickers of allergy or relevant allergens? Int Arch Allergy Immunol 2011;155:191-204.
30. Rodriguez Del Rio P, Diaz-Perales A, Sanchez-Garcia S, Escudero C, Ibanez MD, Mendez-Brea P, et al. Profilin, a change in the paradigm. J Investig Allergol Clin Immunol 2018;28:1-12.
31. Alvarado MI, Jimeno L, De La Torre F, Boissy P, Rivas B, Lazaro MJ, et al. Profilin as a severe food allergen in allergic patients overexposed to grass pollen. Allergy 2014;69:1610-6.
32. Fah J, Wuthrich B, Vieths S. Anaphylactic reaction to lychee fruit: evidence for sensitization to profilin. Clin Exp Allergy 1995;25:1018-23.

33. Reindl J, Anliker MD, Karamloo F, Vieths S, Wuthrich B. Allergy caused by ingestion of zucchini (*Cucurbita pepo*): characterization of allergens and cross-reactivity to pollen and other foods. J Allergy Clin Immunol 2000;106:379-85.
34. Wensing M, Akkerdaas JH, van Leeuwen WA, Stapel SO, Bruijnzeel-Koomen CA, Aalberse RC, et al. IgE to Bet v 1 and profilin: cross-reactivity patterns and clinical relevance. J Allergy Clin Immunol 2002;110:435-42.
35. Asero R, Mistrello G, Roncarolo D, Amato S, Zanoni D, Barocci F, et al. Detection of clinical markers of sensitization to profilin in patients allergic to plant-derived foods. J Allergy Clin Immunol 2003;112:427-32.
36. Asero R, Tripodi S, Dondi A, Di Rienzo Businco A, Sfika I, Bianchi A, et al. Prevalence and clinical relevance of IgE sensitization to profilin in childhood: a multicenter study. Int Arch Allergy Immunol 2015;168:25-31.
37. Cipriani F, Mastrorilli C, Tripodi S, Ricci G, Perna S, Panetta V, et al. Diagnostic relevance of IgE sensitization profiles to eight recombinant *Phleum pratense* molecules. Allergy 2018;73:673-82.
38. Geroldinger-Simic M, Zelniker T, Aberer W, Ebner C, Egger C, Greiderer A, et al. Birch pollen-related food allergy: clinical aspects and the role of allergen-specific IgE and IgG4 antibodies. J Allergy Clin Immunol 2011;127:616-622.e1.
39. Shahali Y, Dadar M. Plant food allergy: influence of chemicals on plant allergens. Food Chem Toxicol 2018;115:365-74.
40. Webber CM, England RW. Oral allergy syndrome: a clinical, diagnostic, and therapeutic challenge. Ann Allergy Asthma Immunol 2010;104:101-8. quiz 9-10, 17.
41. Kleine-Tebbe J, Vogel L, Crowell DN, Haustein UF, Vieths S. Severe oral allergy syndrome and anaphylactic reactions caused by a Bet v 1-related PR-10 protein in soybean, SAM22. J Allergy Clin Immunol 2002;110:797-804.
42. Ballmer-Weber BK, Holzhauser T, Scibilia J, Mittag D, Zisa G, Ortolani C, et al. Clinical characteristics of soybean allergy in Europe: a double-blind, placebo-controlled food challenge study. J Allergy Clin Immunol 2007;119:1489-96.
43. Shakeri-Leidenmuhler S, Lukschal A, Schultz C, Bohdjalian A, Langer F, Birsan T, et al. Surgical elimination of the gastric digestion by Roux-en-Y gastric bypass impacts on food sensitisation—a pilot study. Obes Surg 2015;25:2268-75.
44. Untersmayr E, Jensen-Jarolim E. The role of protein digestibility and antacids on food allergy outcomes. J Allergy Clin Immunol 2008;121:1301-8. quiz 9-10.
45. Blockhuys M, Faber MA, Sabato V, Hubens G, Ebo DG. Bariatric surgery: a novel risk factor for food allergy? Int Arch Allergy Immunol 2017;172:64-6.
46. Faber MA, De Graag M, Van Der Heijden C, Sabato V, Hagendorens MM, Bridts CH, et al. Cor a 14: missing link in the molecular diagnosis of hazelnut allergy? Int Arch Allergy Immunol 2014;164:200-6.
47. Faber MA, Donne I, Herrebosch E, Sabato V, Hagendorens MM, Bridts CH, et al. Sensitization profiles to peanut allergens in Belgium; cracking the code in infants, children and adults. Acta Clin Belg 2016;71:32-7.
48. Karamloo F, Wangorsch A, Kasahara H, Davin LB, Haustein D, Lewis NG, et al. Phenylcoumaran benzylic ether and isoflavonoid reductases are a new class of cross-reactive allergens in birch pollen, fruits and vegetables. Eur J Biochem 2001;268:5310-20.
49. Cadot P, Nelles L, Srahna M, Dilissen E, Ceuppens JL. Cloning and expression of the cyclophilin Bet v 7, and analysis of immunological cross-reactivity among the cyclophilin A family. Mol Immunol 2006;43:226-35.
50. Deifl S, Zwicker C, Vejvar E, Kitzmuller C, Gadermaier G, Nagl B, et al. Glutathione-S-transferase: a minor allergen in birch pollen due to limited release from hydrated pollen. PLoS One 2014;9:e109075.
51. Quiralte J, Palacios L, Rodriguez R, Cardaba B, Arias de Saavedra JM, Villalba M, et al. Modelling diseases: the allergens of *Olea europaea* pollen. J Investig Allergol Clin Immunol 2007;17(Suppl 1):24-30.
52. Barber D, de la Torre F, Feo F, Florido F, Guardia P, Moreno C, et al. Understanding patient sensitization profiles in complex pollen areas: a molecular epidemiological study. Allergy 2008;63:1550-8.
53. Quiralte J, Florido F, Arias de Saavedra JM, Gomez A, Saenz de San Pedro B, Gonzalez E, et al. Olive allergen-specific IgE responses in patients with *Olea europaea* pollinosis. Allergy 2002;57(Suppl 71):47-52.
54. Batanero E, Villalba M, Rodriguez R. Glycosylation site of the major allergen from olive tree pollen. Allergenic implications of the carbohydrate moiety. Mol Immunol 1994;31:31-7.
55. Florido Lopez JF, Quiralte Enriquez J, Arias de Saavedra Alias JM, Saenz de San Pedro B, Martin Casanez E. An allergen from *Olea europaea* pollen (Ole e 7) is associated with plant-derived food anaphylaxis. Allergy 2002;57(Suppl 71):53-9.
56. Pascal M, Munoz-Cano R, Reina Z, Palacin A, Vilella R, Picado C, et al. Lipid transfer protein syndrome: clinical pattern, cofactor effect and profile of molecular sensitization to plant-foods and pollens. Clin Exp Allergy 2012;42:1529-39.
57. Scala E, Till SJ, Asero R, Abeni D, Guerra EC, Pirrotta L, et al. Lipid transfer protein sensitization: reactivity profiles and clinical risk assessment in an Italian cohort. Allergy 2015;70:933-43.
58. Schulten V, Nagl B, Scala E, Bernardi ML, Mari A, Ciardiello MA, et al. Pru p 3, the nonspecific lipid transfer protein from peach, dominates the immune response to its homolog in hazelnut. Allergy 2011;66:1005-13.
59. Lombardero M, Garcia-Selles FJ, Polo F, Jimeno L, Chamorro MJ, Garcia-Casado G, et al. Prevalence of sensitization to Artemisia allergens Art v 1, Art v 3 and Art v 60 kDa. Cross-reactivity among Art v 3 and other relevant lipid-transfer protein allergens. Clin Exp Allergy 2004;34:1415-21.
60. Sanchez-Lopez J, Asturias JA, Enrique E, Suarez-Cervera M, Bartra J. *Cupressus arizonica* pollen: a new pollen involved in the lipid transfer protein syndrome? J Investig Allergol Clin Immunol 2011;21:522-6.
61. Pascal M, Vazquez-Ortiz M, Folque MM, Jimenez-Feijoo R, Lozano J, Dominguez O, et al. Asymptomatic LTP sensitisation is common in plant-food allergic children from the Northeast of Spain. Allergol Immunopathol (Madr) 2016;44:351-8.
62. Mothes-Luksch N, Raith M, Stingl G, Focke-Tejkl M, Razzazi-Fazeli E, Zieglmayer R, et al. Pru p 3, a marker allergen for lipid transfer protein sensitization also in Central Europe. Allergy 2017;72:1415-8.
63. Unsel M, Ardeniz O, Mete N, Ersoy R, Sin AZ, Gulbahar O, et al. Food allergy due to olive. J Investig Allergol Clin Immunol 2009;19:497-9.
64. Charpin D, Pichot C, Belmonte J, Sutra JP, Zidkova J, Chanez P, et al. Cypress pollinosis: from tree to clinic [published online ahead of print April 11, 2017]. Clin Rev Allergy Immunol. https://doi.org/10.1007/s12016-017-8602-y.
65. Caimmi D, Barber D, Hoffmann-Sommergruber K, Amrane H, Bousquet PJ, Dhivert-Donnadieu H, et al. Understanding the molecular sensitization for cypress pollen and peach in the Languedoc-Roussillon area. Allergy 2013;68:249-51.
66. Inomata N, Okazaki F, Moriyama T, Nomura Y, Yamaguchi Y, Honjoh T, et al. Identification of peamaclein as a marker allergen related to systemic reactions in peach allergy. Ann Allergy Asthma Immunol 2014;112:175-177.e3.
67. Tuppo L, Alessandri C, Pomponi D, Picone D, Tamburrini M, Ferrara R, et al. Peamaclein—a new peach allergenic protein: similarities, differences and misleading features compared to Pru p 3. Clin Exp Allergy 2013;43:128-40.
68. Senechal H, Santrucek J, Melcova M, Svoboda P, Zidkova J, Charpin D, et al. A new allergen family involved in pollen food-associated syndrome: Snakin/gibberellin-regulated proteins. J Allergy Clin Immunol 2018;141:411-414.e4.
69. Inomata N, Miyakawa M, Aihara M. High prevalence of sensitization to gibberellin-regulated protein (peamaclein) in fruit allergies with negative immunoglobulin E reactivity to Bet v 1 homologs and profilin: clinical pattern, causative fruits and cofactor effect of gibberellin-regulated protein allergy. J Dermatol 2017;44:735-41.
70. Palacin A, Rivas LA, Gomez-Casado C, Aguirre J, Tordesillas L, Bartra J, et al. The involvement of thaumatin-like proteins in plant food cross-reactivity: a multicenter study using a specific protein microarray. PLoS One 2012;7:e44088.
71. Cortegano I, Civantos E, Aceituno E, del Moral A, Lopez E, Lombardero M, et al. Cloning and expression of a major allergen from *Cupressus arizonica* pollen, Cup a 3, a PR-5 protein expressed under polluted environment. Allergy 2004;59:485-90.
72. Palacin A, Tordesillas L, Gamboa P, Sanchez-Monge R, Cuesta-Herranz J, Sanz ML, et al. Characterization of peach thaumatin-like proteins and their identification as major peach allergens. Clin Exp Allergy 2010;40:1422-30.
73. Asturias JA, Ibarrola I, Bartolome B, Ojeda I, Malet A, Martinez A. Purification and characterization of Pla a 1, a major allergen from *Platanus acerifolia* pollen. Allergy 2002;57:221-7.
74. Enrique E, Cistero-Bahima A, Bartolome B, Alonso R, San Miguel-Moncin MM, Bartra J, et al. *Platanus acerifolia* pollinosis and food allergy. Allergy 2002;57:351-6.
75. Enrique E, Alonso R, Bartolome B, San Miguel-Moncin M, Bartra J, Fernandez-Parra B, et al. IgE reactivity to profilin in *Platanus acerifolia* pollen-sensitized subjects with plant-derived food allergy. J Investig Allergol Clin Immunol 2004;14:335-42.
76. Wangorsch A, Larsson H, Messmer M, Garcia-Moral A, Lauer I, Wolfheimer S, et al. Molecular cloning of plane pollen allergen Pla a 3 and its utility as diagnostic marker for peach associated plane pollen allergy. Clin Exp Allergy 2016;46:764-74.
77. Lauer I, Miguel-Moncin MS, Abel T, Foetisch K, Hartz C, Fortunato D, et al. Identification of a plane pollen lipid transfer protein (Pla a 3) and its immunological relation to the peach lipid-transfer protein, Pru p 3. Clin Exp Allergy 2007;37:261-9.
78. Scala E, Cecchi L, Abeni D, Guerra EC, Pirrotta L, Locanto M, et al. Pla a 2 and Pla a 3 reactivities identify plane tree-allergic patients with respiratory symptoms or food allergy. Allergy 2017;72:671-4.

79. Hemmer W, Focke M, Gotz M, Jarisch R. Sensitization to *Ficus benjamina*: relationship to natural rubber latex allergy and identification of foods implicated in the Ficus-fruit syndrome. Clin Exp Allergy 2004;34:1251-8.
80. Mahillon V, Saussez S, Michel O. High incidence of sensitization to ornamental plants in allergic rhinitis. Allergy 2006;61:1138-40.
81. Focke M, Hemmer W, Wohrl S, Gotz M, Jarisch R. Cross-reactivity between *Ficus benjamina* latex and fig fruit in patients with clinical fig allergy. Clin Exp Allergy 2003;33:971-7.
82. Diez-Gomez ML, Quirce S, Aragoneses 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.
83. Beezhold DH, Sussman GL, Liss GM, Chang NS. Latex allergy can induce clinical reactions to specific foods. Clin Exp Allergy 1996;26:416-22.
84. Brehler R, Theissen U, Mohr C, Luger T. "Latex-fruit syndrome": frequency of cross-reacting IgE antibodies. Allergy 1997;52:404-10.
85. Cabanes N, Igea JM, de la Hoz B, Agustin P, Blanco C, Dominguez J, et al. Latex allergy: position paper. J Investig Allergol Clin Immunol 2012;22:313-30. quiz 30.
86. Santos KS, Gadermaier G, Vejvar E, Arcuri HA, Galvao CE, Yang AC, et al. Novel allergens from ancient foods: Man e 5 from manioc (*Manihot esculenta* Crantz) cross reacts with Hev b 5 from latex. Mol Nutr Food Res 2013;57:1100-9.
87. Yagami A, Nakazawa Y, Suzuki K, Matsunaga K. Curry spice allergy associated with pollen-food allergy syndrome and latex fruit-syndrome. J Dermatol 2009;36:45-9.
88. Gaspar A, Raulf-Heimsoth M, Rihs HP, Pires G, Morais-Almeida M. Hev b 5: latex allergen implicated in clinically relevant cross-reactivity with manioc. J Investig Allergol Clin Immunol 2012;22:450-1.
89. Reche M, Pascual CY, Vicente J, Caballero T, Martin-Munoz F, Sanchez S, et al. Tomato allergy in children and young adults: cross-reactivity with latex and potato. Allergy 2001;56:1197-201.
90. Kostyal DA, Hickey VL, Noti JD, Sussman GL, Beezhold DH. Cloning and characterization of a latex allergen (Hev b 7): homology to patatin, a plant PLA2. Clin Exp Immunol 1998;112:355-62.
91. Sowka S, Hafner C, Radauer C, Focke M, Brehler R, Astwood JD, et al. Molecular and immunologic characterization of new isoforms of the *Hevea brasiliensis* latex allergen hev b 7: evidence of no cross-reactivity between hev b 7 isoforms and potato patatin and proteins from avocado and banana. J Allergy Clin Immunol 1999;104:1302-10.
92. Wagner S, Radauer C, Hafner C, Fuchs H, Jensen-Jarolim E, Wuthrich B, et al. Characterization of cross-reactive bell pepper allergens involved in the latex-fruit syndrome. Clin Exp Allergy 2004;34:1739-46.
93. Beezhold DH, Hickey VL, Kostyal DA, Puhl H, Zuidmeer L, van Ree R, et al. Lipid transfer protein from *Hevea brasiliensis* (Hev b 12), a cross-reactive latex protein. Ann Allergy Asthma Immunol 2003;90:439-45.
94. Faber MA, Sabato V, Bridts CH, Nayak A, Beezhold DH, Ebo DG. Clinical relevance of the *Hevea brasiliensis* lipid transfer protein Hev b 12. J Allergy Clin Immunol 2015;135:1645-8.
95. Raulf-Heimsoth M, Kespohl S, Crespo JF, Rodriguez J, Feliu A, Bruning T, et al. Natural rubber latex and chestnut allergy: cross-reactivity or co-sensitization? Allergy 2007;62:1277-81.
96. Ebo DG, Hagendorens MM, De Knop KJ, Verweij MM, Bridts CH, De Clerck LS, et al. Component-resolved diagnosis from latex allergy by microarray. Clin Exp Allergy 2010;40:348-58.
97. Gurlek F, Unsel M, Ardeniz O, Peker Koc Z, Gulbahar O, Sin AZ, et al. Misleading allergens in the diagnosis of latex allergy: profilin and cross-reactive carbohydrate determinants. Int Arch Allergy Immunol 2018;176:1-7.
98. Drouet M, Le Sellin J, Gay G, el Founini M, Sabbah A. Allergy to Chenopodiaceae (beets, spinach) associated with latex allergy [in French]. Allerg Immunol (Paris) 1994;26:113-4.
99. Maillard H, Machet L, Meurisse Y, Garot D, Toledano C, Jan V, et al. Cross-allergy to latex and spinach. Acta Derm Venereol 2000;80:51.
100. Wopfner N, Gadermaier G, Egger M, Asero R, Ebner C, Jahn-Schmid B, et al. The spectrum of allergens in ragweed and mugwort pollen. Int Archives Allergy Immunol 2005;138:337-46.
101. Wuthrich B, Hofer T. Food allergy: the celery-mugwort-spice syndrome. Association with mango allergy? [in German]. Dtsch Med Wochenschr 1984;109:981-6.
102. Wuthrich B, Stager J, Johansson SG. Celery allergy associated with birch and mugwort pollinosis. Allergy 1990;45:566-71.
103. Stager J, Wuthrich B, Johansson SG. Spice allergy in celery-sensitive patients. Allergy 1991;46:475-8.
104. Diaz-Perales A, Lombardero M, Sanchez-Monge R, Garcia-Selles FJ, Pernas M, Fernandez-Rivas M, et al. Lipid-transfer proteins as potential plant panallergens: cross-reactivity among proteins of Artemisia pollen, Castanea nut and Rosaceae fruits, with different IgE-binding capacities. Clin Exp Allergy 2000;30:1403-10.
105. Egger M, Mutschlechner S, Wopfner N, Gadermaier G, Briza P, Ferreira F. Pollen-food syndromes associated with weed pollinosis: an update from the molecular point of view. Allergy 2006;61:461-76.
106. Leitner A, Jensen-Jarolim E, Grimm R, Wuthrich B, Ebner H, Scheiner O, et al. Allergens in pepper and paprika. Immunologic investigation of the celery-birch-mugwort-spice syndrome. Allergy 1998;53:36-41.
107. Ebner C, Jensen-Jarolim E, Leitner A, Breiteneder H. Characterization of allergens in plant-derived spices: Apiaceae spices, pepper (Piperaceae), and paprika (bell peppers, Solanaceae). Allergy 1998;53(Suppl):52-4.
108. Asero R, Mistrello G, Amato S. The nature of melon allergy in ragweed-allergic subjects: a study of 1000 patients. Allergy Asthma Proc 2011;32:64-7.
109. Vallier P, DeChamp C, Valenta R, Vial O, Deviller P. Purification and characterization of an allergen from celery immunochemically related to an allergen present in several other plant species. Identification as a profilin. Clin Exp Allergy 1992;22:774-82.
110. Bauer L, Ebner C, Hirschwehr R, Wuthrich B, Pichler C, Fritsch R, et al. IgE cross-reactivity between birch pollen, mugwort pollen and celery is due to at least three distinct cross-reacting allergens: immunoblot investigation of the birch-mugwort-celery syndrome. Clin Exp Allergy 1996;26:1161-70.
111. Lukschal A, Wallmann J, Bublin M, Hofstetter G, Mothes-Luksch N, Breiteneder H, et al. Mimotopes for Api g 5, a relevant cross-reactive allergen, in the celery-mugwort-birch-spice syndrome. Allergy Asthma Immunol Res 2016;8:124-31.
112. Figueroa J, Blanco C, Dumpierrez AG, Almeida L, Ortega N, Castillo R, et al. Mustard allergy confirmed by double-blind placebo-controlled food challenges: clinical features and cross-reactivity with mugwort pollen and plant-derived foods. Allergy 2005;60:48-55.
113. Sanchez-Lopez J, Tordesillas L, Pascal M, Munoz-Cano R, Garrido M, Rueda M, et al. Role of Art v 3 in pollinosis of patients allergic to Pru p 3. J Allergy Clin Immunol 2014;133:1018-25.
114. Gao ZS, Yang ZW, Wu SD, Wang HY, Liu ML, Mao WL, et al. Peach allergy in China: a dominant role for mugwort pollen lipid transfer protein as a primary sensitizer. J Allergy Clin Immunol 2013;131:224-226.e1-3.
115. Burbach GJ, Heinzerling LM, Rohnelt C, Bergmann KC, Behrendt H, Zuberbier T, et al. Ragweed sensitization in Europe—GA(2)LEN study suggests increasing prevalence. Allergy 2009;64:664-5.
116. Anderson LB Jr, Dreyfuss EM, Logan J, Johnstone DE, Glaser J. Melon and banana sensitivity coincident with ragweed pollinosis. J Allergy 1970;45:310-9.
117. Simon-Nobbe B, Denk U, Poll V, Rid R, Breitenbach M. The spectrum of fungal allergy. Int Arch Allergy Immunol 2008;145:58-86.
118. Herrera I, Moneo I, Caballero ML, de Paz S, Perez Pimiento A, Rebollo S. Food allergy to spinach and mushroom. Allergy 2002;57:261-2.
119. Bennett AT, Collins KA. An unusual case of anaphylaxis. Mold in pancake mix. Am J Forensic Med Pathol 2001;22:292-5.
120. Airola K, Petman L, Makinen-Kiljunen S. Clustered sensitivity to fungi: anaphylactic reactions caused by ingestive allergy to yeasts. Ann Allergy Asthma Immunol 2006;97:294-7.
121. Jacobson MF, dePorter J. Self-reported adverse reactions associated with mycoprotein (Quorn-brand) containing foods. Ann Allergy Asthma Immunol 2018;120:626-30.
122. Hoff M, Trueb RM, Ballmer-Weber BK, Vieths S, Wuethrich B. Immediate-type hypersensitivity reaction to ingestion of mycoprotein (Quorn) in a patient allergic to molds caused by acidic ribosomal protein P2. J Allergy Clin Immunol 2003;111:1106-10.
123. Faber MA, Pascal M, El Kharbouchi O, Sabato V, Hagendorens MM, Decuyper II, et al. Shellfish allergens: tropomyosin and beyond. Allergy 2017;72:842-8.
124. Ribeiro JC, Cunha LM, Sousa-Pinto B, Fonseca J. Allergic risks of consuming edible insects: a systematic review. Mol Nutr Food Res 2018;62:1700030.
125. Witteman AM, Akkerdaas JH, van Leeuwen J, van der Zee JS, Aalberse RC. Identification of a cross-reactive allergen (presumably tropomyosin) in shrimp, mite and insects. Int Arch Allergy Immunol 1994;105:56-61.
126. Miyazawa H, Fukamachi H, Inagaki Y, Reese G, Daul CB, Lehrer SB, et al. Identification of the first major allergen of a squid (*Todarodes pacificus*). J Allergy Clin Immunol 1996;98(Pt 1):948-53.
127. Leung PS, Chen YC, Mykles DL, Chow WK, Li CP, Chu KH. Molecular identification of the lobster muscle protein tropomyosin as a seafood allergen. Mol Mar Biol Biotechnol 1998;7:12-20.
128. Leung PS, Chu KH. Molecular and immunological characterization of shellfish allergens. Front Biosci 1998;3:d306-12.

129. Leung PS, Chen YC, Chu KH. Seafood allergy: tropomyosins and beyond. J Microbiol Immunol Infect 1999;32:143-54.
130. Reese G, Ayuso R, Lehrer SB. Tropomyosin: an invertebrate pan-allergen. Int Arch Allergy Immunol 1999;119:247-58.
131. Santos AB, Chapman MD, Aalberse RC, Vailes LD, Ferriani VP, Oliver C, et al. Cockroach allergens and asthma in Brazil: identification of tropomyosin as a major allergen with potential cross-reactivity with mite and shrimp allergens. J Allergy Clin Immunol 1999;104(Pt 1):329-37.
132. Asturias JA, Gomez-Bayon N, Arilla MC, Martinez A, Palacios R, Sanchez-Gascon F, et al. Molecular characterization of American cockroach tropomyosin (*Periplaneta americana* allergen 7), a cross-reactive allergen. J Immunol 1999;162:4342-8.
133. Jeong KY, Hong CS, Yong TS. Allergenic tropomyosins and their cross-reactivities. Protein Pept Lett 2006;13:835-45.
134. Kamath SD, Abdel Rahman AM, Komoda T, Lopata AL. Impact of heat processing on the detection of the major shellfish allergen tropomyosin in crustaceans and molluscs using specific monoclonal antibodies. Food Chem 2013;141:4031-9.
135. Yadzir ZH, Misnan R, Bakhtiar F, Abdullah N, Murad S. Tropomyosin, the major tropical oyster *Crassostrea belcheri* allergen and effect of cooking on its allergenicity. Allergy Asthma Clin Immunol 2015;11:30.
136. Mohamad Yadzir ZH, Misnan R, Bakhtiar F, Abdullah N, Murad S. Tropomyosin and actin identified as major allergens of the carpet clam (*Paphia textile*) and the effect of cooking on their allergenicity. Biomed Res Int 2015; 2015:254152.
137. van Ree R, Antonicelli L, Akkerdaas JH, Garritani MS, Aalberse RC, Bonifazi F. Possible induction of food allergy during mite immunotherapy. Allergy 1996;51:108-13.
138. Peroni DG, Piacentini GL, Bodini A, Boner AL. Snail anaphylaxis during house dust mite immunotherapy. Pediatr Allergy Immunol 2000;11:260-1.
139. 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;109:627-9.
140. Pevec B, Pevec MR, Markovic AS, Batista I. House dust mite subcutaneous immunotherapy does not induce new sensitization to tropomyosin: does it do the opposite? J Investig Allergol Clin Immunol 2014;24:29-34.
141. Gamez C, Zafra M, Boquete M, Sanz V, Mazzeo C, Ibanez MD, et al. New shrimp IgE-binding proteins involved in mite-seafood cross-reactivity. Mol Nutr Food Res 2014;58:1915-25.
142. Giuffrida MG, Villalta D, Mistrello G, Amato S, Asero R. Shrimp allergy beyond tropomyosin in Italy: clinical relevance of arginine kinase, sarcoplasmic calcium binding protein and hemocyanin. Eur Ann Allergy Clin Immunol 2014;46:172-7.
143. Thalayasingam M, Gerez IF, Yap GC, Llanora GV, Chia IP, Chua L, et al. Clinical and immunochemical profiles of food challenge proven or anaphylactic shrimp allergy in tropical Singapore. Clin Exp Allergy 2015;45:687-97.
144. Pascal M, Grishina G, Yang AC, Sanchez-Garcia S, Lin J, Towle D, et al. Molecular diagnosis of shrimp allergy: efficiency of several allergens to predict clinical reactivity. J Allergy Clin Immunol Pract 2015;3:521-529.e10.
145. Gamez C, Sanchez-Garcia S, Ibanez MD, Lopez R, Aguado E, Lopez E, et al. Tropomyosin IgE-positive results are a good predictor of shrimp allergy. Allergy 2011;66:1375-83.
146. Farioli L, Losappio LM, Giuffrida MG, Pravettoni V, Micarelli G, Nichelatti M, et al. Mite-induced asthma and IgE levels to shrimp, mite, tropomyosin, arginine kinase, and Der p 10 are the most relevant risk factors for challenge-proven shrimp allergy. Int Arch Allergy Immunol 2017;174: 133-43.
147. Sanchez-Borges M, Fernandez-Caldas E. Hidden allergens and oral mite anaphylaxis: the pancake syndrome revisited. Curr Opin Allergy Clin Immunol 2015;15:337-43.
148. Mangodt EA, Van Gasse AL, Bridts CH, Sabato V, Ebo DG. Simultaneous oral mite anaphylaxis (pancake syndrome) in a father and daughter and a review of the literature. J Investig Allergol Clin Immunol 2015;25:75-6.
149. Hilger C, Kohnen M, Grigioni F, Lehners C, Hentges F. Allergic cross-reactions between cat and pig serum albumin. Study at the protein and DNA levels. Allergy 1997;52:179-87.
150. Asero R, Mistrello G, Falagiani P. Oral allergy syndrome from pork. Allergy 1997;52:684-6.
151. Voltolini S, Spigno F, Cioe A, Cagnati P, Bignardi D, Minale P. Bovine serum albumin: a double allergy risk. Eur Ann Allergy Clin Immunol 2013;45:144-7.
152. Hilger C, Swiontek K, Hentges F, Donnay C, de Blay F, Pauli G. Occupational inhalant allergy to pork followed by food allergy to pork and chicken: sensitization to hemoglobin and serum albumin. Int Arch Allergy Immunol 2010; 151:173-8.
153. Cistero-Bahima A, Enrique E, San Miguel-Moncin MM, Alonso R, Bartra J, Fernandez-Parra B, et al. Meat allergy and cross-reactivity with hamster epithelium. Allergy 2003;58:161-2.
154. Morisset M, Arumugam K, Ollert M, Hilger C. Horse-meat allergy mediated by dog allergy: a case report and review of the literature. Allergo J Int 2016;25: 76-81.
155. Hemmer W, Klug C, Swoboda I. Update on the bird-egg syndrome and genuine poultry meat allergy. Allergo J Int 2016;25:68-75.
156. Quirce S, Maranon F, Umpierrez A, de las Heras M, Fernandez-Caldas E, Sastre J. Chicken serum albumin (Gal d 5*) is a partially heat-labile inhalant and food allergen implicated in the bird-egg syndrome. Allergy 2001;56: 754-62.
157. Nevot Falco S, Casas Ramisa R, Lleonart Bellfill R. Bird-egg syndrome in children [in Spanish]. Allergol Immunopathol (Madr) 2003;31:161-5.
158. Cheikh Rouhou S, Bachouch I, Racil H, Chaouch N, Zarrouk M, Salmi L, et al. Anaphylaxis due to chicken meat [in French]. Rev Mal Respir 2012;29: 98-100.
159. Leser C, Hartmann AL, Praml G, Wuthrich B. The "egg-egg" syndrome: occupational respiratory allergy to airborne egg proteins with consecutive ingestive egg allergy in the bakery and confectionery industry. J Investig Allergol Clin Immunol 2001;11:89-93.
160. Sabato V, Verweij MM, Bridts CH, Levi-Schaffer F, Gibbs BF, De Clerck LS, et al. CD300a is expressed on human basophils and seems to inhibit IgE/FcεRI-dependent anaphylactic degranulation. Cytometry B Clin Cytom 2012; 82:132-8.
161. Santos AF, James LK, Bahnson HT, Shamji MH, Couto-Francisco NC, Islam S, et al. IgG4 inhibits peanut-induced basophil and mast cell activation in peanut-tolerant children sensitized to peanut major allergens. J Allergy Clin Immunol 2015;135:1249-56.
162. Hjort C, Schiotz PO, Ohlin M, Wurtzen PA, Christensen LH, Hoffmann HJ. The number and affinity of productive IgE pairs determine allergen activation of mast cells. J Allergy Clin Immunol 2017;140:1167-1170.e2.
163. Mahajan A, Youssef LA, Cleyrat C, Grattan R, Lucero SR, Mattison CP, et al. Allergen valency, dose, and FcεRI occupancy set thresholds for secretory responses to Pen a 1 and motivate design of hypoallergens. J Immunol 2017;198: 1034-46.
164. Sancho AI, Foxall R, Rigby NM, Browne T, Zuidmeer L, van Ree R, et al. Maturity and storage influence on the apple (*Malus domestica*) allergen Mal d 3, a nonspecific lipid transfer protein. J Agric Food Chem 2006;54:5098-104.
165. Matthes A, Schmitz-Eiberger M. Apple (*Malus domestica* L. Borkh.) allergen Mal d 1: effect of cultivar, cultivation system, and storage conditions. J Agric Food Chem 2009;57:10548-53.
166. Katelaris CH. Should patients with pollen fruit syndrome be prescribed an automatic epinephrine injector? Curr Opin Allergy Clin Immunol 2016;16: 370-4.
167. Bolhaar ST, Tiemessen MM, Zuidmeer L, van Leeuwen A, Hoffmann-Sommergruber K, Bruijnzeel-Koomen CA, et al. Efficacy of birch-pollen immunotherapy on cross-reactive food allergy confirmed by skin tests and double-blind food challenges. Clin Exp Allergy 2004;34:761-9.
168. Mauro M, Russello M, Incorvaia C, Gazzola G, Frati F, Moingeon P, et al. Birch-apple syndrome treated with birch pollen immunotherapy. Int Arch Allergy Immunol 2011;156:416-22.
169. Hansen KS, Khinchi MS, Skov PS, Bindslev-Jensen C, Poulsen LK, Malling HJ. Food allergy to apple and specific immunotherapy with birch pollen. Mol Nutr Food Res 2004;48:441-8.
170. Bucher X, Pichler WJ, Dahinden CA, Helbling A. Effect of tree pollen specific, subcutaneous immunotherapy on the oral allergy syndrome to apple and hazelnut. Allergy 2004;59:1272-6.
171. van Hoffen E, Peeters KA, van Neerven RJ, van der Tas CW, Zuidmeer L, van Ieperen-van Dijk AG, et al. Effect of birch pollen-specific immunotherapy on birch pollen-related hazelnut allergy. J Allergy Clin Immunol 2011;127: 100-101.e1-3.