

Plant Food Allergies: A Suggested Approach to Allergen-Resolved Diagnosis in the Clinical Practice by Identifying Easily Available Sensitization Markers

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Key Words

Food allergy · Nuts · Rosaceae · Diagnosis · Prevention

Abstract

Background: Molecular biology techniques have led to the identification of a number of allergens in vegetable foods, but due to the lack of purified food proteins for routine diagnostic use, the detection of sensitizing allergens remains a nearly impossible task in most clinical settings. The allergen-resolved diagnosis of food allergy is essential because each plant-derived food may contain a number of different allergens showing different physical/chemical characteristics that strongly influence the clinical expression of allergy; moreover, many allergens may cross-react with homologue proteins present in botanically unrelated vegetable foods. **Objective:** Through a review of the available literature, this study aimed to detect 'markers' of sensitization to specific plant food allergens that are easily accessible in the clinical practice. **Results:** There are several 'markers' of sensitization to different allergenic proteins in vegetable foods that can be helpful in the clinical practice. Specific algorithms for patients allergic to Rosaceae and to tree nuts were built. **Conclusion:** Clinical allergologists lacking the assistance of an advanced molecular biology lab may take advantage of some specific clinical data as well as of some 'markers' in the difficult task of correctly diagnosing patients with plant food allergy and to provide them the best preventive advice.

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Introduction

The three main objectives of a clinical allergologist caring for a patient with food allergy should be: (1) detection of the causative food, (2) prevention of further allergic reactions caused by the ingestion of cross-reacting foods and (3) preservation of the patient's quality of life by avoiding unnecessary dietary restrictions.

Plant-derived foods represent by far the most frequent cause of food allergy in adults. Although a systematic study of this type of food allergy was started only in recent years, the use of molecular biology techniques for research has enabled rapid identification, characterization and sequencing of a huge number of allergenic proteins. Based on the combination of four recent review articles [1–4], the main proteins involved in allergy to vegetable foods can be classified as shown in figure 1. The information available in figure 1 is essential for the understanding of the links between many relevant vegetable allergens but, unfortunately, has limited impact on the clinical practice, because most clinicians do not have access to laboratories performing immunoblot analyses and/or N-terminal sequencing, and because both natural and recombinant allergenic molecules for routine diagnostic tests are still lacking. Available routine diagnostic methods for allergies to plant-derived foods, namely skin prick tests (SPTs) with fresh foods, specific IgE measurement and oral challenges (either open or double-blind), are often very sensitive, but none of them give us any information about the allergenic molecule(s) causing the sensitization. Thus, the detection of the sensitizing or triggering

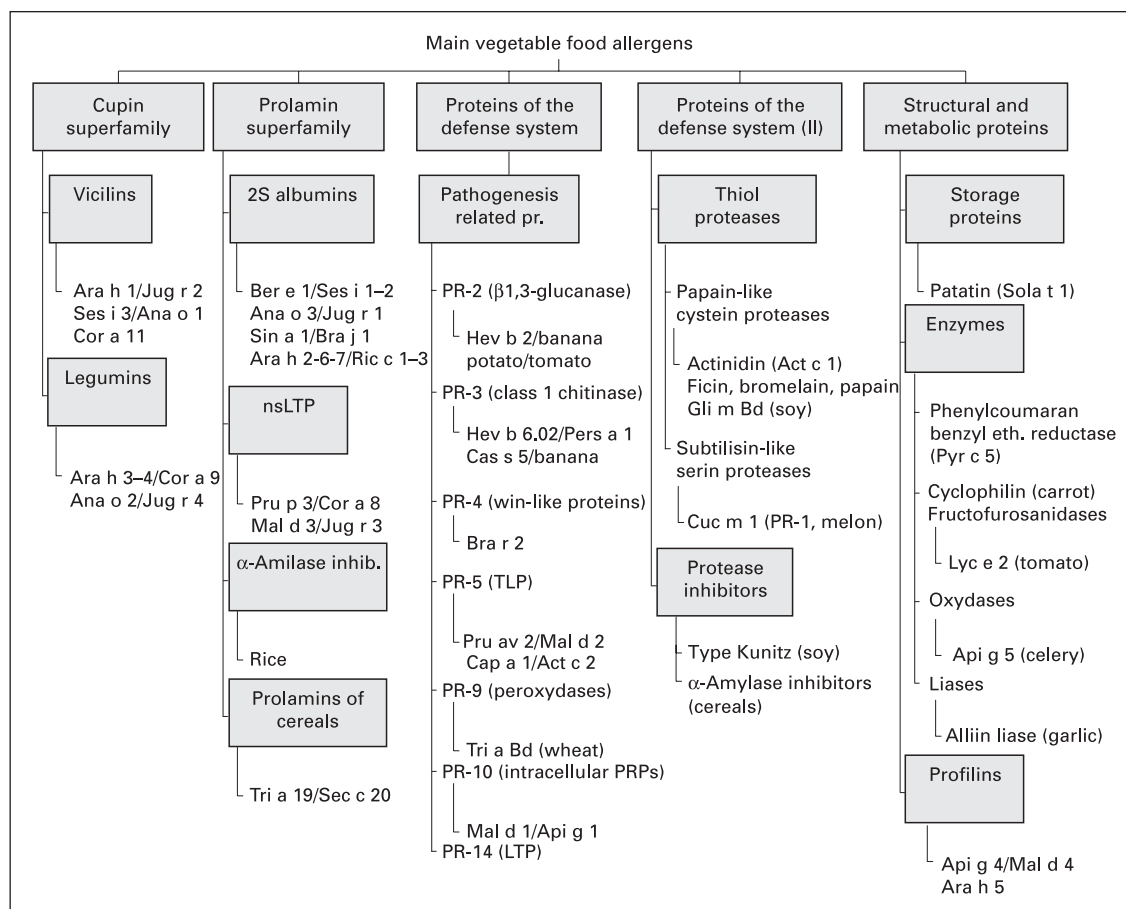


Fig. 1. Biological classification of the main vegetable food allergens. Allergen nomenclature: Act c (kiwi), Ana o (cashew), Api g (celery), Ara h (peanut), Ber e (Brazil nut), Bra r (rapeseed), Cas a (chestnut), Cor a (hazelnut), Cuc m (melon), Jug r (walnut), Lyc e (tomato), Mal d (apple), Pers a (avocado), Pru av (cherry), Pru p (peach), Pyr c (pear), Sec c (rye), Ses i (sesame), Tri a (wheat).

allergen(s) in patients with allergy to plant-derived foods remains a very complex (sometimes impossible) task in most clinical settings.

Diagnosing vegetable food allergy at a molecular level has an extremely high clinical (both prognostic and preventive) relevance for the following reasons:

- 1 Each plant-derived food may contain a number of different allergens.
- 2 Different allergenic proteins in the same food may show different physical/chemical characteristics that strongly influence the clinical expression of allergy. Allergens that are easily destroyed by pepsin digestion generally induce mild symptoms such as the oral allergy syndrome [5], except in situations of gastric hyp acidity [6], and heat-labile allergens may be harmless after various degrees of heat processing. In contrast, pepsin-resistant proteins maintain their

allergenicity throughout the whole gastrointestinal tract and may induce a spectrum of clinical conditions ranging from oral allergy syndrome to anaphylactic shock, depending on a number of variables such as the amount of food ingested, the concentration of the allergen in a specific food, contemporary ingestion of non-allergenic food or association with exercise.

- 3 A certain number of allergenic proteins in vegetable foods are highly conserved and may show immunologic cross-reactivity with homologue proteins present in botanically unrelated sources. The identification of the relevant allergen is essential in order to predict which foods are potentially harmful for a certain patient. To this end, a good knowledge of cross-reacting foods is essential.
- 4 Not all cross-reactivities detected in vitro are clinically equally relevant.

Allergy to Proteins Homologous to Bet v 1

General Information

About 98% of birch pollen-allergic patients are sensitized to the major allergen Bet v 1 [7], a 18-kDa pathogenesis-related protein of class 10; proteins homologous to Bet v 1 have been detected in a number of plant-derived foods.

Clinical Issues

Patients with birch pollen allergy frequently report symptoms following the ingestion of a large spectrum of fruits and vegetables [8, 9], although those most frequently involved in clinically relevant cross-reactions are apple and other fruits of the Rosaceae (including pear, peach, cherry, plum, apricot and almond) [8–10], tree nuts [11], vegetables of the Apiaceae (including celery, carrot, fennel and parsley) [12–16], kiwi [17, 18], soybean [19] and peanut [20]. Virtually all birch pollen-allergic patients are positive on SPTs with many of these fresh fruits and vegetables [21], but only a proportion of them, in general those reporting severe respiratory allergy symptoms or showing the highest levels of birch pollen-specific IgE [22, 23], have food allergy. This is particularly evident for allergies to vegetables that are botanically distant from Rosaceae, like those of the Apiaceae [24].

Many vegetable food proteins homologous to Bet v 1, particularly those from fruits of the Rosaceae, are extremely labile and easily destroyed by heat, oxidation, extraction procedures and pepsin digestion [25, 26]. Clinically, this translates into a good tolerance of heat-processed foods as well as of commercial fruit juices and in symptoms which very rarely differ from oral allergy syndrome [5, 27]. From a diagnostic point of view, such lability is the main reason why most commercial food extracts for SPTs (particularly those of the Rosaceae) are not reliable [28], and SPTs with fresh fruits and vegetables remain the best way to diagnose food allergy in vivo in these patients [28–30]. However, not all Bet v 1-homologous proteins are equally heat and/or pepsin sensitive. Comparatively high rates of systemic reactions from fresh celery, carrot and soybean have been observed in birch pollen-related food allergies [19, 31–34]. Moreover, Gly m 4, the Bet v 1-homologous protein in soybean, was still detectable after 2 h cooking of fresh beans and disappeared only in fermented or heavily heated soy products [19]; not surprisingly, the relatively higher stability of the protein was associated with a high rate of positive SPTs with commercial soybean extract (Stallergenes, Anthony, France) in allergic patients [19]. Finally, subjects mono-

sensitized to Bet v 1 may experience allergic symptoms (oral allergy syndrome in most cases) following the ingestion of cooked celery or roasted hazelnuts [35, 36], which suggests that the Bet v 1-homologous proteins in these foods show a certain degree of heat stability. In their effect, also commercial extracts of hazelnut and celery are much more sensitive than commercial extracts of Rosaceae on SPTs [28, 35].

Practical Markers of Sensitization to Bet v 1-Homologous Proteins

Clearly, neither clinical history nor a positive SPT with fresh vegetable food or commercial food extracts is specific to sensitization to proteins homologous to Bet v 1. IgE to recombinant Bet v 1 (ImmunoCAP, Pharmacia, Uppsala, Sweden) can be adopted as a marker of sensitization to Bet v 1-homologous allergens [37].

Allergy to Profilin

General Information

Profilin is a largely cross-reacting 12- to 15-kDa protein present in all eucaryotic cells [14, 38–40]. It is a minor pollen allergen, and several studies have shown that only 10–20% of patients with pollen allergy are sensitized to this protein [14, 38, 41].

Clinical Issues

Typically, patients sensitized to profilin show skin reactivity as well as specific IgE to virtually all seasonal airborne allergens, with the frequent, notable exception of pellitory pollen [42].

The clinical relevance of profilin sensitization in food allergy has long been debated. In one study, the few patients monosensitized to profilin did not report any relevant symptom following the ingestion of plant-derived foods [41], and another one concluded that IgE cross-reactive against food profilins has no or very little clinical relevance [43]; on the other hand, profilin has been involved in the so-called ‘birch-mugwort-celery-spice’ syndrome and in adverse reactions to Apiaceae [44–47], hazelnut [11], Rosaceae [14, 48], tomato [49], pumpkin seed [50], zucchini [51], lychee [52], pineapple and banana [53], persimmon [54] and melon [55]. Altogether, these studies suggest that probably only a limited proportion of subjects sensitized to profilin develop clinical allergy. Profilin seems susceptible to pepsin digestion [55], and as a consequence, most profilin-allergic patients experience oral allergy syndrome only upon the ingestion of vegeta-

ble foods. Nonetheless, several cases of systemic reactions in subjects sensitized to this protein have been reported to date; however, since most of these patients were also sensitized to other allergens, the role played by profilin in such reactions remains to be established.

Practical Markers of Sensitization to Profilin

As with allergy to proteins homologous to Bet v 1, clinical history and SPTs with fresh foods or commercial food extracts are not specific in most cases. A recent study has shown that allergies to melon, watermelon, citrus fruits, banana and/or tomato can be considered as clinical markers of profilin hypersensitivity, once latex allergy has been ruled out [56]. IgE specific to rBet v 2 (birch profilin) can be detected by a commercial kit (ImmunoCAP, Pharmacia), although the sensitivity of this assay has been questioned [37].

Food Allergies Associated with Mugwort Pollen Allergy

Some patients with mugwort pollen allergy experience food allergy to celery and other spices (the so-called 'mugwort-celery-spice syndrome') [57, 58]. In these patients, allergic reactions may be systemic, as most cross-reacting allergens are both heat and pepsin stable [59, 60]. The allergen identified by Heiss et al. [59] contained a cross-reacting carbohydrate epitope as confirmed by other researchers [61]. The anaphylactogenic activity of IgE specific to cross-reactive carbohydrate moieties of plant glycoproteins has been much debated. Recent studies have shown that IgE to Api g 5, a celery glycoprotein allergen [62], and to Lyc e 2, a glycoallergen of tomato [63], induces in vitro basophil histamine release and has the potential to elicit allergic reactions in vivo. However, in both cases, the allergen concentrations needed to achieve mediator release were relatively high [64]. Other relevant food allergies observed in mugwort pollen-allergic patients include honey [65, 66], chamomile [65, 67] and sunflower seed [65]. Altogether, food allergies associated with mugwort pollen allergy seem rather uncommon.

Allergy to Lipid Transfer Protein

General Information

Lipid transfer proteins (LTPs) are 9- to 10-kDa pathogenesis-related proteins of group 14 [1]. During the last 10 years, several studies have shown the immunologic

cross-reactivity within LTPs from Rosaceae [68–70] and between LTPs from Rosaceae and from botanically unrelated plant-derived foods [71, 72]. Interestingly, peach seems to cause the primary sensitization to this allergen, as no LTP-allergic patient not sensitized to peach has been described so far, and cross-reactivity to LTPs of botanically unrelated vegetable foods seems to depend on the level of peach LTP-specific IgE [73].

Clinical Issues

Due to their pepsin resistance [72] and heat stability [73–77], LTPs are potentially harmful allergens [78]; systemic reactions (including anaphylaxis, urticaria/angioedema and asthma) following the ingestion of Rosaceae [68, 71, 72, 79, 80], walnut and hazelnut [71, 72, 81–83], maize [71, 84], beer [71, 85, 86], grapes [87], mulberry [88], peanut and mustard [71, 72] have been reported in LTP-allergic patients. An interesting feature of allergy to LTP is its geographic distribution; all studies dealing with allergy to this protein have been carried out in Southern Europe, mainly in Italy and Spain. It is still unclear whether genetic or environmental factors are responsible for this fact. In the recent EU-funded study SAFE, including patients from the Netherlands, Austria, Spain and Italy, this distribution pattern was markedly confirmed [89].

Practical Markers of Sensitization to LTP

Typically, patients allergic to LTP frequently report good tolerance of peeled fruits; this is in keeping with the distribution of this protein in vegetable foods [90]. A history of allergic reactions following the ingestion of commercial fruit juices represents another clinical aspect suggesting LTP hypersensitivity. It is possible to take further advantage of the extreme stability of this protein in the routine diagnosis of LTP allergy. In fact, commercial extracts of Prunoideae for SPTs lack labile allergens such as profilin, Bet v 1- and thaumatin-like protein and virtually only contain LTP; this has been shown for plum extract by Dome-Hollister/Stier (Spokane, Wash., USA) and for peach extract by Abello (Lainate, Italy). Therefore, a positive SPT with these extracts is a marker of sensitization to this protein [27, 71, 72, 91]. Recently, Abello has measured the LTP content of its peach extract for SPTs as 30 µg/ml. Similarly, commercial walnut extracts for SPTs do not seem to contain labile allergens [27, 92] and frequently score positive in LTP-allergic patients [27, 73]; this has been shown for commercial walnut extracts by Dome-Hollister/Stier and Abello [27, 73] and by Stallergeres [83]. Clearly, in the case of a positive SPT with a commercial walnut extract, a differential diagnosis

with hypersensitivity to other stable allergens present in the extract, such as seed storage proteins, will be needed (see below).

Allergy to Thaumatin-Like Protein

Thaumatin-like proteins (TLPs) are 30-kDa pathogenesis-related proteins of group 5. They have been recently identified as allergens in apple [93], cherry [94, 95], bell pepper [96], kiwi [97] and grapes [87]. Their real clinical significance remains ill-defined due to the extreme rarity of monosensitized patients (in the recent EU-funded study SAFE, only one of 400 apple-allergic patients from four European countries was monosensitized to TLP). Although TLP seems resistant to proteases and pH- or heat-induced denaturation [98], all patients described so far but one had oral allergy syndrome.

Allergy to Seed Storage Proteins

2S Albumins

General Information

2S albumins are small heterodimeric proteins consisting in most cases (with the exception of peanut) of 2 subunits bound by disulfide bridges.

Clinical Issues

2S albumins are extremely stable and are major allergens in mustard (Sin a 1; Bra j 1) [99, 100], Brazil nut (Ber e 1) [101], walnut (Jug r 1) [102], castor seed (Ric c 1; Ric c 3) [103], sesame seed (Ses i 1; Ses i 2) [104, 105], cashew (Ana o 3), sunflower seed [106], peanut (Ara h 2, 6, 7) [107] and a minor allergen in hazelnut [108]. Interestingly, sensitization to 2S albumins may occur both via the gastrointestinal and the respiratory tract [109, 110]. In a well-known paper, it was the 2S albumin of Brazil nut that was recognized in transgenic soybean by specific IgE present in sera from Brazil nut-allergic subjects [111]. 2S albumins from different sources show a certain sequence identity (for instance, 46% between 2S albumins from walnut and Brazil nut), but comparatively little is known about clinical cross-reactivity reactions. Cross-reactivity is certainly present between the two mustards; moreover, cross-reactivity between 10-kDa allergens in sesame seed and poppy seed [112], sunflower seed and mustard [113] and walnut and hazelnut [114] has been described.

Vicilin-Like Proteins and Legumin-Like Proteins

General Information

Vicilin-like proteins include major allergens from peanut (Ara h 1) [115], lentil (Len c 1) [116, 117], hazelnut (Cor a 11) [118], walnut (Jug r 2) [119], cashew (Ana o 1) [120] and sesame (Ses i 3) [105].

Legumin-like proteins include allergens from peanut (Ara h 3) [121], hazelnut (Cor a 9) [108], cashew (Ana o 2) [122] and walnut (Jug r 4) [123].

Clinical Issues

Despite the presence of homologous proteins in peanuts and tree nuts, those allergic to one are unlikely to be allergic to the other, although high rates of in vitro and skin test cross-sensitization have been shown in peanut-allergic patients [124]. In some cases, cross-reactions within Leguminosae have been reported [125]. In contrast, clinical cross-reactivity between tree nuts in patients sensitized to vicilins and legumins is rather frequent [123], although it is not the rule; in this sense, a 37% risk has been calculated [126]. Several combinations of cross-reactions are reported in the literature: walnut/hazelnut/Brazil nut [114], coconut/walnut [127], coconut/hazelnut [128], peanut/almond [129], pistachio/cashew [130]. Clinically, patients hypersensitive to seed storage proteins frequently experience severe systemic allergic reactions due to the extreme heat and pepsin resistance of these allergens [116].

Practical Markers of Sensitization to Seed Storage Proteins

A history of anaphylaxis following the ingestion of sesame seed, sunflower seed, mustard or tree nuts in a patient not sensitized to peach and/or other Rosaceae (except almond) suggests hypersensitivity to seed storage proteins. The stability of these allergens also translates into an excellent sensitivity of commercial food extracts for SPTs [82, 112–114, 131]. Commercial walnut extracts by Bencard (UK) [128], ALK/Abello, Home-Hollister/Stier [113, 114, 128] and Stallergenes [81] have shown these properties. It is possible to take much advantage of the fact that these extracts do not contain labile allergens [92] to detect patients hypersensitive to stable allergens (either LTPs or seed storage proteins). The results of SPTs with commercial peach extract (containing LTPs but not seed storage proteins) will provide a differential diagnosis. Commercial hazelnut extracts for SPTs score strong-

Table 1. Diagnostic algorithm for patients with a history of Rosaceae allergy confirmed by positive SPT with fresh fruit and/or RAST

	A	B	C	D
Systemic symptoms (urticaria, angioedema, anaphylaxis)?	No	No	No/Yes	No/Yes
Is peeled fruit tolerated better than fruit with peel?	No	No	Yes	Yes
Symptoms from commercial juices or heat-processed food?	No	No	Yes	Yes
Oral allergy syndrome eating melon, watermelon, tomato and citrus fruits?	No	No/Yes	No	No/Yes
Is SPT with birch pollen positive?	Yes	Yes	No	Yes
Are SPTs with seasonal airborne allergens all positive?	No	Yes	No	No/Yes
Is SPT with commercial peach extract positive?	No	No	Yes	Yes
Specific IgE for rBet v 2?	No	Yes	No	No/Yes
Is SPT with natural rubber latex positive?	No	No	No	No

Diagnosis, further investigations and prevention: Case A: patients sensitized to proteins homologue to Bet v 1. Risk of systemic reactions is very low. Evaluate possible reactivity to botanically unrelated foods (tree nuts, Apiaceae, kiwi, etc.) Avoid only offending foods (these can be generally eaten if heat processed). Case B: patients sensitized to profilin. Risk of systemic reactions is low. Check hypersensitivity to other possible cross-reacting vegetable foods. Avoid only offending foods (it is possible to test tolerance of heat-processed foods). Case C: patients sensitized to LTP. Test cross-sensitivity to tree nuts, maize, barley, peanut and mustard; in view of the positive predictive value of SPT and high specific IgE levels and of the potential severity of adverse reactions [72, 73], foods positive on SPT/RAST should be avoided. Case D: cosensitization to LTP + Bet v 1-homologue proteins and/or profilin. Behave as for LTP.

Table 2. Diagnostic algorithm for patients with a history of tree nut allergy confirmed by positive SPT with fresh fruit and/or RAST

	A	B	C	D
Systemic symptoms (urticaria, angioedema, anaphylaxis)?	No	No	No/Yes	No/Yes
Symptoms also with roasted or otherwise heat-processed foods?	No	No	Yes	Yes
Is SPT with birch pollen positive?	Yes	Yes	No	No
Are SPTs with seasonal airborne allergens all positive?	No	Yes	No	No
Is SPT with commercial peach extract positive?	No	No	Yes	No
Is SPT with commercial hazelnut extract positive?	Yes	No/Yes	Yes	Yes
Is SPT with commercial walnut extract positive?	No	No	Yes	Yes
Specific IgE for rBet v 2?	No	Yes	No	No
Is SPT with natural rubber latex positive?	No	No	No	No

Diagnosis, further investigations and prevention: Case A: patient sensitized to proteins homologue to Bet v 1. Risk of systemic reactions is very low. Evaluate possible reactivity to botanically unrelated foods (Rosaceae, Apiaceae, kiwi, etc.). Avoid only offending foods (most of these can be eaten if heat processed). Case B: patient sensitized to profilin. Risk of systemic reactions is low. Check hypersensitivity to other possible cross-reacting vegetable foods. Avoid only offending foods (it is possible to assess tolerance to offending foods if these are heat processed). Case C: patient sensitized to LTP. Assess cross-sensitivity to Rosaceae, maize, barley, peanut and mustard by SPT/RAST; in view of the positive predictive value of SPT and high specific IgE levels and of the potential severity of adverse reactions [72, 73], foods positive on SPT/RAST should be avoided. Case D: patient sensitized to seed storage proteins. Assess possible sensitivity to potentially hazardous foods other than the offending one, including sesame seed, poppy seed, sunflower seed, cashew, peanut, almond, castor seed and Brazil nut. Consider possible avoidance of foods positive on SPT/RAST.

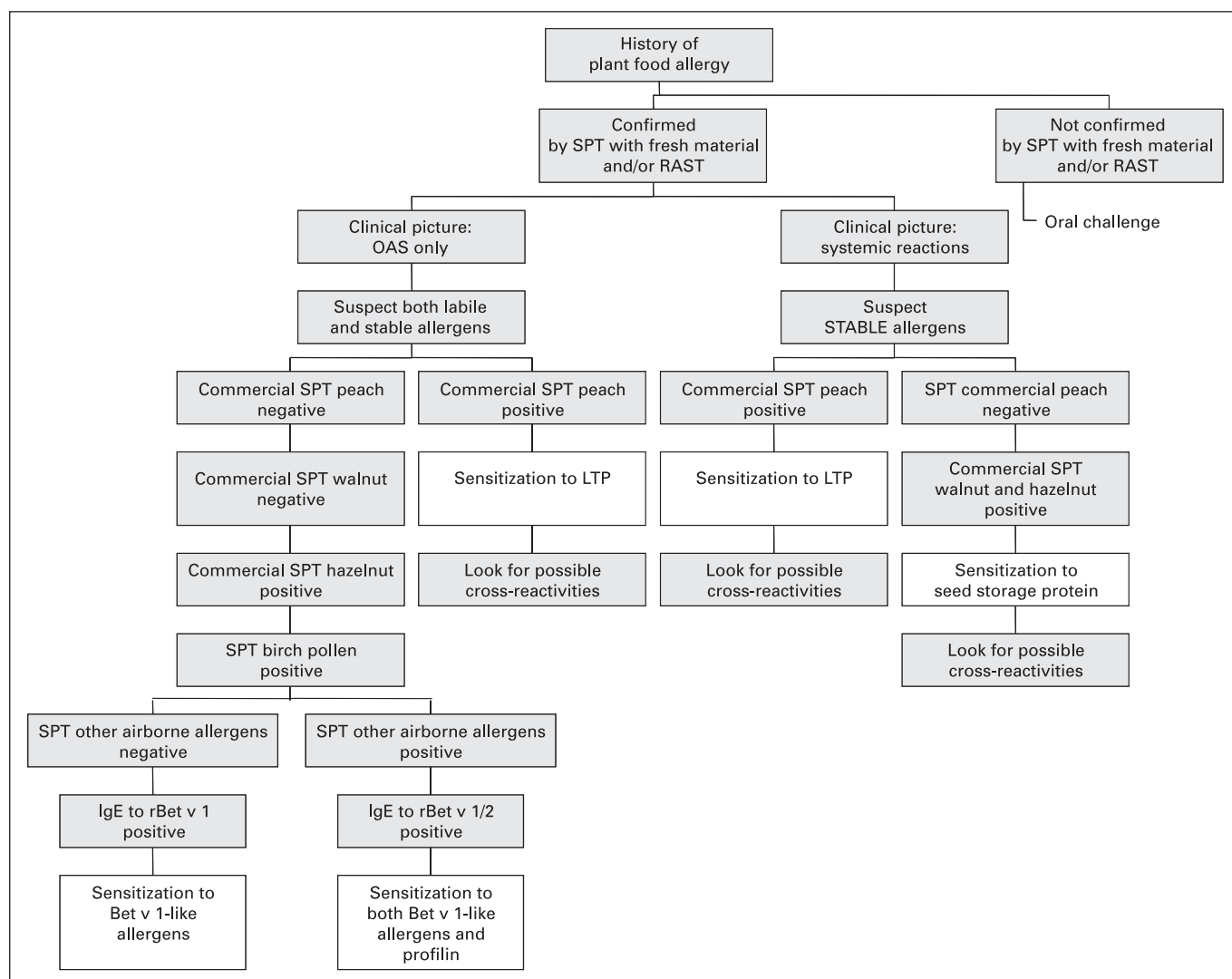


Fig. 2. A suggested algorithm for patients allergic to Rosaceae or tree nuts.

ly positive in patients hypersensitive to seed storage proteins, but as such extracts also contain variable amounts of Cor a 1, the Bet v 1-homologue allergen [28, 132], such extracts will be useful to diagnose hazelnut allergy, but not for an allergen-resolved diagnosis.

Suggested Diagnostic Algorithms for Patients Allergic to Rosaceae and/or Tree Nuts

By the proper use of the markers discussed above and by means of a limited number of questions regarding clinical features and of laboratory investigations, it is possible

to approach an allergen-resolved diagnosis of vegetable food allergy in a large number of patients. Two diagnostic algorithms for patients with a history of allergy to Rosaceae and tree nuts are suggested in tables 1 and 2, respectively; in each case, the investigations needed to prevent further allergic reactions from botanically unrelated vegetable foods as well as some practical advices have been provided at the end of the tables. The data from both tables have been summarized in graphic form in figure 2.

Conclusion

Allergy to plant-derived foods is extremely variable both in clinical presentation and in dangerousness due to the different chemical and physical properties of allergens involved. In view of this fact and of the frequent occurrence of cross-reactivity between highly conserved allergenic proteins in botanically unrelated sources [133], prevention probably represents the most important (but also

the most difficult) task of clinical allergologists. Until a large number of purified (either natural or recombinant) food-allergenic proteins are available for routine diagnosis, clinicians who are not associated with sophisticated laboratories will have to face the puzzle of identifying relevant vegetable food allergens using only clinical data and indirect 'markers'. A good knowledge of these (limited) means is essential to succeed as much as possible in this difficult task.

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