

Identification of European Allergy Patterns to the Allergen Families PR-10, LTP, and Profilin from *Rosaceae* Fruits

Maj-Britt Schmidt Andersen · Sharon Hall ·
Lars Ove Dragsted

© Humana Press Inc. 2009

Abstract High fruit intakes are associated with significant health benefits but fruit allergy sufferers may be discouraged from eating fruit due to the symptoms they experience. Knowledge about allergens involved in fruit allergy and the frequent cross-reactions to other allergens is essential to (a) design the best strategy for fruit allergy testing (b) prescribe optimal avoidance diets, and (c) design technological solutions for development of hypoallergenic fruits. The objective of this review was to investigate whether some characteristic disease entities could be identified in Europe for allergy to *Rosaceae* fruits. Five allergy patterns were found involving the allergen families PR-10, LTP, and profilin. In the Western Mediterranean area allergies to *Rosaceae* fruits are caused by monosensitization to LTP, monosensitization to profilin, or co-sensitization to both these allergens. On the contrary, monosensitization to PR-10 and, to a lesser degree, co-sensitization to profilin and PR-10 is dominant in Northern and Central Europe. LTP sensitization is present both in pollinosis and non-pollinosis patients and is associated with peach allergy in particular. The disease pattern for patients sensitized to profilin is characterized by

several concomitant allergies including grass and other pollens, *Rosaceae* and non-*Rosaceae* fruits. Finally, PR-10 sensitization is primarily associated to concomitant birch pollen and apple allergy.

Keywords Allergens · Avoidance diets · European allergy patterns · Fruit allergy · *Rosaceae*

Introduction

Regular intake of fruit promotes good health and has been demonstrated to be preventive for development of several chronic diseases [1, 2]. Out of these, evidence is strongest for an inverse association between fruit intake and cardiovascular disease risk and in meta-analyses of observational studies, a relative risk reduction of 11–23% for stroke [3, 4] and 7–13% for coronary heart disease [5, 6] have been calculated for daily fruit intakes above 160 g. Fruit intakes are generally below recommended levels in Europe [7] and one likely barrier for fruit consumption is the presence of diagnosed or perceived fruit allergy, as fruit allergy sufferers have decreased fruit availability due to avoidance of allergy-causing fruits. The prevalence of fruit allergy is hard to determine as valid tests and standard testing procedures are lacking. In a review by Zuidmeer et al. [8], perceived fruit allergy affected 2.2–11.5% of children aged 0–6 years and 0.4–6.6% of adults worldwide based on self-reported data. These numbers most likely represent an overestimation, as cases of self-reported allergy normally substantially outnumber cases with clinical relevance in questionnaire surveys [8–10]. The wide ranges in occurrence determinations probably reflect differences in fruit allergy prevalence between countries. A likely explanation for this could be that fruit allergy patterns or susceptibilities to development of fruit

M.-B. S. Andersen · L. O. Dragsted
Faculty of Life Sciences, Department of Human Nutrition,
University of Copenhagen,
Copenhagen, Denmark

S. Hall
Warwick HRI, University of Warwick,
Coventry, UK

L. O. Dragsted (✉)
30 Rolighedsvej,
1958 Frederiksberg C, Denmark
e-mail: ldra@life.ku.dk

allergies differ among populations. In support of such a hypothesis, various disease characteristics have been demonstrated in studies including subjects from different European countries [11, 12]. Furthermore, the reported dominant allergy-causing fruits vary between countries. In Northern and Central Europe, allergy to apple is most widespread [13–16], while strawberry and peach most often cause allergy in Southern Europe [17–19]. Knowledge about involved allergens and cross-reactions in fruit allergy is of importance for the allergist to design the best test strategy for patients suffering from fruit allergy and for the fruit allergy sufferers themselves who need a strategy to increase the fruit content of their diets without suffering allergic symptoms. In addition, development of hypoallergenic fruits and applicability of these for the diets of fruit allergy sufferers depends on disease characteristics [20].

The objective of this review is to identify whether separate or overlapping disease entities for fruit allergy can be identified in Europe. This is done by comparing data from studies where frequent cross-reactions between fruits and pollens or prevalence of sensitization to specific allergens have been investigated. As *Rosaceae* fruits most often cause allergy, the review is limited to *Rosaceae* fruits and the most important allergen families in these; PR-10, LTP and profilin.

Method

Literature searches were carried out in “MEDLINE” and “Web of Science”. Keywords and search strategies are listed in Table 1. Only articles written in English or German were included. In addition to the search results, reference lists from included articles were reviewed. The literature search was completed by 9/5-2009.

Main types of fruit allergy and disease determinants

Fruit allergy is a multifactorial immunological disease with highly individual features. Development of fruit allergy is initiated by a sensitization process, in which an IgE response against an allergen is generated. In most cases, the allergen originates from a pollen source which cross-reacts with allergens from fruits due to similarities in protein structure [21, 22]. Such types of fruit allergies are designated as a class 2 (Fig. 1a). Class 2 fruit allergies are also called the pollen food syndrome [23]. They usually involve labile allergens and therefore sensitization is only possible through the respiratory passages.

Although fruit allergies of class 2 dominate, at least one fruit allergen has been identified that is likely capable of causing sensitization independently of pollen allergens

[24, 25]. This type of fruit allergy is designated as a class 1 (Fig. 1b). Allergens involved in class 1 fruit allergy are resistant to proteolysis and sensitization is thought to take place in the gastrointestinal tract [26]. Allergies of both class one and two can involve one or more fruits depending on the degree of cross-reactions to other fruits. In addition, a patient can be co-sensitized to more allergens, further increasing the potential number of allergy-causing fruits.

Presence of sensitization to one or more allergens in a patient does not necessarily predict clinical relevance, as sensitizations can also be latent [22, 27]. In Fig. 2, suggested main determinants for sensitization, cross-reactivity and symptom development are summarized.

In order to identify the characteristic fruit allergy patterns in Europe, sensitization patterns of allergens and frequent cross-reactions between fruits and pollens should be known. Furthermore, the clinical relevance of the common sensitization patterns must be considered.

Allergen families in *Rosaceae* fruits

Most plant allergens belong to a limited number of protein families and therefore show similarities in primary and/or tertiary structure across different species [28]. The official list of allergens in *Rosaceae* fruits according to the Allergen Nomenclature Sub-Committee [29] are shown in Table 2. As the allergens primarily belong to the three protein families PR-10, LTP and profilin, these are most central for studying allergy patterns and consequently the focus of this review.

Development of fruit allergies of class 2 with concomitant allergies to pollens and *Rosaceae* fruits are in the majority of cases caused by PR-10, profilin and LTP proteins from the most widespread and frequent pollen sources in Europe. These pollen allergens are listed in Table 3.

PR-10 allergens

Allergens in the PR-10 family are intracellular pathogenesis-related (PR) proteins with a molecular mass around 17–18 kD [28, 30]. Their biological function is unknown and the protein sequence is highly variable, also within the same species [31]. A high degree of structural homology has been demonstrated between Mal d 1 from apple and Bet v 1 from birch [32, 33] and between PR-10 proteins from different *Rosaceae* fruits [34]. In accordance with this, cross-reactivity between Bet v 1, Mal d 1, Pyr c 1, and Pru av 1 have been demonstrated in inhibition experiments with serum pools from fruit-allergic patients [32, 35, 36], PR-10 proteins are heat labile and unstable to pepsin digestion [34, 37, 38]. It

Table 1 Literature search strategy

Database	Keywords	Search strategy	Number of hits
MEDLINE, Advanced Ovid Search	1: Aller*	1 a 2 Limits: review	168
	2: Fruit*	1 a 2 a 3	133
	3: Prevalence	1 a 4	66
	4: <i>Rosaceae</i>	1 a 5 Limits: Human	470
	5: Apple* OR Pear* OR Peach* OR Plum* OR Apricot* OR Cherr* OR Strawberr* OR Raspberr*	6	131
	6: “Mal d” OR “Pru p” OR “Pru av” OR “Pru ar” OR “Pyr c” OR “Pru d” OR “Fra a” OR “Rub i”		
Web of Science, Search	1: Allerg* ^a	1 a 2 a 3	54
	2: Fruit* ^a	1 a 2 a 4	157
	3: Review ^a	1 a 5	96
	4: Prevalence ^a	1 a 6	248
	5: <i>Rosaceae</i> ^a	1 a 7	178
	6: Apple* OR Pear* OR Peach* OR Plum* OR Apricot* OR Cherr* OR Strawberr* OR Raspberr* ^b		
	7: (Mal d) OR (Pru p) OR (Pru av) OR (Pru ar) OR (Pyr c) OR (Pru d) OR (Fra a) OR (Rub i) ^a		

List of keywords and search strategies applied in the search for articles

a AND

^a Topic as search field

^b Title as search field

has been demonstrated in several studies that IgE reactivity to PR-10 proteins is absent following heat-treatment of fruits [37–40].

LTP allergens

LTP is a subgroup of PR-14 proteins, which protect the plant against bacteria, fungi, and possibly virus and non-biotic stress factors [25]. LTP allergens from *Rosaceae* fruits belong to a protein class called nonspecific LTP1. These allergens have a structural sequence homology above 80% and a molecular mass of approximately 9 kDa. [41, 42]. Cross-reactivity between Pru p 3, Pru ar 3, Pru d 3, Mal d 3, and Art v 3 have been demonstrated in inhibition experiments using serum pools from patients with fruit allergies [24, 43–46]. Two epitopes that could likely be

responsible for the cross-reactivity among LTP from *Rosaceae* fruits have been identified in Borges et al. [47]. Contrary to the PR-10 family, LTP proteins from pollens and fruits show less sequence homology. As a consequence of this, LTP proteins are more rarely implicated in the pollen–food syndrome [48]. An important common characteristic among LTP proteins is a structure with eight cysteine residues forming four disulfide bridges [41]. Due to the stability of the sulfide bonds, the allergens are heat-stable and are not degraded by gastric digestion [38, 41, 49]. IgE reactivity to LTP is therefore retained after heat-treatment of fruits [39, 50]. LTP proteins are primarily located in the peel of peaches, apples, and cherries and consequently, peeled fruits are tolerable for some LTP fruit allergy sufferers [20, 51–53]. However, this is not a general characteristic for *Rosaceae* fruits and LTP has been

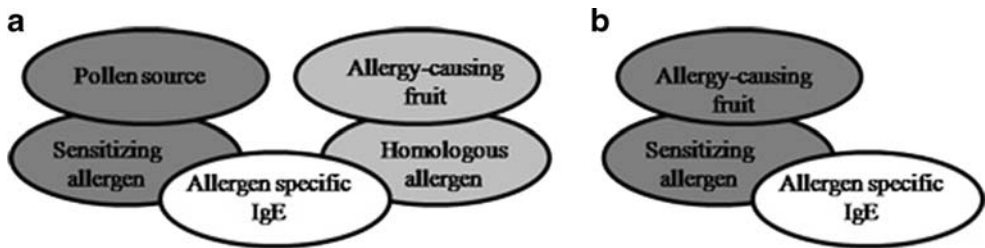
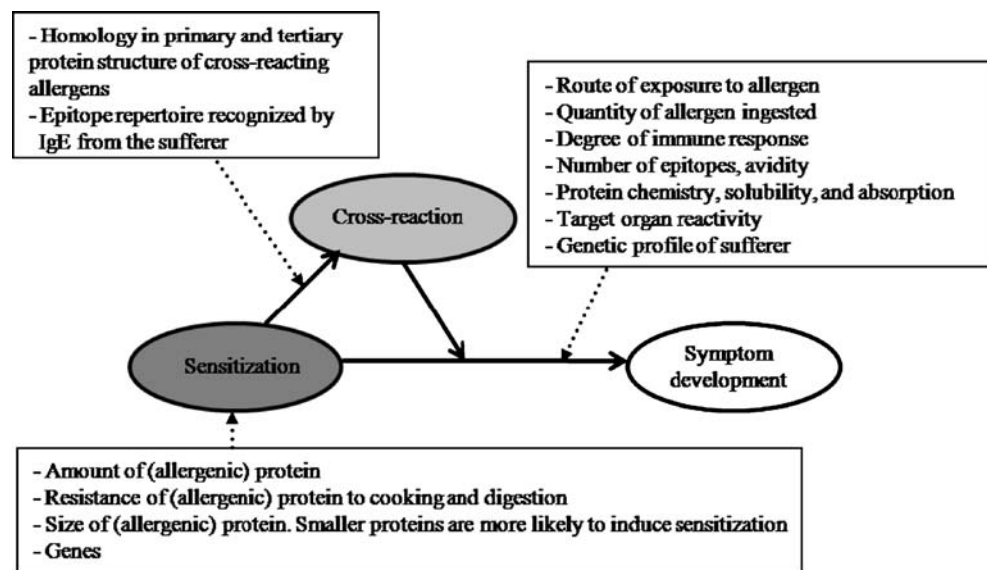


Fig. 1 Main types of fruit allergy. Ovals in dark gray represent sources of primary sensitization, light gray represent cross-reactions. **a** Class 2 fruit allergy: the sensitizing allergen originates from a pollen

source, which then cross-reacts to one or more fruit allergens. **b** Class 1 fruit allergy: the sensitizing allergen originates from a fruit. Cross-reactions to other fruits containing similar allergens are possible

Fig. 2 Determinants for sensitization, cross-reactions and symptom development in fruit allergy [21, 26, 27, 99–101]



reported to be more equally distributed between pulp and peel in plums and apricot [54].

Profilin allergens

Profilins are the most widespread allergens throughout the plant kingdom. They are present in the cytosol of all eukaryotic cells in which they function as structural proteins by participating in the regulation of actin filament polymerization [28]. The molecular mass of profilins is 12–15 kDa and the molecular structure is highly conserved with 70–85% homology among different species. Inhibition experiments with serum pools from patients with fruit allergies have demonstrated cross-reactivity between the profilins Mal d 4, Pyr c 4, Pru av 4, Bet v 2 [35, 55]. In addition highly conserved regions that likely function as epitopes responsible for allergenic cross-reactivity between fruits and pollens have been identified in this group of allergens. The presence of IgE antibodies to these epitopes has been associated with allergic reactivity to a high number of fruits [56, 57]. Profilin allergens are not heat-

stable and they are vulnerable to gastric digestion [28, 38, 58].

Sensitization patterns in Europe to *Rosaceae* allergen families

To ascertain the relative importance of the allergen families PR-10, LTP and profilin in *Rosaceae* fruit allergy, results from studies investigating sensitization patterns to purified or recombinant allergens in patients with allergy to one or more *Rosaceae* fruits were collated and are listed in Table 4. Only studies carried out in Europe for which the country of origin of the patients with *Rosaceae* allergy, and the percentage of those patients sensitized to PR-10, LTP and/or profilin allergens could be determined, have been included in the table. Overall, 27 studies fulfilled these inclusion criteria. Sixteen studies were carried out with Spanish patients, six with Italian patients, and four with German patients. In addition, there was one study from each of the following countries; Portugal, Switzerland,

Table 2 List of allergens from *Rosaceae* fruits and family classification

Fruit	Protein family			
	PR-10	LTP	Profilins	Other
Apple (<i>Malus domestica</i>)	Mal d 1	Mal d 3	Mal d 4	Mal d 2 (PR-5)
Peach (<i>Prunus persica</i>)	Pru p 1	Pru p 3	Pru p 4	
Sweet cherry (<i>Prunus avium</i>)	Pru av 1	Pru av 3	Pru av 4	Pru av 2 (PR-5)
Apricot (<i>Prunus armeniaca</i>)	Pru ar 1	Pru ar 3		
Pear (<i>Pyrus communis</i>)	Pyr c 1	Pyr c 3	Pyr c 4	Pyr c 5
European plum (<i>Prunus domestica</i>)		Pru d 3		
Strawberry (<i>Fragaria ananassa</i>)	Fra a 1	Fra a 3	Fra a 4	
Red raspberry (<i>Rubus idaeus</i>)	Rub i 1	Rub i 3		

Table 3 List of the most widespread pollen allergens in Europe belonging to the protein families PR-10, PR-14, and profilin [29, 77]

Pollen	Protein family		
	PR-10	PR-14	Profilins
Birch (<i>Betula verrucosa</i> HH)	Bet v 1		Bet v 2
Mugwort (<i>Artemisia vulgaris</i> HH)		Art v 3	Art v 4
London Plane tree (<i>Platanus acerifolia</i> HH)		Pla a 3	
Oriental Plane tree (<i>Platanus orientalis</i> HH)		Pla or 3	
Timothy (Grass) (<i>Phleum pratense</i> HH)			Phl p 12

Austria, and The Netherlands. Generally, there is good accordance as regards sensitization patterns in Table 4 between studies including only confirmed clinically relevant cases and studies where patients were included based solely on patient histories and positive IgE and/or SPT tests. Therefore, these two types of studies have been combined. Several different purified or recombinant allergen sources have been applied in the studies. Although the prevalence of sensitization to each allergen family is dependent on the origin of the allergens applied, the differences seen in Table 4 are minor and therefore it is reasonable to discuss sensitization patterns in general, regardless of allergen origin. Furthermore, recombinant allergens have been demonstrated to be equally valid for testing compared to purified natural allergens [59–61].

Spain and Portugal

Spain and Portugal are geographically close and as the results from the study carried out in Portugal are comparable to the results from the Spanish studies, these are considered together. PR-10 sensitization seems to be of minor relevance, as only 0–13% of patients are sensitized to this allergen in 14 out of 16 studies and none of these PR-10 sensitized patients are monosensitized. Profilin sensitization has been detected in 0–75% of the Spanish and Portuguese patients and higher prevalence of sensitization to this allergen is found in patients with concomitant grass pollen allergy. As up to 56% of the profilin-sensitized patients are monosensitized, presence of allergy can probably be ascribed to profilin sensitization in some patients with concomitant pollinosis. LTP sensitization is dominant in Spain and Portugal and has been detected in 47–100% of the patients. The highest prevalence of LTP sensitization is found in studies where patients had concomitant plane tree or mugwort allergies or where patients were free from pollinosis. In concordance with this, Pru p 3 sensitization was significantly associated with absence of pollinosis in the study by Fernandez-Rivas et al. [62] (Table 4). The Spanish study where allergy to strawberry was an inclusion criterion for patients has a divergent sensitization pattern with higher prevalence of PR-10 and profilin sensitization and lower prevalence of LTP sensitization

compared to the studies where inclusion criteria required the observation of peach or cherry allergies. As the same tendency can be seen for Italian patients (Table 4) this suggests that LTP sensitization is less dominant in strawberry allergy. However, more studies are needed to investigate this further. Based on the available studies, peach is the most significant allergy-causing fruit in Spain followed by apple, pear and cherry and sensitization patterns to allergens for each of these individual fruits appear to be concordant.

Italy

For studies carried out in Italy, the prevalence of PR-10 sensitization is 0–91% and closely associated to prevalence of birch pollen allergy. The prevalence of profilin sensitization is 0–50% and could likely be associated with grass pollinosis although grass pollen allergy is less frequently reported in the Italian studies. In concordance with this, patients with IgE towards Bet v 2 were sensitized to grass in all cases, while grass sensitization was less widespread in the group monosensitized to Bet v 1 in the study by Rossi et al. [63] (Table 4). LTP sensitization is dominant in patients without concomitant pollen allergies and in studies including patient groups with lower prevalence of birch and grass pollinosis. It has not been possible to evaluate the extent of monosensitization in the majority of the Italian studies. However, all allergen families seem to be clinically relevant as a considerable percentage of the patients are monosensitized to each of them depending on the study population. Peach, cherry, and apple allergies are dominant.

Austria, Switzerland, Germany, and The Netherlands

Based on the available studies in Table 4, the sensitization patterns in Austria, Switzerland, Germany, and The Netherlands are similar and therefore these are considered together. PR-10 is the dominant allergen with 84–100% of the patients being sensitized and 26–75% monosensitized. Like in Italy, PR-10 sensitization is strongly associated to birch pollinosis rather than specific fruits. Prevalence of profilin sensitization is 15–74% with highest numbers in studies where grass pollinosis was reported. Further

Table 4 Results from studies where sensitization to isolated allergens has been tested

C ^a	N ^b	Patient characteristics		PR-10 ^c	Profilin ^c	LTP ^c	Ref.
		Allergy to <i>Rosaceae</i> fruits ^c	Allergy to pollens ^d				
ES	16	Peach (100%) Apple (81%) Pear (56%)	Grass (100%) Birch (75%) Olive (69%)	6.25% Bet v 1 (I) (0% MS)	69% <i>L. Perenne</i> (I) (62% MS) 44% <i>L. Perenne</i> (S)		[78]
ES	36	Peach (100%)	Plane tree (100%)			85% nPru p 3 (I)	[79]
ES	22	Peach (100%) Apple (68%) Pear (55%) Cherry (27%) Apricot (23%) Plum (23%) Strawberry (14%)	Grass (100%)		75% <i>L. Perenne</i> (I ⁶) 47% <i>L. Perenne</i> (S)		[65]
ES	5	Peach (100%)	Grass (100%) Olive (100%)	0% rBet v 1 (I)	80% rBet v 2 (I)		[80]
ES	9	Peach (100%)	Mugwort (100%)			89% nPru p 3 (I) 89% nArt v 3 (I) 100% nPru p 3 (I) 92% nPru p 3 (S) 77% nMal d3 (S) 36% nArt v 3 (S)	[44]
ES	47	Peach (100%) Apple (51%)	Pollinosis (83%) Mugwort (57%)				[81]
ES	18	Peach (78%) Apple (39%) Pear (22%) Strawberry (17%) Cherry (6%) Plum (6%)	Grass (83%) Olive (72%) NP (17%)	6% Bet v 1 (I) (0% MS)	56% Bet v 2 (I) (50% MS)		[82]
ES	10	Peach (100%)	Plane tree (0%)			100% (I) nPru p 3	[79]
ES	7	Peach (100%) CR Apple (14%)	Birch (100%)		57% nPru p 4 (I)	100% nPru p 3 (I)	[74]
ES	25	Peach (100%) CR	Pollinosis (100%). Pollen sources NR.		56% rBet v 2 (I) 56% rPru p 4 (I) (56% MS)	44% nPru p 3 (S) (44% MS)	[83]
ES	76	Peach (100%) CR	Grass (72%) Olive (42%) Cypress (21%) Plane tree (3%) NP (22%)	7% rBet v 1 (I)	34% rBet v 2 (I)	62% nPru p 3 (S)	[62]

Table 4 (continued)

C ^a	N ^b	Patient characteristics		PR-10 ^c	Profilin ^c	LTP ^c	Ref.
		Allergy to <i>Rosaceae</i> fruits ^c	Allergy to pollens ^d				
ES	30	Peach (100%) CR	Birch (10%) Grass (50%)	13% rBet v 1 and/or rMal d 1 (I)	20% rBet v 2 (I) 20% rPhl p 12 (I) 17% rMal d 4 (I)	93% nPru p 3 (S) 90% rPru p 3 (I) 80% rMal d 3 (I)	[84]
ES	62	Peach (100%) CR	Pollinosis (79%). Pollen sources NR	7% rBet v 1 (I)	32% rBet v 2 (I)	65% nPru p 3 (S)	[85]
ES	6	Peach (100%) CR	Birch (17%) Grass (83%)	50% nMad d 1 (S) 50% rMal d 1 (I) 50% rBet v 1 (I)	67% rMal d 4 (I)	50% nPru p 3 (S) 33% rPru p 3 (I) 33% rMal d 3 (I)	[60]
ES	8	Peach (100%) CR Cherry (12.5%) Strawberry (12.5%)	Birch (0%)		0% nPru p 4 (I)	100% nPru p 3 (I)	[74]
ES	11	Peach (91%) Apple (91%) Cherry (36%) Plum (36%) Pear (27%) Apricot (18%)	NP (100%)	0% Bet v 1 (I ^f)	0% Profilin unspec. (I ^f) 0% Profilin unspec. (S)		[65]
ES	4	Peach (100%) CR	NP (100%)		25% rBet v 2 (I) 25% rPru p 4 (I) (25% MS)	75% nPru p 3 (S) (75% MS)	[83]
ES	7	Cherry (100%)	Grass (14%) Mugwort (29%) Plane tree (71%) NP (29%)	0% rPru av 1 (S)	14% rPru av 4 (S)	100% rPru av 3 (S) (86% MS)	[64]
ES	4	Cherry (100%)		0% rPru av 1 (I)	0% rPru av 4 (I)	100% rPru av 3 (I)	[38]
ES	19	Strawberry (100%)	Grass (100%) Olive (95%) Plane tree (21%) Cypress (11%)	47% nMal d 1 (I) (5% MS)	68% rMal d 4 (I) (32% MS)	47% nMal d 3 (I) (5% MS)	[86]
PT ⁴	25	Peach (100%) CR		4% rPru p 1 (I ^g) (0% MS)	12% rPru p 4 (I ^g) (4% MS)	96% rPru p 3 (I ⁷) (84% MS)	[87]
IT	24	Apple (92%) Peach (13%) Cherry (13%) Apricot (13%) Pear (4%)	<i>Fagales</i> (100%) (birch, hazel or alder)	88% Bet v 1 (I) (67% MS)	33% Bet v 2 (I) (13% MS)		[63]

Table 4 (continued)

C ^a	N ^b	Patient characteristics		PR-10 ^c	Profilin ^c	LTP ^c	Ref.
		Allergy to <i>Rosaceae</i> fruits ^c	Allergy to pollens ^d				
IT	8	Strawberry (100%)	Birch (63%) Grass (50%) Olive (38%) Ragweed (38%)	63% nMal d 1 (I) (12.5% MS)	50% rMal d 4 (I) (25% MS)	13% nMal d 3 (I) (0% MS)	[86]
IT	32	Apple (100%) CR Peach (41%) Cherry (41%) Apricot (31%) Plum (19%) Pear (16%) Strawberry (3%)	Birch (100%) Grass (59%)	91% nMal d 1 (I) (38% MS)	50% nMal d 4 (I) (0% MS)	28% nMal d 3 (I) (3% MS)	[75]
IT	11	Apple (100%) CR Cherry (55%) Apricot (27%) Peach (27%) Pear (18%) Plum (9%) Strawberry (9%)	Birch (0%) Grass (0%) Mugwort (27%) Ragweed (18%) <i>Parietaria</i> (9%)	0% nMal d 1 (I)	0% nMal d 4 (I)	100% nMal d 3 (I)	[75]
IT	21	Apricot (100%) CR Peach (76%) Cherry (43%) Apple (24%) Plum (19%)	Birch (67%) Grass (43%) Mugwort (14%)	57% nPru ar 1 (I)	19% nPru ar 4 (I)	100% nPru ar 3 (I)	[24]
IT	16	Plum (100%) CR Peach (100%) Cherry (63%) Apricot (63%) Apple (19%)	Birch (69%) Grass (94%) Mugwort (6.25%)	56% nPru d 1(I)		75% nPru d 3 (I)	[46]
IT	7	Cherry (100%) CR		29% rPru av 1 (I)	29% rPru av 4 (I)	100% rPru av 3 (I) (57% MS)	[88]
IT	9	Apricot (100%) CR Peach (78%) Apple (44%) Cherry (33.3%) Plum (22%)	NP (100%)	0% nPru ar 1 (I)	0% nPru ar 4 (I)	100% nPru ar 3 (I)	[24]
IT	7	Plum (100%) CR Peach (100%) Cherry (71%) Apricot (29%) Apple (14%)	NP (100%)	0% nPru d 1(I)		100% Pru d 3 (I)	[46]
CH	24	Cherry (100%) CR	Birch (96%) Grass (75%) Mugwort (17%)	92% rPru av 1 (S) (75% MS)	17% rPru av 4 (S) (0% MS)	4% rPru av 3 (S) (4% MS)	[64]
AT	29	<i>Rosaceae</i> (primarily Apple)	Birch (83%) Grass or Weed (45%)	100% rBet v 1 (S) (86% MS)	15% rBet v 2 (S) (0% MS)		[89]

Table 4 (continued)

C ^a	N ^b	Patient characteristics		PR-10 ^c	Profilin ^c	LTP ^c	Ref.
		Allergy to <i>Rosaceae</i> fruits ^c	Allergy to pollens ^d				
DE	19	Cherry (100%)	Birch (100%)	89% rBet v 1 (I) 89% rPru av 1 (I) 84% nMal d 1(I) (68% MS)	26% rBet v 2 (I) (5% MS)		[61]
DE	101	Cherry (100%) Apricot (96%) Peach (57%) Pear (53%) Strawberry (25%) Plum (9%) Apricot (8%)	Birch (100%)	96% rPru av 1 (I) (76% MS)	16% rPru av 4 (I) (1% MS)	3% rPru av 3 (I) (0% MS)	[88]
DE	20	Apple (100%)	Birch (100%)	100% rBet v 1 (I)	20% rBet v 2 (I)		[90]
DE	16	Pear (100%)	Birch (100%)	100% rBet v 1 (I) 100% rPyr c 1 (I) (50% MS)	50% rBet v 2 (I)		[91]
NL	23	Apple (100%)	Birch, Grass or Mugwort (100%)	100% rBet v 1 (S, I) (30% MS)	70% nBet v 2 or <i>L. Perenne</i> (S, I) (0% MS)		[68]
NL	19	Peach (100%)	Birch, Grass or Mugwort (100%)	100% rBet v 1 (S, I) (26% MS)	74% nBet v 2 (S, I) (0% MS)		[68]

^a C country: AT Austria, CE Central Europe, CH Switzerland, DE Germany, ES Spain, IT Italy, NL The Netherlands, PT Portugal

^b N number of subjects

^c Selection criteria for patients in each study were based on the first mentioned fruit in each box and confirmed by patient history and positive IgE test and/or SPT test. CR in brackets indicates that the clinical relevance of the allergy has been tested in the study by open or blinded food challenges. Concomitant allergies to *Rosaceae* fruits listed in the table are based solely on patient history and were not reported in all studies. The percentage of patients with allergies to the different fruits is written in brackets.

^d The percentage of patients allergic to the different pollens is written in brackets. Presence of concomitant pollen allergies was not reported fully in all studies. Not reported (NR); No pollinosis (NP)

^e I IgE-based in vitro test (RAST, EAST, immunoblot or CAP). Unless otherwise stated, the detection limits for positive reaction used in the studies was 0.35 kU/l; S SPT test, MS monosensitized. As data was not available at the individual level for all studies, the percentage of patients monosensitized to each of the included allergens in a study could not be determined in all cases.

^f Detection limit in IgE test 0.7 kU/l

^g Detection limit in IgE test 0.1 kU/l

supporting the link between grass pollinosis and profilin sensitization, all profilin-sensitized patients had concomitant grass pollen allergy in the Swiss study [64] (Table 4). LTP sensitization is almost absent in Austria, Switzerland, Germany, and The Netherlands as

only 3–4% of the patients are sensitized to this allergen. The most important allergy-causing fruits are probably apple, peach, and cherry. However, prevalence of concomitant allergies to other *Rosaceae* fruits was only reported in one study.

Sensitization patterns in Europe to *Rosaceae* fruits

As patients in the included studies in Table 4 were selected based on presence of specific *Rosaceae* fruit allergies, it is not possible to evaluate which fruit and pollen allergies are typically associated from the studies in this table. Therefore, studies investigating significant associations in sensitization patterns to fruits and pollens are listed in Table 5. According to the studies in Table 5, significant associations between allergies to the *Rosaceae* fruits apple, peach, pear, plum, cherry, and apricot have been demonstrated independently of country. However, in Northern and Central Europe (Sweden, Denmark, Estonia, Lithuania, The Netherlands and Switzerland), allergy to *Rosaceae* fruits are in all cases significantly associated with birch pollinosis, which is not the case for studies carried out in Spain (Table 5). In one of the Italian studies, allergies to *Rosaceae* were both significantly associated and not associated to pollen allergies indicating that more different fruit allergy patterns can be found in this country. Interestingly, in one of the Spanish and one of the Italian studies, sensitization patterns were investigated for profilin-sensitized patients only. According to the results from these studies, profilin sensitization was significantly associated with allergy to melon, watermelon, citrus fruits, and banana and not *Rosaceae* fruits. As melon and watermelon were associated with grass pollen allergy in the Italian study and grass pollinosis were characteristic for profilin-sensitized patients in Table 4, these results suggest that profilin sensitization is not limited to *Rosaceae* fruits. As opposed to this, PR-10 sensitization was only significantly associated with *Rosaceae* fruits in the Italian study (Table 5).

Discussion

Fruit allergy patterns in Europe

As judged from sensitization patterns to allergens, *Rosaceae* fruits, and pollens in Tables 4 and 5, the disease patterns vary across Europe, with considerable differences between Western Mediterranean countries and Northern and Central Europe with Italy holding an intermediate position. This has also been confirmed in a study including 398 patients with an allergy to apple from The Netherlands, Austria, Italy, and Spain [11].

In the Western Mediterranean areas, PR-10 sensitization is almost absent, which can probably be explained by a low distribution of birch trees [65]. However, sensitization to both Bet v 1 and Bet v 2 has been demonstrated in a birch-free area in Italy, where it was explained by exposure to other *Fagales* pollen species (hazel and alder), which could

likely cross-react with birch pollen allergens [66]. Such reactivity patterns therefore probably explain the few cases of PR-10 sensitization in Spain and Portugal. In an inhibition study with Spanish patients, it was demonstrated that PR-10 was not involved in cross-reactivity between grass, birch, and peach, confirming the minor role of PR-10 allergens [67]. In addition, a Spanish study including 92 patients with a history of allergy to apple found a significant association between sensitization to Mal d 3 and Mal d 4 and outcome of double-blind placebo-controlled food challenge (DBPCFC), while sensitization to Mal d 1 were not associated with symptom development. These results suggest that PR-10 sensitization is not clinically relevant in this part of Europe. The major allergen in the Western Mediterranean areas is LTP and judged from the studies in Table 4, this allergen can be involved in both class 1 and class 2 allergies, with mugwort and plane tree pollen as likely primary sensitizers in the latter. It has been demonstrated that extracts from grass and birch pollen do not inhibit binding of IgE antibodies to *Rosaceae* fruits in a serum pool from Spanish LTP sensitized patients, as opposed to mugwort pollen, which did inhibit IgE binding [65]. Therefore, it is likely, that presence of grass and birch pollinosis is not associated to LTP sensitization. Profilin sensitization is the second most important allergen in the Western Mediterranean countries and both monosensitization to profilin and co-sensitization to profilin and LTP seem to be of clinical relevance (Table 4). According to the results in Table 5, profilin sensitization is associated with both *Rosaceae* and non-*Rosaceae* fruits, which is concordant with the ubiquitous nature of profilin in plants. Two other studies have confirmed this tendency [65, 68]. In one of these studies, carried out in Spain, profilin-sensitized patients allergic to *Rosaceae* fruits and pollens, were sensitized to both a higher number of fruits and a wider variety of fruits, including fruits outside the *Rosaceae* family. Conversely, patients without pollinosis were not sensitized to profilin and primarily demonstrated reactivity to *Rosaceae* fruits only [65]. In the second study, profilin sensitization was associated with a higher number of positive IgE reactions to both different plant foods and pollens [68]. Sensitization to more pollens was also a characteristic for profilin-sensitized patients in a study by Mari et al. [66]. The characteristic Western Mediterranean allergy patterns seem to be similar for all *Rosaceae* fruits with only strawberry as a possible exception. However, peach allergy is most widespread and probably the primary sensitizer in most cases.

In Northern and Central Europe *Rosaceae* fruit allergies of class 1 and LTP sensitization are almost absent. The major class 2 fruit allergy pattern characteristic for this area is the association between birch pollen allergy and *Rosaceae* fruit allergy, with PR-10 as the most frequent

Table 5 Results from cross-sectional studies investigating associations between allergies to fruits and pollens

C ^a	No. ^b	Selection criteria ^c	Method	Significant associations between pollen and fruit allergies and different fruit allergies	Ref.
ES	61	PF and PO	SPT	For profilin-sensitized patients: melon, watermelon and banana	[92]
ES	35	PF and PO	SPT	Apple, pear and plum	[17]
ES	95	PO	SPT	Peach and apple; Peach and pear; Peach and plum	[17]
ES	22	RF (confirmed by DBPCFC), PO (59%)	DBPCFC	Peach, plum, apple and apricot	[93]
IT	262	PF	SPT	Apple, pear, and cherry were associated with birch Melon, watermelon, and orange were associated with grass Apple, watermelon, and melon were associated with mugwort Melon and cherry were associated with <i>parietaria</i> Peach, plum, cherry, and apricot Apple and cherry; Apple and pear; Melon and watermelon	[94]
IT	71	PF	SPT	For profilin-sensitized patients: melon, watermelon, banana, citrus fruits For PR-10 sensitized patients: apple, cherry, <i>Rosaceae</i> fruits	[95]
CH	111	PF (Apple, melon, peach, carrot, potato and/or celery) and PO (Birch, ragweed and/or grass)	CAP	Two patterns of reactivity in patients: (1) Birch and apple (2) Allergy to all included plant foods and pollens	[96]
NL	43	FR (confirmed by RAST) and birch	RAST	Apple, peach, pear and cherry	[97]
SE	293	PF and birch	SPT	Apple, Peach, pear, plum, cherry and apricot were associated with birch	[98]
SE	467	F	SPT	Apple, pear, Kiwi and stone fruits were associated with birch	[13]
SE, DK, EE, LT, RU	685	F	SPT	Apple, peach, pear, plum, apricot and kiwi were associated with birch	[14]

^a C country: CH Switzerland, DK Denmark, EE Estonia, ES Spain, IT Italy, LT Lithuania, NL The Netherlands, PT Portugal, RU Russia, SE Sweden

^b N number of subjects

^c Abbreviations used for patient histories of allergy: PO (pollen allergy), F (food allergy), FR (fruit allergy)

DBPCFC double-blind placebo-controlled food challenge. PF (plant food allergy), RF *Rosaceae* fruits

cross-reacting allergen. Although several *Rosaceae* fruits can be involved, apple is most frequently associated with birch pollen allergy. In a Finnish study [69], it has been demonstrated that apple extract did not inhibit birch extract when using a serum pool from 20 patients with an allergy to apple, confirming that birch pollen is likely the primary sensitizer. The second most widespread allergy pattern in Central- and Northern Europe involves profilin. However, no clear associations between profilin-sensitized patients and pollen allergies can be determined from the existing studies. It is likely that grass pollen is a primary sensitizer like in the Western Mediterranean countries, but monosensitization to profilin seems to be less common in Northern- and Central Europe as judged from the results in Table 4. The clinical relevance of

profilin is therefore hard to determine. In the Swiss study in Table 5, two significant associations were found of which one involved several pollens and plant foods, while the other involved only birch and apple. This result could likely be explained by profilin sensitization and PR-10 sensitization, respectively, and suggests that profilin sensitization is associated with presence of several concomitant allergies.

The *Rosaceae* fruit allergy patterns in Italy is a special case, as both the Mediterranean and the Northern and Central European allergy patterns can be found in this country. In accordance with this, it has been demonstrated in one Italian study that the frequency of LTP sensitization was higher in the Southern parts of the country, where pollen-associated fruit allergy was almost absent. Conversely, pollen-

associated fruit allergies dominated in the Northern parts of the country [70].

In Fig. 3, the major *Rosaceae* fruit allergy patterns in Europe are summarized. The cause for the geographic differences in fruit allergies is unknown, but a likely explanation is differences in pollen exposures. Furthermore, genetic as well as cultural differences, such as eating habits, possibly have an impact [13, 71, 72].

Limitations in findings

The studies reviewed in Tables 4 and 5 are limited to relatively few countries, which implies a risk for biased findings. The allergy pattern for the Western Mediterranean area and Northern- and Central Europe may therefore be altered, if future studies in neighboring countries, reveal alternative allergy patterns. A limited number of patients are included in the majority of studies and generally, the subjects are selected based on predefined criteria. The results from some studies might therefore be emphasized too much in the interpretation of allergy patterns. In continuation of this, the relative importance of the allergy patterns depicted in Fig. 3 is impossible to confirm at this time. Furthermore, peach allergy and apple allergy are by far the best studied, and it cannot be left out that allergy patterns might deviate slightly if more studies were carried out for other *Rosaceae* fruits such as strawberry. Although PR-10, profilin, and LTP allergen families are the most important cross-reacting allergens, some *Rosaceae* fruits contain other allergens (Table 1) and as these have not been taken into account in this review additional allergy patterns of *Rosaceae* fruits can probably be found.

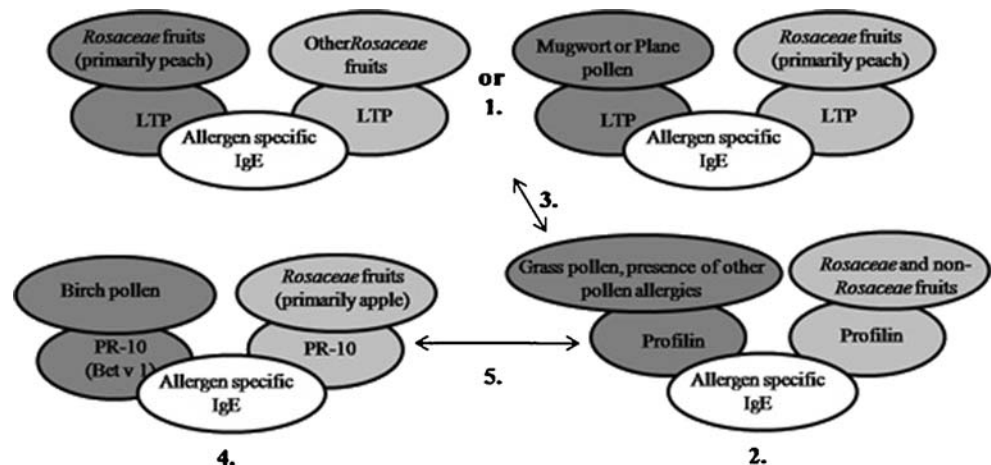
The studies carried out investigating fruit allergies generally do not report the full clinical patient histories of pollen and fruit allergies and as these are closely linked to allergen sensitization patterns this is an important shortcoming. Furthermore, sensitizations to all three major

allergen families have not been determined in all studies and co-sensitizations to more allergens might therefore be more widespread than the results from Table 4 suggests. Finally, many studies only report data at the group level which limits the possibilities to identify associations between allergen sensitization patterns and specific allergies to fruits and pollens.

Applicability of allergy patterns in the diagnosis of fruit allergy and prescription of avoidance diets

Fruit allergy diagnosis is often established based on patient history of adverse reactions to fruit combined with a positive SPT and in vitro IgE test to fresh or commercial fruit extracts [22]. However, due to the various sensitization patterns across Europe, knowledge about the fruits involved is not optimal in order to prescribe the safest and most restricted avoidance diets, at this time. For example, heat-treated fruits will be tolerable for PR-10 and profilin fruit allergy sufferers as regards IgE-mediated reactions but not for LTP fruit allergy sufferers. On the contrary, peeled fruits will only be an alternative for some groups of LTP sensitized patients. In a study by Asero et al. [73], it was demonstrated that banana and melon were safe fruits to consume for patients monosensitized to LTP based on open food challenges and SPT tests with 49 patients. These examples illustrate that availability of fruits for fruit allergy sufferers could be increased in a safer way by applying purified or recombinant allergens for testing rather than fruit extracts. In addition, new hypoallergenic fruits could be developed that are suitable for patients with specific allergy patterns. Knowledge about the widespread allergy patterns in Europe, as illustrated in Fig. 3 will make it easier to assess which allergens are most relevant to test for a given patient history of *Rosaceae* fruit allergy. Furthermore, the results in Table 4 suggest that the allergen source used for testing is of minor importance to establish whether a patient is

Fig. 3 Illustration of the most widespread *Rosaceae* fruit allergy patterns in Europe. Ovals in dark gray represent sources of primary sensitization, light gray represent cross-reactions. Arrows indicate co-sensitization. Entities with numbers 1 (LTP), 2 (profilin) and 3 (co-sensitization to LTP and profilin) are characteristic for Western Mediterranean areas. Entities with numbers 4 (PR-10) and 5 (co-sensitization to PR-10 and profilin) are characteristic for Central- and Northern Europe



sensitized to a specific allergen family and therefore the number of test materials could likely be reduced considerably by using purified or recombinant allergens.

Although knowledge about involved allergens could probably improve the safety of prescribed diets, there are still several important issues to clarify. One of the major limitations in the studies included in this review is the cross-sectional design which implies that knowledge about disease development of fruit allergies over time is lacking [21]. Determinants for development of allergies to more fruits are therefore unknown. Furthermore, the tolerable amounts of allergens might change over time depending on allergen exposure. It has been demonstrated in challenge tests that the amount of fruit tolerated before symptom development varies highly among fruit allergy sufferers [74–76] and therefore some fruit allergy sufferers might be able to eat fruits in small portions without developing symptoms. However, this is not advisable if tolerance levels to allergens thereby decreases.

Conclusion

Sensitization patterns to the major allergen families, PR-10, LTP, and profilin, in *Rosaceae* fruit allergenicity seem to vary characteristically across Europe, with considerable differences between the Western Mediterranean areas and Central and Northern Europe. If the knowledge about disease patterns is combined with patient disease history, procedures for fruit allergy testing can likely be optimized by the use of purified or recombinant allergens. Furthermore, such testing can be beneficial for fruit allergy sufferers as knowledge about involved allergens may contribute to increased and safer fruit availability.

Perspectives

The results from the review have been used to draft a web site for fruit allergy sufferers, where they can identify their type of fruit allergy and find information about fruit products they can tolerate. In addition, the latest research on hypoallergenic fruits, such as naturally low-allergenic and genetically modified cultivars, will be presented. Besides dissemination of knowledge to increase fruit availability among fruit allergy sufferers, the web site could contribute to the identification of how fruit allergy sufferers perceive their fruit allergy in relation to fruit consumption. This information portal will be drafted as a part of the ISAFRUIT project (www.isafruit.org), an EU FP6 integrated project aimed to remove barriers to fruit consumption. Future work in the area of fruit allergy could aim to identify associations between numbers and types of the fruits,

pollens, and allergens involved, in order to investigate whether the fruit allergy patterns outlined in this paper can be further verified and specified. Additionally, it would be interesting to carry out systematic studies that covered wider parts of Europe and longitudinal studies to investigate development of fruit allergies over time.

References

1. Vainio H, Weiderpass E (2006) Fruit and vegetables in cancer prevention. *Nutrition and Cancer-An International Journal* 54 (1):111–142
2. Hamer M, Chida Y (2007) Intake of fruit, vegetables, and antioxidants and risk of type 2 diabetes: systematic review and meta-analysis. *J Hypertens* 25(12):2361–2369
3. He FJ, Nowson CA, MacGregor GA (2006) Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. *Lancet* 367(9507):320–326
4. Dauchet L, Amouyel P, Dallongeville J (2005) Fruit and vegetable consumption and risk of stroke—a meta-analysis of cohort studies. *Neurology* 65(8):1193–1197
5. He FJ, Nowson CA, Lucas M, MacGregor GA (2007) Increased consumption of fruit and vegetables is related to a reduced risk of coronary heart disease: meta-analysis of cohort studies. *J Hum Hypertens* 21(9):717–728
6. Dauchet L, Amouyel P, Hercberg S, Dallongeville J (2006) Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies. *J Nutr* 136(10):2588–2593
7. Increasing Fruit Consumption to Improve Health (2008) ISAFRUIT Forum. *Scripta Horticulturae*. Report No. 8, Oct 28
8. Zuidmeer L, Goldhahn K, Rona RJ, Gislason D, Madsen C, Summers C et al (2008) The prevalence of plant food allergies: a systematic review. *J Allergy Clin Immunol* 121(5):1210–1218
9. Young E, Stoneham MD, Petruckevitch A, Barton J, Rona R (1994) A population study of food intolerance. *Lancet* 343 (8906):1127–1130
10. Alvarado MI, Pérez M (2006) Study of food allergy in the Spanish population. *Allergol Immunopathol* 34(5):185–193
11. Fernandez-Rivas M, Bolhaar S, Gonzalez-Mancebo E, Asero R, van Leeuwen A, Bohle B et al (2006) Apple allergy across Europe: how allergen sensitization profiles determine the clinical expression of allergies to plant foods. *J Allergy Clin Immunol* 118(2):481–488
12. Reuter A, Lidholm J, Andersson K, Ostling J, Lundberg M, Scheurer S et al (2006) A critical assessment of allergen component-based in vitro diagnosis in cherry allergy across Europe. *Clin Exp Allergy* 36(6):815–823
13. Eriksson NE, Moller C, Bengtsson U, Wihl JA (2004) Food hypersensitivity in patients of Swedish allergy centers. *Allergologie* 27(6):233–243
14. Eriksson NE, Moller C, Werner S, Magnusson J, Bengtsson U, Zolubas M (2004) Self-reported food hypersensitivity in Sweden, Denmark, Estonia, Lithuania, and Russia. *J Investig Allergol Clin Immunol* 14(1):70–79
15. Woods RK, Abramson M, Bailey M, Walters EH (2001) International prevalences of reported food allergies and intolerances. Comparisons arising from the European Community Respiratory Health Survey (ECRHS) 1991–1994. *Eur J Clin Nutr* 55(4):298–304
16. Zuberbier T, Edenharter G, Worm M, Ehlers I, Reimann S, Hantke T et al (2004) Prevalence of adverse reactions to food in Germany—a population study. *Allergy* 59(3):338–345

17. Cuesta-Herranz J, Lazaro M, Figueredo E, Igea JM, Umpierrez A, De-Las-Heras M (2000) Allergy to plant-derived fresh foods in a birch- and ragweed-free area. *Clin Exp Allergy* 30 (10):1411–1416
18. Lázaro M, Cuesta J, Igea JM (1999) Allergy to *Rosaceae*: the peach. *Alergol Immunol Clin* 14(4):234–240
19. Falcao H, Lunet N, Lopes C, Barros H (2004) Food hypersensitivity in Portuguese adults. *Eur J Clin Nutr* 58(12):1621–1625
20. Primavesi L, Brenna OV, Pompei C, Pravettoni V, Farioli L, Pastorello EA (2006) Influence of cultivar and processing on cherry (*Prunus avium*) allergenicity. *J Agric Food Chem* 54 (26):9930–9935
21. Sicherer SH (2001) Clinical implications of cross-reactive food allergens. *J Allergy Clin Immunol* 108(6):881–890
22. Asero R, Ballmer-Weber BK, Beyer K, Conti A, Dubakiene R, Fernandez-Rivas M et al (2007) IgE-Mediated food allergy diagnosis: current status and new perspectives. *Mol Nutr Food Res* 51(1):135–147
23. Hofmann A, Burks AW (2008) Pollen food syndrome: update on the allergens. *Curr Allergy and Asthma Rep* 8 (5):413–417
24. Pastorello EA, D'Ambrosio FP, Pravettoni V, Farioli L, Giuffrida G, Monza M et al (2000) Evidence for a lipid transfer protein as the major allergen of apricot. *J Allergy Clin Immunol* 105 (2):371–377
25. Salcedo G, Sanchez-Monge R, Barber D, az-Perales A (2007) Plant non-specific lipid transfer proteins: an interface between plant defence and human allergy. *Biochimica et Biophysica Acta-Molecular and Cell Biology of Lipids* 1771(6):781–791
26. Nicoletti C, Temblay JN, Ivory K (2007) The immune system and allergic responses to food. In: Mills C, Wichers H, Hoffmann-Sommergruber K (eds) *Managing allergens in food*. Woodhead, Cambridge, pp 29–46
27. Bousquet J, Anto JM, Bachert C, Bousquet PJ, Colombo P, Cramer R et al (2006) Factors responsible for differences between asymptomatic subjects and patients presenting an IgE sensitization to allergens. A GA(2)LEN project. *Allergy* 61(6):671–680
28. Breiteneder H, Radauer C (2004) A classification of plant food allergens. *J Allergy Clin Immunol* 113(5):821–830
29. International Union of Immunological Societies. Allergen Nomenclature Sub-Committee. <http://www.allergen.org/Allergen.aspx>. 9-5-2009. Ref Type: Internet Communication
30. Midoro-Horiuti T, Brooks EG, Goldblum RM (2001) Pathogenesis-related proteins of plants as allergens. *Ann Allergy Asthma Immunol* 87(4):261–271
31. Puehringer HM, Zinoecker I, Marzban G, Katinger H, Laimer M (2003) MdAP, a novel protein in apple, is associated with the major allergen Mal d 1. *Gene* 321:173–183
32. Ebner C, Birkner T, Valenta R, Rumpold H, Breitenbach M, Scheiner O et al (1991) Common epitopes of birch pollen and apples—studies by Western and Northern Blot. *J Allergy Clin Immunol* 88(4):588–594
33. Vanekkrebitz M, Hoffmannsommergruber K, Machado MLD, Susani M, Ebner C, Kraft D et al (1995) Cloning and sequencing of Mal-D-1, the major allergen from apple (*Malus domestica*), and its immunological relationship to Bet-V-1, the major birch pollen allergen. *Biochem Biophys Res Commun* 214(2):538–551
34. Gaier S, Marsh J, Oberhuber C, Rigby NM, Lovegrove A, Alessandri S et al (2008) Purification and structural stability of the peach allergens Pru p 1 and Pru p 3. *Mol Nutr Food Res* 52: S220–S229
35. Ebner C, Hirschwehr R, Bauer L, Breiteneder H, Valenta R, Ebner H et al (1995) Identification of allergens in fruits and vegetables—Ige cross-reactivities with the important birch pollen allergens Bet-V-1 and Bet-V-2 (birch profilin). *J Allergy Clin Immunol* 95(5):962–969
36. Scheurer S, Son DY, Boehm M, Karamloo F, Franke S, Hoffmann A et al (1999) Cross-reactivity and epitope analysis of Pru a 1, the major cherry allergen. *Mol Immunol* 36(3):155–167
37. Bohle B, Zwoelfer B, Heratizadeh A, Jahn-Schmid B, Antonia YD, Alter M et al (2006) Cooking birch pollen-related food: divergent consequences for IgE- and T cell-mediated reactivity in vitro and in vivo. *J Allergy Clin Immunol* 118(1):242–249
38. Scheurer S, Lauer I, Foetisch K, Moncin MSM, Retzek M, Hartz C et al (2004) Strong allergenicity of Pru av 3, the lipid transfer protein from cherry, is related to high stability against thermal processing and digestion. *J Allergy Clin Immunol* 114(4):900–907
39. Asero R, Mistrello G, Roncarolo D, Amato S (2006) SPT with heat-processed apple peel extract to detect LTP hypersensitivity. *European annals of allergy and clinical immunology* 38 (10):351–354
40. Hsieh LS, Moos M, Lin Y (1995) Characterization of apple 18 and 31 kD allergens by microsequencing and evaluation of their content during storage and ripening. *J Allergy Clin Immunol* 96 (6):960–970
41. Salcedo G, Sanchez-Monge R, az-Perales A, Garcia-Casado G, Barber D (2004) Plant non-specific lipid transfer proteins as food and pollen allergens. *Clin Exp Allergy* 34(9):1336–1341
42. Diaz-Perales A, Garcia-Casado G, Sanchez-Monge R, Garcia-Selles FJ, Barber D, Salcedo G (2002) cDNA cloning and heterologous expression of the major allergens from peach and apple belonging to the lipid-transfer protein family. *Clin Exp Allergy* 32(1):87–92
43. Pastorello EA, Pravettoni V, Farioli L, Rivolta F, Conti A, Ispano M et al (2002) Hypersensitivity to mugwort (*Artemisia vulgaris*) in patients with peach allergy is due to a common lipid transfer protein allergen and is often without clinical expression. *J Allergy Clin Immunol* 110(2):310–317
44. Lombardero M, Garcia-Selles FJ, Polo F, Jimeno L, Chamorro MJ, Garcia-Casado G et al (2004) 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* 34(9):1415–1421
45. Diaz-Perales A, Lombardero M, Sanchez-Monge R, Garcia-Selles FJ, Pernas M, Fernandez-Rivas M et al (2000) 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* 30 (10):1403–1410
46. Pastorello EA, Farioli L, Pravettoni V, Giuffrida MG, Ortolani C, Fortunato D et al (2001) Characterization of the major allergen of plum as a lipid transfer protein. *Journal of Chromatography B-Analytical Technologies in the Biomedical and Life Sciences* 756(1–2):95–103
47. Borges JP, Barre A, Culerrier R, Grainer C, Didier A, Rouge P (2008) Lipid transfer proteins from *Rosaceae* fruits share consensus epitopes responsible for their IgE-binding cross-reactivity. *Biochem Biophys Res Commun* 365(4):685–690
48. Pastorello EA, Robino AM (2004) Clinical role of lipid transfer proteins in food allergy. *Mol Nutr Food Res* 48(5):356–362
49. van Ree R (2002) Clinical importance of non-specific lipid transfer proteins as food allergens. *Biochem Soc Trans* 30:910–913
50. Asero R, Mistrello G, Roncarolo D, Amato S, Falagiani P (2003) Analysis of the heat stability of lipid transfer protein from apple. *J Allergy Clin Immunol* 112(5):1009–1011
51. Carnes J, Fernandez-Caldas E, Gallego MT, Ferrer A, Cuesta-Herranz J (2002) Pru p 3 (LTP) content in peach extracts. *Allergy* 57(11):1071–1075
52. Fernandez-Rivas M, Cuevas M (1999) Peels of *Rosaceae* fruits have a higher allergenicity than pulps. *Clin Exp Allergy* 29 (9):1239–1247

53. Marzban G, Puehringer H, Dey R, Brynda S, Ma Y, Martinelli A et al (2005) Localisation and distribution of the major allergens in apple fruits. *Plant Sci* 169(2):387–394
54. Borges JP, Jauneau A, Brule C, Culerrier R, Barre A, Didier A et al (2006) The lipid transfer proteins (LTP) essentially concentrate in the skin of *Rosaceae* fruits as cell surface exposed allergens. *Plant Physiol Biochem* 44(10):535–542
55. Scheurer S, Wangorsch A, Nerkamp J, Skov PS, Ballmer-Weber B, Wuthrich B et al (2001) Cross-reactivity within the profilin panallergen family investigated by comparison of recombinant profilins from pear (*Pyr c* 4), cherry (*Pru av* 4) and celery (*Api g* 4) with birch pollen profilin Bet v 2. *Journal of Chromatography B-Analytical Technologies in the Biomedical and Life Sciences* 756(1–2):315–325
56. Fedorov AA, Ball T, Mahoney NM, Valenta R, Almo SC (1997) The molecular basis for allergen cross-reactivity: crystal structure and IgE-epitope mapping of birch pollen profilin. *Structure* 5(1):33–45
57. Radauer C, Willeroeder M, Fuchs H, Hoffmann-Sommergruber K, Thalhamer J, Ferreira F et al (2006) Cross-reactive and species-specific immunoglobulin E epitopes of plant profilins: an experimental and structure-based analysis. *Clin Exp Allergy* 36(7):920–929
58. Ma Y, Zuidmeer L, Bohle B, Bolhaarz STH, Gadermaier G, Gonzalez-Mancebo E et al (2006) Characterization of recombinant Mal d 4 and its application for component-resolved diagnosis of apple allergy. *Clin Exp Allergy* 36(8):1087–1096
59. Diaz-Perales A, Sanz ML, Garcia-Casado G, Sanchez-Monge R, Garcia-Selles FJ, Lombardero M et al (2003) Recombinant Pru p 3 and natural Pru p 3, a major peach allergen, show equivalent immunologic reactivity: a new tool for the diagnosis of fruit allergy. *J Allergy Clin Immunol* 111(3):628–633
60. Gamboa PM, Sanz ML, Lombardero M, Barber D, Sanchez-Monge R, Goikoetxea MJ et al (2009) Component-resolved in vitro diagnosis in peach-allergic patients. *J Investig Allergol Clin Immunol* 19(1):13–20
61. Scheurer S, Metzner K, Haustein D, Vieths S (1997) Molecular cloning, expression and characterization of Pru a 1, the major cherry allergen. *Mol Immunol* 34(8–9):619–629
62. Fernandez-Rivas M, Gonzalez-Mancebo E, Rodriguez-Perez R, Benito C, Sanchez-Monge R, Salcedo G et al (2003) Clinically relevant peach allergy is related to peach lipid transfer protein, Pru p 3, in the Spanish population. *J Allergy Clin Immunol* 112(4):789–795
63. Rossi RE, Monasterolo G, Operti D, Corsi M (1996) Evaluation of recombinant allergens Bet v 1 and Bet v 2 (profilin) by Pharmacia CAP system in patients with pollen-related allergy to birch and apple. *Allergy* 51(12):940–945
64. Ballmer-Weber BK, Scheurer S, Fritsche P, Enrique E, Cistero-Bahima A, Haase T et al (2002) Component-resolved diagnosis with recombinant allergens in patients with cherry allergy. *J Allergy Clin Immunol* 110(1):167–173
65. Fernandez-Rivas M, van Ree R, Cuevas M (1997) Allergy to *Rosaceae* fruits without related pollinosis. *J Allergy Clin Immunol* 100(6):728–733
66. Mari A, Wallner M, Ferreira F (2003) Fagales pollen sensitization in a birch-free area: a respiratory cohort survey using Fagales pollen extracts and birch recombinant allergens (rBet v 1, rBet v 2, rBet v 4). *Clin Exp Allergy* 33:1419–1428
67. Cuesta-Herranz J, Lazaro M, Martinez A, Figueredo E, Palacios R, de-Las-Heras M et al (1999) Pollen allergy in peach-allergic patients: sensitization and cross-reactivity to taxonomically unrelated pollens. *J Allergy Clin Immunol* 104(3):688–694
68. Wensing M, Akkerdaas JH, van Leeuwen A, Stapel SO, Bruijnzeel-Koomen CAFM, Aalberse RC et al (2002) IgE to Bet v 1 and profilin: cross-reactivity patterns and clinical relevance. *J Allergy Clin Immunol* 110(3):435–442
69. Bjorksten F, Halmeppuro L, Hannuksela M, Lahti A (1980) Extraction and properties of apple allergens. *Allergy* 35(8):671–677
70. Asero R, Antonicelli L, Arena A, Bommarito L, Caruso B, Crivellaro M et al (2009) EpidemAAITO: features of food allergy in Italian adults attending allergy clinics: a multi-centre study. *Clin Exp Allergy* 39(4):547–555
71. Fernandez-Rivas M, Miles S (2004) Food allergies: clinical and psychosocial perspectives. In: Mills ENC, Shewry PR (eds) *Plant food allergens*. Blackwell, Oxford, pp 1–23
72. Ballmer-Weber BK (2002) Lipid transfer protein as a potential panallergen? *Allergy* 57(10):873–875
73. Asero R, Mistrello G, Roncarolo D, Amato S (2007) Detection of some safe plant-derived foods for LTP-allergic patients. *Int Arch Allergy Immunol* 144:57–63
74. Pastorello EA, Farioli L, Pravettoni V, Ortolani C, Ispano M, Monza M et al (1999) The major allergen of peach (*Prunus persica*) is a lipid transfer protein. *J Allergy Clin Immunol* 103(3):520–526
75. Pastorello EA, Pravettoni V, Farioli L, Ispano M, Fortunato D, Monza M et al (1999) Clinical role of a lipid transfer protein that acts as a new apple-specific allergen. *J Allergy Clin Immunol* 104(5):1099–1106
76. Pastorello EA, Ortolani C, Farioli L, Pravettoni V, Ispano M, Borga A et al (1994) Allergenic cross-reactivity among peach, apricot, plum, and cherry in patients with oral allergy syndrome—an in-vivo and in-vitro study. *J Allergy Clin Immunol* 94(4):699–707
77. D'Amato G, Cecchi L, Bonini S, Nunes C, Nnesi-Maesano I, Behrendt H et al (2007) Allergenic pollen and pollen allergy in Europe. *Allergy* 62(9):976–990
78. van Ree R, Fernandez-Rivas M, Cuevas M, Vanwijngaarden M, Aalberse RC (1995) Pollen-related allergy to peach and apple—an important role for profilin. *J Allergy Clin Immunol* 95(3):726–734
79. Lauer I, Miguel-Moncin MS, Abel T, Foetisch K, Hartz C, Fortunato D et al (2007) 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* 37(2):261–269
80. Daschner A, Crespo JF, Pascual CY (1998) Specific IgE to recombinant vegetal panallergen (rBet v 2) and fruit allergy in pollinic patients. *Allergy* 53(6):614–618
81. Garcia-Selles FJ, az-Perales A, Sanchez-Monge R, Alcantara M, Lombardero M, Barber D et al (2002) Patterns of reactivity to lipid transfer proteins of plant foods and *Artemisia* pollen: an in vivo study. *Int Arch Allergy Immunol* 128(2):115–122
82. Díez-Gómez ML, Quirce S, Cuevas M, Sánchez-Fernández C, Baz G, Moradiellos FJ et al (1999) Fruit-pollen-latex cross-reactivity: implication of profilin (Bet v 2). *Allergy* 54(9):951–961
83. Rodriguez-Perez R, Fernandez-Rivas M, Gonzalez-Mancebo E, Sanchez-Monge R, az-Perales A, Salcedo G (2003) Peach profilin: cloning, heterologous expression and cross-reactivity with Bet v 2. *Allergy* 58(7):635–640
84. Gamboa PM, Cáceres O, Antepara I, Sanchez-Monge R, Ahrazem O, Salcedo G et al (2007) Two different profiles of peach allergy in the north of Spain. *Allergy* 62:408–414
85. Gonzalez-Mancebo E, Rodriguez-Perez R, Alonso MD, Rosado A, Tejedor MA, Vila C et al (2002) Peach allergy. Clinical characteristics and allergen sensitization in 84 patients evaluated by DBPCFC. *Allergy* 57:27
86. Zuidmeer L, Salentijn E, Rivas MF, Mancebo EG, Asero R, Matos CI et al (2006) The role of profilin and lipid transfer protein in strawberry allergy in the Mediterranean area. *Clin Exp Allergy* 36(5):666–675

87. Rodrigues-Alves R, Lopez A, Pereira-Santos MC, Lopes-Silva S, Spínola-Santos A, Costa C et al (2009) Clinical, anamnestic and serological features of peach allergy in Portugal. *Int Arch Allergy Immunol* 149:65–73
88. Scheurer S, Pastorello EA, Wangorsch A, Kastner M, Hausteiner D, Vieths S (2001) Recombinant allergens Pru av 1 and Pru av 4 and a newly identified lipid transfer protein in the in vitro diagnosis of cherry allergy. *J Allergy Clin Immunol* 107(4):724–731
89. Pauli G, Oster JP, Deviller P, Heiss S, Bessot JC, Susani M et al (1996) Skin testing with recombinant allergens rBet v 1 and birch profilin, rBet v 2: diagnostic value for birch pollen and associated allergies. *J Allergy Clin Immunol* 97(5):1100–1109
90. Erdmann SM, Sachs B, Schmidt A, Merk HF, Scheiner O, Moll-Sladowy S et al (2005) In vitro analysis of birch-pollen-associated food allergy by use of recombinant allergens in the basophil activation test. *Int Arch Allergy Immunol* 136(3):230–238
91. Karamloo F, Scheurer S, Wangorsch A, May S, Hausteiner D, Vieths S (2001) Pyr c 1, the major allergen from pear (*Pyrus communis*), is a new member of the Bet v 1 allergen family. *Journal of Chromatography B-Analytical Technologies in the Biomedical and Life Sciences* 756(1–2):281–293
92. Asero R, Monsalve R, Barber D (2008) Profilin sensitization detected in the office by skin prick test: a study of prevalence and clinical relevance of profilin as a plant food allergen. *Clin Exp Allergy* 38(6):1033–1037
93. Rodriguez J, Crespo JF, Lopez-Rubio A, de la Cruz-Bertolo J, Ferrando-Vivas P, Vives R et al (2000) Clinical cross-reactivity among foods of the *Rosaceae* family. *J Allergy Clin Immunol* 106(1):183–189
94. Ortolani C, Ispano M, Pastorello E, Bigi A, Ansaloni R (1988) The oral allergy syndrome. *Annals of Allergy* 61(6):47–52
95. Asero R, Mistrello G, Roncarolo D, Amato S, Zanoni D, Barocci F et al (2003) Detection of clinical markers of sensitization to profilin in patients allergic to plant-derived foods. *J Allergy Clin Immunol* 112(2):427–432
96. Bircher AJ, Vanmelle G, Haller E, Curty B, Frei PC (1994) IgE to food allergens are highly prevalent in patients allergic to pollens, with and without symptoms of food allergy. *Clin Exp Allergy* 24(4):367–374
97. Calkhoven PG, Aalbers M, Koshte VL, Pos O, Oei HD, Aalberse RC (1987) Cross-reactivity among birch pollen, vegetables and fruits as detected by IgE antibodies is due to at least three distinct cross-reactive structures. *Allergy* 42(5):382–390
98. Eriksson NE, Formgren H, Svenonius E (1982) Food hypersensitivity in patients with pollen allergy. *Allergy* 37(6):437–443
99. Sicherer SH (2000) Determinants of systemic manifestations of food allergy. *J Allergy Clin Immunol* 106(5):251–257
100. Holm J, Baerentzen G, Gajhede M, Ipsen H, Larsen JN, Lowenstein H et al (2001) Molecular basis of allergic cross-reactivity between group 1 major allergens from birch and apple. *Journal of Chromatography B* 756(1–2):307–313
101. Ferreira F, Hawranek T, Gruber P, Wopfner N, Mari A (2004) Allergic cross-reactivity: from gene to the clinic. *Allergy* 59(3):243–267