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Lipid Transfer Protein Sensitization: Risk of Anaphylaxis and Molecular Sensitization Profile in Pru p 3-Sensitized Patients

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Keywords
Lipid transfer proteins · Pru p 3 · Component-resolved diagnosis · Anaphylaxis · Risk factors

Abstract
Background: Component-resolved diagnosis reveals the IgE response to many inhaled, food, and other allergens, improving the understanding and diagnosis of allergic diseases. ***Objective:*** The aims of the study are to study the recognition of different lipid transfer proteins (LTPs) and other allergen families in a large group of people sensitized to Pru p 3 and to analyze the relationship between the clinical entities and the allergens. ***Methods:*** This cross-sectional study included a large cohort of patients with positive skin tests to peach fruit and Pru p 3 specific IgE antibodies. Respiratory and food allergy symptoms were collected, and we performed prick tests with pollen, plant food, and other allergens plus the ImmunoCAP ISAC assay. ***Results:*** Our sample consisted of 421 people with a mean age of 33.25 years (range 16–68); 54.6% were women. Clinical entities included anaphylaxis (37.1%), urticaria (67.9%), and oral allergy syndrome (59.1%). Rhinitis, rhinoconjunctivitis, and/or asthma were diagnosed in 71.8% of the participants. The most pronounced correlation existed between sensitization to Pru p 3 and to Jug r 3, Pla a 3, Ara h 9, and Cor a 8. We found a higher incidence of anaphylaxis in people with 5 or more recognized LTPs. No association was observed between inhaled and food allergies. ***Conclusion:*** Most Pru p 3-sensitized participants were sensitized to additional allergens from the same family and, to a lesser extent, to other allergens, mainly in the profilin and PR-10 protein families. Anaphylaxis occurred in more than a third of the cases evaluated, and almost three-quarters of them had respiratory symptoms. Respiratory and food allergies involving LTPs do not seem to be associated.

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Introduction

Food allergy is increasing, with fruits and tree nuts among the most common source of allergens in adults living in the Mediterranean region [1, 2]. Lipid transfer proteins (LTPs) are one of the protein families most commonly involved [3], and plant allergy due to LTP sensitization is frequently associated with polysensitization, with a variable degree of cross-reactivity between different fruits, plant foods, and pollen. This poses challenges for managing allergies, potentially affecting the quality of life of people who avoid eating several foods.

LTPs are a class of low-molecular-weight, hydrophobic proteins, with highly conserved structures comprising 4 intramolecular disulfide bonds, making them very resistant to proteolysis and harsh food-processing conditions [4, 5]. These are strong allergens that, in most cases, sensitize through the gut and share epitopes with proteins of different sources, including plants and pollen. Peach LTP, Pru p 3, is a primary sensitizer in the Mediterranean area and the most frequent food allergen [1, 2, 6, 7]. Reported cases of LTP allergy are also increasing elsewhere, including in Northern Europe, China, and Japan [8–10]. These publications reflect substantial heterogeneity between geographic areas, so further research is needed to assess local and regional variations. LTPs have also been described in a wide number of pollen like *Ambrosia artemisiifolia*, *Artemisia vulgaris*, *Platanus acerifolia*, and *Cannabis sativa*, among others. Art v 3 and Pla a 3 can elicit rhinitis in sensitized patients due to a primary sensitization to Pru p 3. In these cases, primary sensitization can occur by the inhalation route [7, 11–13].

Component-resolved diagnosis measures specific IgE (sIgE) against individual allergen molecules (purified native or recombinant), enabling the identification of the patient's recognition profile and potential cross-reactivities. The microarray (ImmunoCAP ISAC) involves a multiplex format, measuring many allergens at once [14], which makes it a high-capacity tool for diagnosing multiple allergens, such as pollen [15, 16] (grass, cypress, olive tree, plane tree, and wall pellitory) and food allergens, including peach and nuts [17, 18].

In this study, we analyze the molecular sensitization profile and clinical entities in a large group of people sensitized to Pru p 3, who were referred to our allergy center. The main aim was to establish the relationship between anaphylaxis and LTP sensitization, although allergens of other well-known families were also considered.

Materials and Methods

Patient Selection

A cross-sectional study was conducted. Our sample was drawn from 2,100 patients, aged 16–90 years, with a history of allergy to food or other allergens and referred to our center from 2015 to 2019. Inclusion criteria were (1) sensitization by skin prick test (SPT) to peach peel (commercialized extract containing 30 μg/mL of Pru p 3 by ALK-Abelló [19]) and (2) a positive sIgE to Pru p 3. Exclusion criteria were not having signed the informed consent, pregnancy, being under 16, and/or having a psychiatric illness.

All patients underwent SPT to pollen, plant food, and other common environmental allergens (see online suppl. Table 1; see www.karger.com/doi/10.1159/000511977 for all online suppl. material); 10 mL of peripheral blood was taken for the in vitro assays. sIgE was carried out with 112 ImmunoCAP ISAC (Phadia; Thermo Fisher Scientific, Uppsala, Sweden). The composition of the array is described elsewhere [20].

In addition to peach LTP (Pru p 3), other LTPs included in the array were Ara h 9, Art v 3, Cor a 8, Jug r 3, Pla a 3, and Tri a 14. Respiratory and IgE-mediated food allergy symptoms were collected, and a questionnaire was implemented as reported [21–23]. All participants signed written informed consent, and the local Ethics Committee approved the study.

Skin Prick Test

A 1-mm-tip, single-use prick lancet (ALK-Abelló) was used to perform SPTs with commercial whole extracts (ALK-Abelló) of common inhalant allergens (grass, mugwort, wall pellitory, pigweed, olive tree, cypress, plane tree, prickly saltwort, birch, dust mites, *Alternaria alternata*, *Aspergillus fumigatus*, and cat and dog dander), and plant food allergens, which included common nuts (walnut, hazelnut, almond, chestnut, sunflower seed, pine nut, and pistachio) and peanut, following standard protocols [24].

Specific IgE Determination

Sera of all the recruited patients was tested with a microarray immunoassay (ImmunoCAP ISAC), following the manufacturer's protocol [25].

Statistical Analysis as Described

Quantitative variables were expressed as means, medians, and range and qualitative variables by absolute frequencies and percentages. Quantitative variables were analyzed by Student's *t* test and/or Mann-Whitney U test, as appropriate. Associations between explanatory and outcome variables were estimated by calculating the odds ratio (OR) and 95% confidence interval (CI) for quantitative variables and by applying the χ^2 or Fisher's exact test to the qualitative variables. Multivariable logistic regression was performed to determine the association between anaphylaxis and the sensitization to LTPs and the rest of the variables included in the study. The statistical software used was SPSS v.24.

Results

Of the 2,100 patients evaluated, we included 421 who were sensitized to Pru p 3: 93.0% reported food allergy, 71.5% also experienced respiratory symptoms, and 6.9%

Table 1. Prevalence of LTPs in our group (N = 421) with the analysis of reciprocal relationships between Pru p 3 and the nsLTPs studied

Allergen species	LTP	Prevalence of sensitization (n)	Pru p 3 correlation (p value)
Prunus persica	Pru p 3	100.0% (421)	
Juglans regia	Jug r 3	83.1% (350)	**0.849**** (<0.01)
Platanus acerifolia	Pla a 3	73.0% (307)	**0.761**** (<0.01)
Arachis hypogaea	Ara h 9	71.5% (301)	**0.718**** (<0.01)
Corylus avellana	Cor a 8	64.4% (271)	0.625** (<0.01)
Artemisia vulgaris	Art v 3	62.0% (261)	0.501** (<0.01)
Olea europaea	Ole e 7	25.0% (105)	0.166** (<0.01)
Triticum aestivum	Tri a 14	13.5% (57)	0.364** (<0.01)
Parietaria judaica	Par j 2	6.2% (26)	0.057** (<0.01)

Pearson's correlation coefficient values are shown for paired molecular allergens. A correlation coefficient of 0.7–1 indicates a strong positive association (bold), and of 0.3–0.7, a moderate positive association. LTP, lipid transfer protein. ** The correlation is significant at the 0.01 level (two-tailed).

were asymptomatic. In line with the inclusion criteria, all patients had a positive SPT to peach peel and a positive in vitro sIgE to Pru p 3.

Participants' mean age was 33.25 years (range 16–68; median 32), and 54.6% were women. No significant differences were observed in the LTP IgE recognition between genders. A family history of atopy was reported in 71% of the cases. We observed no significant association between the size of the wheal in the SPT with peach peel and the presence of anaphylaxis.

Plant Food and Pollen Sensitization

SPT Sensitization Profile

All the recruited patients underwent SPT to plant food allergens, including the most relevant tree nuts in our area. The most prevalent was peanut (81% positive), followed by walnut and hazelnut. The least prevalent was pine nut, which was positive in just 14% of the cases (online suppl. Table 2).

Regarding SPT to pollen, the most prevalent was olive tree, followed by mugwort, grass, pigweed, and *Salsola kali*. Three-quarters of participants (74%) were sensitized to 2 or more kinds of pollen, and only 10.5% were monosensitized (online suppl. Table 3).

Molecular Allergen Sensitization Profile

When we analyzed the sensitization to the different LTPs included in the microarray, the most prevalent was Jug r 3, which was positive in 83% of the cases, followed by Pla a 3 (73%) and Ara h 9 (71%). Par j 2 was positive in just 6.2% of the participants (Table 1). We observed a strong positive correlation between Pru p 3 and Jug r 3, Pla a 3, and Ara h 9. There was no positive correlation with Ole e 7, Par j 2, or Tri a 14 (online suppl. Table 4).

With respect to the other families of allergens represented in the microarray, 7.6% of the patients were sensitized to at least one of the included profilins: Hev b 8, Mer a 1, Bet v 2, and/or Phl p 12. Of this group, 70% were sensitized to 4 or more profilins. In addition, 4.8% of the patients were sensitized to at least one of the PR-10 included in the microarray: Mal d 1, Pru p 1, Bet v 1, Aln g 1, Act d 8, Ara h 8, and Gly m 4; similarly to the profilins, 70% were sensitized to 4 or more PR-10. The group of polcalcins showed the lowest in prevalence (sensitization of 4%), including Bet v 4 and Phl p 7; 82% (14/17 patients) were sensitized to both.

Relationship between Food Allergy and Respiratory Symptoms

Participants were categorized into 4 groups by clinical entities: group A, anaphylaxis (37.1% of the cases); group B, urticaria (67.9%); group C, oral allergy syndrome (59.1%); and group D, no food allergy symptoms (6.9%). There were no statistically significant differences between the levels of sIgE among the 4 groups ($p > 0.05$ in all cases). There was no association between these entities and rhinitis, rhinoconjunctivitis, and/or asthma.

A small proportion presented eosinophilic esophagitis (2.1%) or only gastrointestinal symptoms (<2%). Additionally, 71.5% had rhinitis or rhinoconjunctivitis, and 29.7%, asthma.

Of the total study sample, 62% were sensitized to Art v 3, with only 11% of these simultaneously recognizing Art v 1. Regarding Pla a 3, 73% were sensitized, with concomitant reactivity to Pla a 1 or Pla a 2 in just 21% of them.

Risk of Anaphylaxis

The risk of anaphylaxis increased in people sensitized to Ara h 9 ($p = 0.003$) or Pla a 3 ($p = 0.010$) (Table 2) and in those with 5 or more LTP sensitizations ($p < 0.001$, OR 2.19, 95% CI 1.43–3.37). The frequency of anaphylaxis was significantly lower in those presenting 2 or fewer LTP reactivities ($p = 0.04$, OR 0.39, 95% CI 0.16–0.98) (online suppl. Table 4; online suppl. Fig. 1). Interestingly, almost half of the patients were positive to 6 LTPs (including, in addition to Pru p 3, Jug r 3, Pla a 3, Ara h 9, Cor a 8, and Art v 3) (Fig. 1). Sensitization to Tri a 14, Ole e 7, and/or

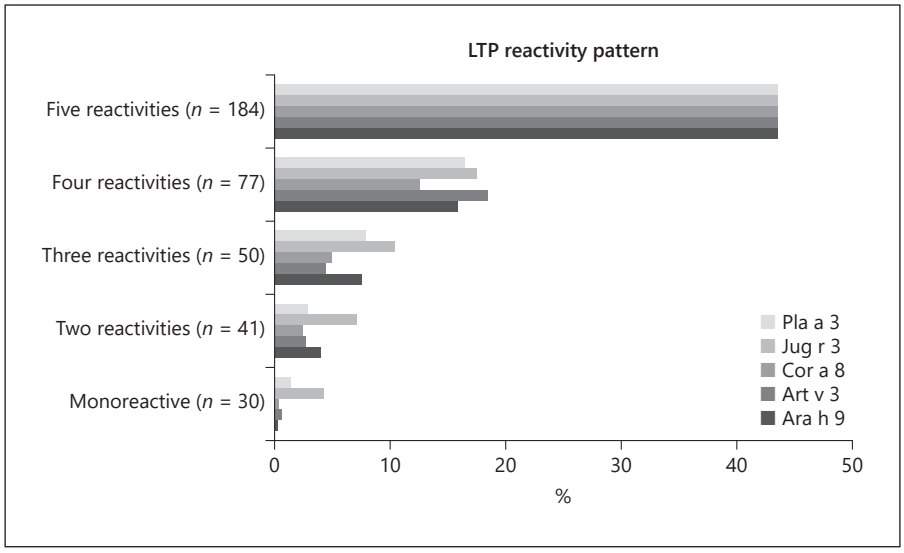

Fig. 1. Prevalence of LTP reactivity. All participants were sensitized to Pru p 3 (9.3% monoreactive). LTP, lipid transfer protein.

Table 2. Association between explanatory variables and anaphylaxis

Variable	*B*	Standard error	Wald	df	*p* value	OR	95% CI	
Female	−0.033	0.338	0.009	1	0.92	0.97	0.50	1.88
Family history of atopy	0.081	0.361	0.051	1	0.82	**1.09**	0.54	2.20
Age	0.014	0.015	0.823	1	0.36	**1.01**	0.98	1.05
Rhinitis	0.278	0.395	0.495	1	0.48	**1.32**	0.61	2.87
Asthma	0.316	0.382	0.687	1	0.41	**1.37**	0.65	2.90
Peanut	0.103	0.062	2.794	1	0.095	**1.11**	0.98	1.25
Walnut	0.085	0.065	1.698	1	0.19	**1.09**	0.96	1.24
Sunflower seed	0.023	0.052	0.198	1	0.66	**1.02**	0.92	1.13
Hazelnut	−0.011	0.060	0.035	1	0.85	0.99	0.88	1.11
Almond	−0.019	0.060	0.100	1	0.75	0.98	0.87	1.10
Ara h 2	0.242	0.323	0.558	1	0.46	**1.27**	0.68	2.40
Ara h 9	0.227	0.077	8.580	1	0.003	**1.26**	1.08	1.46
Pla a 3	0.140	0.054	6.658	1	0.010	**1.15**	1.03	1.28
Tri a 14	0.128	0.150	0.723	1	0.40	**1.14**	0.85	1.53
Ole e 7	−0.073	0.043	2.907	1	0.088	0.93	0.86	1.01
Art v 3	−0.085	0.061	1.950	1	0.16	0.92	0.82	1.04
Phl p 12	−0.135	0.230	0.345	1	0.56	0.87	0.56	1.37
Pru p 1	−2.256	1.457	2.398	1	0.12	0.11	0.01	1.82

CI, confidence interval; df, degrees of freedom; OR, odds ratio. The statistical models used, Hosmer and Lemeshow test and the area under the ROC curve, are considered adequate if $p > 0.05$ and $p < 0.05$, respectively, as occurred in our results. The risk of anaphylaxis is higher when OR >1 (bold).

Par j 2 were not included in this association because none of them significantly augmented the risk of anaphylaxis.

When we looked at the relationship between SPT to pollen and different clinical entities, the proportion of anaphylaxis in people sensitized to pollen was 37%, similar to cases that were negative in the pollen SPT (36%). Although the percentage of anaphylaxis was lower in participants sensitized to profilin and/or PR-10 (28 and 25%, respectively), the difference was not statistically significant. Presenting sensitization to polcalcin Bet v 4 was significantly associated with a lower risk of anaphylaxis ($p < 0.05$).

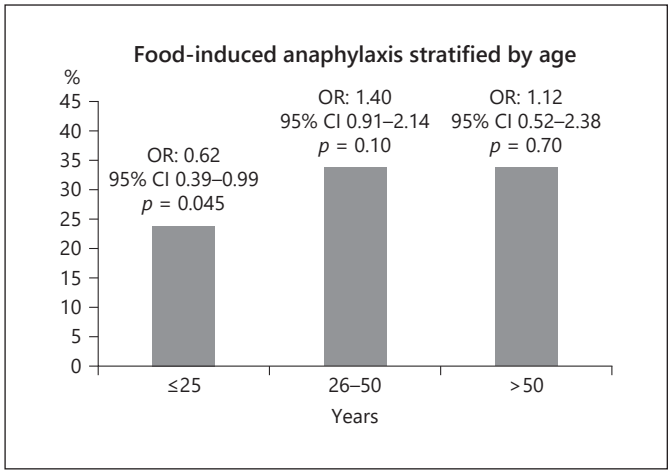

Fig. 2. Prevalence of food-induced anaphylaxis stratified by age in our Pru p 3-sensitized group. OR, odds ratio; CI, confidence interval.

We also observed a lower incidence of anaphylaxis in participants aged 25 or younger (Fig. 2). However, there were no significant differences between the mean values of sIgE to Pru p 3 in patients younger versus older than 25 years (4.76 vs. 4.74 ISU, respectively).

Discussion

Our aim was to evaluate the relationship between anaphylaxis and IgE response in a large group of people sensitized to Pru p 3, analyzing the clinical entities reported by the patients, the sensitization to other molecular components included in the microarray 112 ImmunoCAP ISAC (Phadia; Thermo Fisher Scientific), and the relationship between food and inhaled allergens. Our results show a similar pattern of sensitization as in other studies [2], although artemisia and plane tree showed higher positive values than expected.

We did not observe any relationship between the skin test response to peach or other food allergens and anaphylaxis or other patient-reported symptoms, as reported elsewhere [26, 27]. Although the most frequent entity in our group was urticaria, occurring in 67.9% of the cases, anaphylaxis occurred in more than a third of the cases. Only a minority of participants sensitized to Pru p 3 tolerated peach fruit. When food allergy symptoms were compared between participants grouped according to respiratory allergies, no significant differences were observed; these findings are consistent with previous studies [28–30]. Thus, although food and respiratory allergies are entities that occur in atopic patients and can be interrelated [31, 32], in our LTP-sensitized group, they appeared to be independent phenomena.

In our study, the most prevalent LTP after Pru p 3 was Jug r 3, followed by Pla a 3, Ara h 9, and Cor a 8; the least recognized were Ole e 7, Tri a 14, and Par j 2. The LTP profile observed in our population was similar to that published in other studies in the Mediterranean area and elsewhere [8–10, 12, 28, 33–38]. In our region, walnut is widely consumed, and it is possible that some of our patients were primarily sensitized to Jug r 3 instead of Pru p 3. Compared to Ara h 9, the prevalence of sensitization to Ara h 1 and Ara h 3 was low (2%), indicating that Ara h 9 was the most important component involved in peanut sensitization in our area, as also reported by Vereda et al. [36] in peanut-allergic patients. In fact, in these cases, the primary sensitizer appears to be Pru p 3, with people responding to Ara h 9 due to cross-reactivity [35, 36]. Although the presence of plane tree sensitization was not high in our population, Pla a 3 was the third most prevalent LTP; cross-reactivity is the probable explanation. In our sample, we believe that Pru p 3 acts as the primary allergen, and responses to Pla a 3 are due to cross-sensitization. In fact, Pla a 3 was significantly associated with anaphylaxis. It has also been linked to severe food reactions, and together with Art v 3, to respiratory symptoms in LTP-allergic individuals [37, 38]. Our results showed no significant association between Pru p 3 and Ole e 7 or Par j 2, thus confirming the observations in other studies [8, 28, 39] and supporting the lack of cross-reactivity between peach LTP and those pollen LTPs. We considered that the high prevalence of sensitization to Ole e 7 in our population could just be due to the sensitization to olive tree pollen, as this allergen is the most frequently recognized after Ole e 1 [40].

The association between sensitization to Ara h 9 or Pla a 3 and anaphylaxis was significant. Scala et al. [28] reported that people who reacted to >5 LTPs experienced a greater number of food-induced systemic reactions. This finding was replicated in our cohort. Interestingly, more than half of the patients were positive to 5 or more LTPs (including Pru p 3, Jug r 3, Pla a 3, Ara h 9, Cor a 8, and Art v 3). With this in mind, 261 patients of our study group were immune-reactive to 5 or more LTP molecules studied, likely reflecting a degree of common epitope recognition.

The amino acidic sequence homology with Pru p 3 among the different LTPs included in the array is as follows: Jug r 3 (65%), Ara h 9 (62%), Cor a 8 (60%), Art v 3

(51%), Pla a 3 (46%), and Tri a 14 (47%). Pollen LTPs Ole e 7 and Par j 2 present <35% of sequence identity with Pru p 3 [41]. From our data, we hypothesize that Ara h 9, Cor a 8, and Jug r 3, with corresponding amino acid sequence identities, are associated, alongside with Pru p 3, with plant food-pollen sensitization [30].

Most of the profilin-sensitized patients recognized 2 or more profilins, including those that were not relevant in our population, reinforcing the concept that this is a panallergen that cross-reacts with the other members of this family. In this study, we found that sensitization to Pru p 1, a PR-10 protein, or Phl p 12, a profilin, was negatively associated with the development of anaphylaxis; however, it was not statistically significant. Although some studies found that sensitization to Pru p 1, Pru p 4, or Phl p 12 was associated with a lower probability of anaphylaxis [11, 42], we could not confirm this finding. However, all of these studies come from Northern or Central European countries [30, 43], where sensitization to these allergens is much higher than in Southern Europe [44, 45].

One limitation of this study is that the cases were selected based on diagnosis of LTP allergy, which was made through clinical history and sIgE test to Pru p 3 rather than on food challenge. Another limitation is that other common allergenic foods may be also involved in our population, like apples, oranges, cabbage, and mustard, which do not have the corresponding LTP representative in the array. Palacin has shown that LTPs of these allergens, as well as others, are relevant in inducing sensitization [46].

We conclude that, in our study group, one-third of the people sensitized to Pru p 3 developed anaphylaxis. Sensitization to 5 or more LTPs was a predictor (risk factor) of anaphylaxis. Our data suggest that there is no association between LTP sensitization and respiratory symptoms.

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Statement of Ethics

This study was approved by the Ethics Committee of Alicante and was conducted according to the Declaration of Helsinki, good clinical practice, and local regulations.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Maria Ruano-Zaragoza has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data and has been involved in drafting the manuscript or revising it critically for important intellectual content. Teodorikez Wilcox Jiménez-Rodríguez has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data and has been involved in drafting the manuscript or revising it critically for important intellectual content.

Victor Soriano-Gomis has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data and has been involved in drafting the manuscript or revising it critically for important intellectual content. Angel Esteban-Rodriguez has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data and has been involved in drafting the manuscript or revising it critically for important intellectual content.

Antonio Palazón-Bru has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data and has been involved in drafting the manuscript or revising it critically for important intellectual content. Purificación González-Delgado has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data and has been involved in drafting the manuscript or revising it critically for important intellectual content.

Miguel Blanca has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data and has been involved in drafting the manuscript or revising it critically for important intellectual content. Javier Fernández-Sánchez has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data and has been involved in drafting the manuscript or revising it critically for important intellectual content.

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