

REVIEW

The clinical relevance of lipid transfer protein

R. Asero¹  | M. Piantanida² | E. Pinter³ | V. Pravettoni²¹Ambulatorio di Allergologia, Clinica San Carlo, Paderno Dugnano, Italy²UOC Immunologia e Allergologia, IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy³UOC Immunologia Clinica A, Policlinico Umberto I, Roma, Italy**Correspondence**

Dr. Riccardo Asero, Ambulatorio di Allergologia, Clinica San Carlo, Paderno Dugnano (MI), Italy.

Email: r.asero@libero.it

Summary

Despite a huge number of studies, many aspects of the lipid transfer protein (LTP) syndrome, the most frequent primary food allergy in Mediterranean countries, remain unclear. Its peculiar geographical distribution, along with the extreme variability of its clinical expression, makes this type of food allergy something unique in the panorama of IgE-mediated food-induced allergic reactions. This review article tried to summarize the current knowledge about the most important aspects of LTP sensitization and allergy, along with the importance of positive and negative co-factors in the clinical expression of the syndrome as well as the issues regarding the cross-reactivity between LTPs present in botanically related and unrelated foods. Further, the possible absence of the protein from some plant foods is discussed.

KEYWORDS

anaphylaxis, food allergy, lipid transfer protein, oral allergy syndrome

1 | INTRODUCTION

Non-specific lipid transfer protein (LTP) is by far the most frequent cause of primary food allergy in adults living in the Mediterranean area¹ where it also induces the largest number of food-dependent anaphylactic reactions.² Based on its widespread distribution throughout the plant kingdom and on the elevated homology between LTPs from botanically unrelated foods,³ LTP-sensitized patients may experience adverse reactions upon the ingestion of a large array of plant foods.⁴ LTPs resist to both heat and pepsin digestion which makes them able to reach the intestinal tract in an unmodified form,^{3,5} an essential condition to induce systemic reactions. Furthermore, Pru p 3, the peach LTP, seems to pass the gut epithelium by a fast transcellular route which is not used by other less allergenic LTPs (LTP1), thus inducing the production of Th2 cytokines. This kind of passage underlines the importance of Pru p 3 as a sensitizer.⁶ Pastorello et al⁷ identified in Pru p 3 molecule two immunodominant reactive regions able to act on Pru p 3-specific T cells, inducing the production of IL-4, thus reflecting the Th2-dominant response.

2 | GEOGRAPHICAL DISTRIBUTION

Despite the slowly growing number of sparse reports suggesting the presence of LTP sensitization and LTP-linked food allergies in

different parts of the world, including China,^{8,9} Australia,¹⁰ and Central Europe,¹¹⁻¹⁵ due to unclear reasons, the so-called LTP syndrome remains essentially Mediterranean based and even within Mediterranean countries like Italy, a gradient exists in the prevalence of LTP sensitization between northern and southern regions.¹ The reasons for this peculiar geographical distribution are still poorly defined; the hypothesis of a primary sensitization through the airways associated with the local presence of homologous pollen allergens in LTP-endemic areas such as Pla a 3 from plane, Art v 3 from mugwort, Ole e 7 from olive, or cypress remains unproven so far¹⁶ with the possible exception of China where a link with mugwort pollen allergy seems stronger.⁸ Altogether, one gets the impression that the presence of birch pollen is protective against LTP-allergic symptoms and that the higher the levels of birch pollen are, the lower the prevalence of LTP hypersensitivity in a certain area is.¹⁷ The patterns of sensitization to food allergens, including LTP, differ in different areas of the world, in part due to variations in environmental pollen exposures. For instance, as shown for the peanut, allergic patients do not react to the same allergens: in Spain, 60% of patients are sensitized to peanut LTP (Ara h 9) while these proportions are 7.7% and 14.3% in the United States and in Sweden, respectively. By contrast, sensitization to peanut seed storage proteins (Ara h 1, Ara h 2, Ara h 3) is much higher in the United States and in Sweden than in Spain (ie, Ara h 2 sensitization is 42% in Spain, 90% in the United States, and 74.3% in Sweden).¹⁸

A Spanish study¹⁹ investigated major and minor pan-allergens in pollen-sensitized patients finding an average prevalence of peach allergy (associated with Pru p 3 sensitization) of 12.6% in all the investigated areas. The prevalence was higher in paediatric patients (22%) than in adults (11%), thus supporting the concept that an early Pru p 3 sensitization may be related to a larger extent to different dietary habits than to pollen sensitization.

3 | CLINICAL ISSUES

One of the most intriguing aspects in LTP hypersensitivity is the extreme variability of its clinical expression. An impressive amount of studies has been carried out showing that the clinical impact of LTP sensitization may range from null to anaphylactic shock. Many patients remain symptomless despite strong LTP sensitization.²⁰⁻²² The reasons for this are still ill-defined, but it has been shown that co-factors are often needed for the clinical expression of LTP hypersensitivity (see beyond). It is well known that LTP is probably the main cause of food-induced contact urticaria (CU), at least in Spain. Peach-induced CU may remain the only sign of LTP hypersensitivity in more than 60% of patients.²³ The essential role of peach fuzz in causing histamine release following contact with the skin has been suggested by the absence of any skin reactivity following skin rubbing with nectarine, a fruit that is genetically identical to peach but whose surface is bald.²⁴ In effect, peach fuzz contains large amounts of LTP²⁵ and it cannot be excluded that the skin represents a major pathway leading to sensitization to the protein. The oral allergy syndrome (ie, the occurrence of itching and tingling of the lips, oral mucosa, tongue, and upper airways immediately after ingesting the offending food) is probably the most frequent clinical expression of LTP hypersensitivity.^{23,26} This sort of adverse reaction may remain the only one for years or even lifelong, probably until a co-factor causing an "upgrade" in clinical severity intervenes. Isolated gastrointestinal symptoms (nausea, vomiting, diarrhoea) may follow the ingestion of LTP-containing foods, although in most cases, such symptoms accompany systemic symptoms such as urticaria/angioedema or anaphylaxis. As mentioned before, LTP is the major cause of food-induced anaphylaxis in Italian adults, although the proportion between anaphylactic episodes and number of sensitized patients is by far lower than that observed for nuts, peanuts, or shrimp.² In this sense, LTP can be regarded as a potentially harmful but "benign" allergen.

4 | TISSUE DISTRIBUTION OF LTP IN PLANT-DERIVED FOODS AND DIFFERENT LTP FAMILIES

Most LTP is located in the superficial layers in a number of fruits, including *Rosaceae* (peach, apple, pear, plum, cherry, and apricot), melon, and watermelon, which is not particularly surprising in view of the defensive role of the protein. However, in some fruits, LTP

seems to be present in higher amounts in seeds that are eaten along with the pulp; kiwi and tomato are two examples in this sense.²⁷⁻²⁹ Other edible seeds, such as almond (notably, another member of the *Rosaceae* family), behave differently; although almond seed in se does not seem to contain significant amounts of LTP, it is nonetheless surrounded by a peel that is frequently eaten as well and that probably contains it.

The plant LTP family includes two subfamilies showing a slightly different molecular mass: 9-kDa LTP1, including the large majority of these proteins, and the 7-kDa LTP2, including a much more limited number of representatives, mostly in cereals and tomato. The 7-kDa LTP in tomato seeds shares some structural features with peach LTP, but displays individual features responsible for monospecific IgE binding.²⁹ The two families share the general molecular structure but show a rather low sequence similarity (about 30% identity) and differ in cysteines residues sited along the molecules.³⁰ Another relevant LTP is Par j 2, the major Parietaria pollen allergen, which has a molecular mass of 11 kDa and is unrelated to food LTPs.

5 | THE RELEVANCE OF CO-FACTORS IN LTP HYPERSENSITIVITY

As a difference from allergies to other stable plant food allergens such as the seed storage proteins, the clinical expression of LTP hypersensitivity often requires one or more co-factors. In some cases, the co-factor is represented simply by the isolated ingestion of the offending food after fasting³¹; as the same food may have been always tolerated before, it is possible that an empty gastrointestinal tract absorbs the allergen more rapidly or that in such conditions, pepsin digestion of the food matrix is more efficient, resulting in an increased concentration of the allergen that comes in contact with the gut mucosa. Another classical co-factor is exercise. LTP is the most frequent sensitizer in Italians with food-dependent exercise-induced anaphylaxis.³² Another interesting aspect is the frequent association between LTP hypersensitivity and adverse reactions to non-steroidal anti-inflammatory drugs (NSAIDs).³³⁻³⁶ It was recently shown that NSAIDs are able to enhance IgE-mediated activation of basophils, an effect that can be essential for the occurrence of severe reactions in patients who are only slightly sensitized to certain foods.³⁷

Along with negative co-factors, "positive" co-factors exist as well. Several lines of evidence suggest that the co-sensitization to birch pollen (ie, the major allergen Bet v 1, a PR-10 protein) and/or to the plant pan-allergen profilin is protective against severe allergic reactions induced by LTP-containing fruits and vegetables.^{17,38}

6 | SPECIFIC IGE LEVELS AND CROSS-REACTIVITY ISSUES

In LTP-allergic patients, sensitization profiles are extremely heterogeneous, and individual cross-reactivity patterns may range from a single LTP to many different LTPs.³ Patients sensitized to more than

five different LTPs (from food or pollens) show a significantly higher propensity to develop severe symptoms upon the ingestion of offending foods.¹⁷ The positive association between peach LTP-specific IgE levels and the number of botanically unrelated, co-recognized plant foods has been demonstrated some time ago³⁹; further, in LTP-hypersensitive patients, the levels of IgE specific for different food sources follow a rather precise and predictable hierarchical order that starts with peach, followed by apple, walnut, hazelnut, peanut, lentil, maize, soybean, tomato, kiwi, sesame, mustard, melon, and celery,⁴⁰ although such order is not necessarily paralleled by clinical allergy to the corresponding foods. Another interesting observation is that in adult patients, the level of IgE to Pru p 3, the peach LTP, is inversely related to the age at onset of peach-induced severe symptoms.⁴¹ On the other hand, the levels of specific IgE for non-*Rosaceae* foods are only partially predictive of clinical allergy due to a significant overlap between asymptomatic patients showing elevated levels and patients with a history of severe reactions showing rather low levels.⁴²

The cross-reactivity between peach and other *Prunoideae* has been investigated by Italian authors.²⁶ Analysing a population of peach-allergic patients, with skin prick test and specific serum IgE positive also for apricot, plum, and cherry, it was found that 36% of them were tolerant to all the other *Prunoideae* and 31% were tolerant to some of them. Thus, not all the patients sensitized to LTP and allergic to one or more LTP vegetable sources are symptomatic for all the other existing LTPs. The sensitization alone without clinical symptoms is not a sufficient criterion for eliminating a large amount of LTP-containing foods if these are well tolerated. The fact remains that it is currently impossible to predict hypersensitivity and clinical allergy to a specific food other than *Rosaceae* on the basis of Pru p 3 IgE levels alone. In the clinical practice, SPTs with a large spectrum of foods containing LTP are generally carried out in order to detect to which of them the patient is sensitized and, hence, potentially at risk to react to. Of course, this can be easily carried out if the patient is monosensitized to LTP but becomes virtually impossible in the presence of co-sensitization to Bet v 1-related allergens or profilin. In those cases, molecular in vitro diagnosis has to be carried out with the few currently available LTPs (Pru p 3, Ara h 9, Cor a 8, Jug r 3, Mal d 3, and Tri a 14). IgE testing can be carried out as singleplex (ImmunoCAP) or multiplex (ISAC microarray). The choice between the two methods (the former is quantitative and probably more sensitive; the latter is semi-quantitative and probably less sensitive, but able to test many other allergens at the same time) depends on the number of positive fruits/vegetables on in vivo testing, on the availability of the microarray, as well as on cost/benefit or economic considerations that may also change from one country to another based on the reimbursements by the NHS.

7 | OFFENDING FOODS/SAFE FOODS

The most frequent offending food in LTP-endemic areas is unquestionably the peach, which is also considered as the most probable

cause of LTP sensitization. This fruit seems to contain most if not all LTP epitopes and scores regularly positive on in vitro and/or in vivo tests even in patients who tolerate it and react to other plant-derived foodstuff. Based on sequence similarity between LTPs, it is not surprising that after the peach, the most offending foods belong to the *Rosaceae/Prunoideae* family (apple, pear, apricot, plum, almond, etc), followed by walnut, hazelnut, and peanut. Allergic reactions to other plant-derived foods, including cereals (maize on one side, wheat, rice, barley, and spelt on the other), tomato, fennel, onion, celery, saffron, and broccoli, are much rarer and occur generally in patients showing very elevated IgE levels to Pru p 3.

In the last years, some vegetable foods have been added to the "LTP syndrome list" of potentially offending foods, and a correlation between Pru p 3 IgE-specific levels and symptom progression has been investigated. In particular, Italian researchers studied rice, fennel, and tomato allergy due to LTP sensitization and its correlation with peach allergy. With rice, symptomatic patients were all Pru p 3-positive and the presence of rice-induced symptoms correlated with Pru p 3 IgE levels.⁴³ LTP has also been identified as the major allergen of fennel, able to induce severe symptoms after its ingestion in patients presenting severe symptom to peach.⁴⁴ Finally, a direct correlation between Pru p 3 IgE levels and severity of tomato symptoms was observed.⁴⁵

Some authors, investigating the thermostability of purified peach LTP and peamaclein, demonstrated that Pru p 3 becomes sensitive to gastric and intestinal digestion after heating at 100–120°C for 20 minutes.⁴⁶ However, these experiments were performed with purified isolated proteins which could anyway show a different behaviour in vivo into the whole fruit because of the possible interaction with the food matrix. In fact, for peach and other LTP-containing foods (ie, tomato, maize), the persistence of LTP allergenicity in spite of strong thermal and industrial treatments has been demonstrated.^{47–49}

Some "LTP-safe" plant foods seem to exist as well. In one study, carrot, banana, melon, and potato scored negative on SPT and were clinically tolerated by all LTP-allergic patients studied.⁵⁰ In effect, the edible part of carrot does not contain LTP at all,⁵¹ as is the case of melon, whose LTP is located on the skin and may induce contact urticaria after handling.⁵² In contrast, a lipid transfer protein has been isolated from banana and was possibly involved (along with other allergens) in adverse reactions to this fruit in a selected paediatric population.⁵³

The sources of LTP reported to cause clinical food allergy along with Pru p 3 IgE levels reported in the literature are summarized in Table 1. Even if a cut-off level has been detected in the study by Pastorello et al,³⁸ the levels of IgE to Pru p 3 in different allergic populations show much variation.

8 | CONCLUSIONS

Several aspects of LTP-allergic syndrome remain poorly defined. Clinically, it is still unclear how sensitization to this protein occurs

TABLE 1 Sources of LTP reported to cause clinical allergy; IgE levels towards Pru p 3 are shown when available

Offending food	Official name	Pru p 3 IgE levels (kUA/L)	No of allergic patients/no of LTP-positive patients	Age (mean)	Reference
Peach	Pru p 3 (1, 2)	n.a.	15/15	17-52 (29)	Pastorello, JACI 1999
		0.47-44.80	43/38	6-43 (27)	Hartz, Int Arch Allergy Immunol 2010
		0.12-100	148/104	13-62 (37)	Pastorello, Int Arch Allergy Immunol 2011
		1.40-9.60	72/69	23-39 (34)	Azofra, Int Arch Allergy Immunol 2016
Apricot	Pru ar 3 (1, 2)	n.a.	30/30	18-45 (27)	Pastorello, JACI 2000
Plum	Pru d 3 (1, 2)	n.a.	23/19	18-45 (30)	Pastorello, J Chromatogr B Biomed Sci Appl 2001
Cherry	Pru av 3 (1, 2)	4.21 ^c	1/1	6	Calvani, Isr Med Assoc J 2015
		0.47-21.50	22/17	7-43 (27)	Hartz, Int Arch Allergy Immunol 2010
		n.a.	15/6	n.a.	Scheurer, JACI 2004
		n.a.	33/9	8-47 (28)	Ballmer-Weber, JACI 2002
Apple	Mal d 3 (1,2)	n.a.	43/20	15-55 (28)	Pastorello, JACI 1999
		1816-3085 ^b	4/4	n.a.	Asero, JACI 2003
		0-0.75 ^b	81/38	24-39 (31)	Gomez, PLoS One 2014
Grape	Vit v 1 (1, 2)	n.a.	14/10	23-47 (31)	Pastorello, JACI 2003
		n.a.	1/1	27	Schad, Int Arch Allergy Immunol 2005
		n.a.	37/27	2-19 (8)	Vassilopoulou, Int Arch Allergy Immunol 2007
Melon	Cuc m LTP (2)	n.a.	14/13	11-55 (30)	Gandolfo-Cano, Br J Dermatol 2014
Tomato	Sola l 3 (1, 2)	n.a.	5/5	22-41 (28)	Lorenz, JACI 2006
	Sola l 6 (1, 2)	n.a.	40/18	11-58 (29)	Pravettoni, J Agric Food Chem 2009
		n.a.	123/35	mean age: 29	López-Matas, J Investig Allergol Clin Immunol 2015
		0.20-100	50/35	6-61 (37)	Mascheri, J Investig Allergol Clin Immunol 2015
		n.a.	22/5	20-58 (34)	Martín-Pedraza, Mol Nutr Fod Res 2016
Walnut	Jug r 3 (1, 2)	n.a.	46/42	12-60 (30)	Pastorello, JACI 2004
Hazelnut	Cor a 8 (1, 2)	n.a.	7/7	19-34 (26)	Pastorello, JACI 2002
		n.a.	57/16	n.a.	Hansen, JACI 2009
		0.66-27.20	26/22	8-43 (28)	Hartz, Int Arch Allergy Immunol 2010
		0.71-23.00	20/20	17-60 (33)	Schulten, Allergy 2011
Peanut	Ara h 9 (1, 2)	0.18-53.38	18/15	mean age: 30	Ma, Int Arch Allergy Immunol 2016
		0.14-100	51/46	15-48 (30)	Javaloyes, JACI 2012
		n.a.	42/19	7-57 (27)	Krause, JACI 2009
Almond	Pru du 3 (1, 2)	n.a.	1/1	17	Garrido-Fernández, J Investig Allergol Clin Immunol 2009
Chestnut	Cas s 8 (1, 2)	0.50-1.50 ^b	12/11	17-46 (27)	Sánchez-Monge, JACI 2006
Kiwi	Act c 10 (1, 2)	1.01-9.35	7/7	16-40 (29)	Bernardi, PLoS One 2011
	Act d 10 (1, 2)				
Green bean	Pha v 3 (1, 2)	1.90-21.30	5/5	18-39 (29)	Pastorello, J Agric Food Chem 2010
		0.80-17.60	10/10	19-40 (29)	Zoccatelli, Mol Immunol 2010
Lentil	Len c 3 (1, 2)	6.70-41	5/3	6-44 (28)	Akkerdaas, Int Arch Allergy Immunol 2012
Rice	Ory s 14 (2)	n.a.	3/3	26-41 (32)	Enrique, JACI 2005
		n.a.	3/3	25-50 (35)	Asero, Int Arch Allergy Immunol 2007
		4.19-100	10/10	32-62 (44)	Pastorello, Int Arch Allergy Immunol 2013
Maize	Zea m 14 (1, 2)	n.a.	22/19	12-50 (29)	Pastorello, JACI 2000
		n.a.	7/7	19-49 (35)	Pastorello, JACI 2003
		n.a.	19/14	12-65 (33)	Pastorello, Anal Bioanal Chem 2009

(Continues)

TABLE 1 (Continued)

Offending food	Official name	Pru p 3 IgE levels (kUA/L)	No of allergic patients/no of LTP-positive patients	Age (mean)	Reference
Wheat	Tri a 14 (1, 2)	0.30-1.42 ^b	40/24	17-60 (36)	Palacin, JACI 2007
		n.a.	22/9	n.a.	Pastorello, Int Arch Allergy Immunol 2007
		0.23-1.23 ^b	8/4	20-53 (35)	Palacin, Int Arch Allergy Immunol 2010
		2.42-34.70	3/3	15-21 (18)	Pastorello, Ann Allergy Asthma Immunol 2014
		1.88 ^c	1/1	15	Calvani, Isr Med Assoc J 2015
Spelt	Tri s 14 (2)	n.a.	1/1	n.a.	Pastorello, JACI 2001
Barley and beer	Hor v 14 (2)	n.a.	1/1	7	Nemni, Pediatr Allergy Immunol 2013
		n.a.	4/4	22-38	García-Casado, JACI 2001
		n.a.	7/2	n.a.	Curioni, Clin Exp Allergy 1999
Strawberry	Fra a 3 (1, 2)	n.a.	28/5	11-44 (27)	Zuidmeer, Clin Exp Allergy 2006
Goji berries	Lyc ba 3 (2)	n.a.	2/2	27;13	Monzón Ballarín, J Investig Allergol Clin Immunol 2011
Mulberry	Mor n 3 (1, 2)	n.a.	1/1	46	Navarro, Allergy 1997
		n.a.	3/3	n.a.	Ciardiello, Allergy 2010
Blueberry	Vac m 3 (2)	3.36	1/1	21	Gebhardt, Allergy 2009
Raspberry	Rub i 3 (1, 2)	n.a.	8/3	20-46 (33)	Marzban, Mol Nutr Food Res 2008
		1.94	1/1	52	Ciprandi, Eur Ann Allergy Clin Immunol 2014
Red currant	Rib r 3 (2)	17.03	1/1	19	Tomás, J Investig Allergol Clin Immunol 2012
Dragon fruit	Hyl un LTP (2)	n.a.	1/1	19	Kleinheinz, JACI 2009
Pomegranate	Pun g 1 (1, 2)	n.a.	6/6	24-45 (33)	Bolla, Int Arch Allergy Immunol 2014
		12 ^c	1/1	18	Almeida, Allergol Immunopathol (Madr) 2015
Orange	Cit s 3 (1, 2)	0.11-2.60 ^b	27/13	0.5-19 (13)	Ahrazem, Int Arch Allergy Immunol 2005
		n.a.	1/1	21	de las Marinas, J Investig Allergol Clin Immunol 2013
Mandarin	Cit r 3 (1, 2)	n.a.	1/1	24	Ebo, Int Arch Allergy Immunol 2007
Sunflower seed	Hel a 3 (1, 2)	n.a.	1/1	22	Yagami, Allergy 2010
		n.a.	1/1	40	Ukleja-Sokołowska, Int J Immunopat Pharm 2016
Lettuce	Lac s 1 (1, 2)	n.a.	14/10	22-43 (31)	San Miguel-Moncín, Allergy 2003
		0.66-60.40	29/27	6-38 (28)	Hartz, Mol Immunol 2007
		n.a.	2/2	22;40	Bascones, J Investig Allergol Clin Immunol 2009
		n.a.	42/31	16-60 (34)	Muñoz-García, Mol Nutr Food Res 2013
		0.56-43.30	30/29	16-60 (33)	Muñoz-García, J Investig Allergol Clin Immunol 2017
Asparagus	Aspa o 1 (1, 2)	n.a.	18/9	9-68 (32)	Díaz-Perales, JACI 2002
		n.a.	27/10	9-78 (37)	Tabar, Clin Exp Allergy 2004
Onion	All c 3 (2)	23.07	1/1	19	Enrique, Ann Allergy Asthma Immunol 2007
Garlic	n.a.	n.a.	1/1	35	Asero, JACI 1998
Fennel	Phoe v 3 (2)	0.12-100	58/34	13-70 (38)	Pastorello, J Agric Food Chem 2013
Celery	Api g 2 (1, 2)	n.a.	32/12	21-62 (41)	Vejvar, Mol Nutr Food Res 2013
		12.20-73.20 ^a	10/10	10-56 (29)	Gadermaier, PLoS One 2011
Cabbage	Bra o 3 (1, 2)	0.30-1.20 ^b	17/16	17-43 (31)	Palacín, JACI 2006
Parsley	Pet c 3 (2)	2.10	1/1	26	Cordobés-Durán, J Investig Allergol Clin Immunol 2007
Mustard	Sin a 3 (1, 2)	n.a.	15/9	18-54 (31)	Sirvent, Clin Exp Allergy 2009
Saffron	Cro s 3 (2)	0.26-0.96 ^b	6/3	9-61 (29)	Gómez-Gómez, J Investig Allergol Clin Immunol 2010

official name: 1 = IUIS; 2 = Allergome. n.a. = not available.

^ang/mL.

^bO.D., ELISA.

^cISU, ImmunoCAP ISAC units.

(an issue that is probably related to the geographical distribution of this type of allergy) and why only part of sensitized subjects have an overt food allergy while others need co-factors to react to foods or do not react at all despite similar specific IgE levels. Another important point is the only partial predictability of the cross-reactivity between different plant-derived foods in the single sensitized patients. Nonetheless, our knowledge of LTP allergy is slowly increasing and oral immunotherapy is presently available in some countries like Spain⁵⁴ where the syndrome is extremely common with the aim to increase the provocation threshold of severely allergic patients.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

ORCID

R. Asero  <http://orcid.org/0000-0002-8277-1700>

REFERENCES

1. Asero R, Antonicelli L, Arena A, et al. EpidemAAITO: features of food allergy in Italian adults attending allergy clinics: a multicentre study. *Clin Exp Allergy*. 2009;39:547-555.
2. Asero R, Antonicelli L, Arena A, et al. Causes of food-induced anaphylaxis in Italian adults: a multicentre study. *Int Arch Allergy Immunol*. 2009;150:271-277.
3. Egger M, Hauser M, Mari A, Ferreira F, Gadermaier G. The role of lipid transfer proteins in allergic diseases. *Curr Allergy Asthma Rep*. 2010;10:326-335.
4. Asero R, Mistrello G, Roncarolo D, et al. Immunological cross-reactivity between lipid transfer proteins from botanically unrelated plant-derived foods: a clinical study. *Allergy*. 2002;57:900-906.
5. Asero R, Mistrello G, Roncarolo D, et al. Lipid transfer protein: a pan-allergen in plant-derived foods that is highly resistant to pepsin digestion. *Int Arch Allergy Immunol*. 2000;122:20-32.
6. Tordillas L, Gomez-Casado C, Garrido-Arandia M, et al. Transport of Pru p 3 across gastrointestinal epithelium – an essential step toward the induction of food allergy? *Clin Exp Allergy*. 2013;43:1374-1383.
7. Pastorello EA, Monza M, Pravettoni V, et al. Characterization of the T-cell epitopes of the major peach allergen Pru p 3. *Int Arch Allergy Immunol*. 2010;153:1-12.
8. Gao ZS, Yang ZW, Wu SD, et al. Peach allergy in China: a dominant role for mugwort pollen lipid transfer protein as a primary sensitizer. *J Allergy Clin Immunol*. 2013;131:224-226.
9. Ma S, Nie L, Li H, Wang R, Yin J. Component-Resolved Diagnosis of Peanut Allergy and Its Possible Origins of Sensitization in China. *Int Arch Allergy Immunol*. 2016;169:241-248.
10. Murad A, Katelaris CH, Baumgart K. A case study of apple seed and grape allergy with sensitization to nonspecific lipid transfer protein. *Asia Pac Allergy*. 2016;6:129-132.
11. Metz-Favre C, Pauli G, Bessot JC, De Blay F. Molecular allergology in practice: an unusual case of LTP allergy. *Eur Ann Allergy Clin Immunol*. 2011;43:193-195.
12. Ebo DG, Ahrazem O, Lopez-Torres G, Bridts CH, Salcedo G, Stevens WJ. Anaphylaxis from mandarin (*Citrus reticulata*): identification of potential responsible allergens. *Int Arch Allergy Immunol*. 2007;144:39-43.
13. Faber MA, Van Gasse AL, Decuyper II, et al. IgE-reactivity profiles to nonspecific lipid transfer proteins in a northwestern European country. *J Allergy Clin Immunol*. 2017;139:679-682.
14. Flinterman AE, Akkerdaas JH, den Hartog Jager CF, et al. Lipid transfer protein-linked hazelnut allergy in children from a non-Mediterranean birch-endemic area. *J Allergy Clin Immunol*. 2008;121:423-428.
15. Mothes-Luksch N, Raith M, Stingl G, et al. Pru p 3, a marker allergen for lipid transfer protein sensitization also in Central Europe. *Allergy*. 2017 Mar 2; <https://doi.org/10.1111/all.13151>.
16. Asero R, Pravettoni V. Anaphylaxis to plant foods and pollen allergens in patients with lipid transfer protein syndrome. *Curr Opin Allergy Clin Immunol*. 2013;13:379-385.
17. Scala E, Till SJ, Asero R, et al. Lipid transfer protein sensitization: reactivity profiles and clinical risk assessment in an Italian cohort. *Allergy*. 2015;70:933-943.
18. Vereda A, van Hage M, Ahlstedt S, et al. Peanut allergy: Clinical and immunologic differences among patients from 3 different geographic regions. *J Allergy Clin Immunol*. 2011;127:603-607.
19. Barber D, de la Torre F, Feo F, et al. Understanding patient sensitization profiles in complex pollen areas: a molecular epidemiological study. *Allergy*. 2008;63:1550-1558.
20. Rodriguez J, Crespo JF, Lopez-Rubio A, et al. Clinical cross-reactivity among foods of the Rosaceae family. *J Allergy Clin Immunol*. 2000;106:183-189.
21. González-Mancebo E, González-de-Olano D, Trujillo MJ, et al. Prevalence of sensitization to lipid transfer proteins and profilins in a population of 430 patients in the south of Madrid. *J Investig Allergol Clin Immunol*. 2011;21:278-282.
22. Pascal M, Vazquez-Ortiz M, Folque MM, et al. Asymptomatic LTP sensitization is common in plant-food allergic children from the Northeast of Spain. *Allergol Immunopathol (Madr)*. 2016;44:351-358.
23. Cuesta-Herranz J, Lázaro M, de las Heras M, Lluch M, Figueredo E, Umpierrez A, Hernandez J, Cuesta C. Peach allergy pattern: experience in 70 patients. *Allergy*. 1998;53:78-82.
24. Asero R. Peach-induced contact urticaria is associated with lipid transfer protein sensitization. *Int Arch Allergy Immunol*. 2011;154:345-348.
25. Asero R, Mistrello G, Amato S, Roncarolo D, Martinelli A, Zaccarini M. Peach fuzz contains large amounts of lipid transfer protein: is this the cause of the high prevalence of sensitization to LTP in Mediterranean countries? *Eur Ann Allergy Clin Immunol*. 2006;38:118-121.
26. Pastorello EA, Ortolani C, Farioli L, et al. 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*. 1994;94:699-707.
27. Bernardi ML, Giangrieco I, Camardella L, et al. Allergenic lipid transfer proteins from plant-derived foods do not immunologically and clinically behave homogeneously: the kiwifruit LTP as a model. *PLoS ONE*. 2011;6:e27856.
28. Pravettoni V, Primavesi L, Farioli L, et al. Tomato allergy: detection of IgE-binding lipid transfer proteins in tomato derivatives and in fresh tomato peel, pulp, and seeds. *J Agric Food Chem*. 2009;57:10749-10754.
29. Giangrieco I, Alessandri C, Rafaianni C, et al. Structural features, IgE binding and preliminary clinical findings of the 7kDa Lipid Transfer Protein from tomato seeds. *Mol Immunol*. 2015;66:154-163.
30. Yeats TH, Rose JK. The biochemistry and biology of extracellular plant lipid-transfer proteins (LTPs). *Protein Sci*. 2008;17:191-198.
31. Arena A. Anaphylaxis to apple: is fasting a risk factor for LTP-allergic patients? *Eur Ann Allergy Clin Immunol*. 2010; 42:155-158.
32. Romano A, Scala E, Rumi G, et al. Lipid transfer proteins: the most frequent sensitizer in Italian subjects with food-dependent exercise-induced anaphylaxis. *Clin Exp Allergy*. 2012;42:1643-1653.

33. Asero R. Hypersensitivity to lipid transfer protein is frequently associated with chronic urticaria. *Eur Ann Allergy Clin Immunol.* 2011;43:19-21.
34. Pascal M, Muñoz-Cano R, Reina Z, et al. Lipid transfer protein syndrome: clinical pattern, cofactor effect and profile of molecular sensitization to plant-foods and pollens. *Clin Exp Allergy.* 2012;42:1529-1539.
35. Cardona V, Luengo O, Garriga T, et al. Co-factor-enhanced food allergy. *Allergy.* 2012;67:1316-1318.
36. Nucera E, Di Rienzo A, Ricci AG, Buonomo A, Mezzacappa S, Schiavino D. Adverse reactions to nonsteroidal anti-inflammatory drugs and hypersensitivity to lipid transfer proteins. *Adv Dermatol Allergol.* 2016;33:309-310.
37. Pascal M, Muñoz-Cano R, Milà J, et al. Nonsteroidal anti-inflammatory drugs enhance IgE-mediated activation of human basophils in patients with food anaphylaxis dependent on and independent of nonsteroidal anti-inflammatory drugs. *Clin Exp Allergy.* 2016;46:1111-1119.
38. Pastorello EA, Farioli L, Pravettoni V, et al. Pru p 3-sensitized Italian peach-allergic patients are less likely to develop severe symptoms when also presenting IgE antibodies to Pru p 1 and Pru p 4. *Int Arch Allergy Immunol.* 2011;156:362-372.
39. Asero R, Mistrello G, Roncarolo D, Amato S. Relationship between peach lipid transfer protein specific IgE levels and hypersensitivity to non-Rosaceae vegetable foods in patients allergic to lipid transfer protein. *Ann Allergy Asthma Immunol.* 2004;92:268-272.
40. Asero R. In patients with LTP syndrome food-specific IgE show a predictable hierarchical order. *Eur Ann Allergy Clin Immunol.* 2014;46:142-146.
41. Pastorello EA, Farioli L, Stafylaraki C, et al. Anti-rPru p 3 IgE levels are inversely related to the age at onset of peach-induced severe symptoms reported by peach-allergic adults. *Int Arch Allergy Immunol.* 2013;162:45-49.
42. Asero R, Arena A, Cecchi L, et al. Are IgE levels to foods other than rosaceae predictive of allergy in lipid transfer protein-hypersensitive patients? *Int Arch Allergy Immunol.* 2011;155:149-154.
43. Pastorello EA, Scibilia J, Farioli L, et al. Rice allergy demonstrated by double-blind placebo-controlled food challenge in peach-allergic patients is related to lipid transfer protein reactivity. *Int Arch Allergy Immunol.* 2013;161:265-273.
44. Pastorello EA, Farioli L, Stafylaraki C, et al. Fennel allergy is a lipid-transfer protein (LTP)-related food hypersensitivity associated with peach allergy. *J Agric Food Chem.* 2013;61:740-746.
45. Mascheri A, Farioli L, Pravettoni V, et al. Hypersensitivity to Tomato (*Lycopersicon esculentum*) in Peach-Allergic Patients: rPrup 3 and rPrup 1 Are Predictive of Symptom Severity. *J Invest Allergol Clin Immunol.* 2015;25:183-189.
46. Tuppo L, Spadaccini R, Alessandri C, et al. Structure, stability, and IgE binding of the peach allergen Peamaclein (Pru p 7). *Biopolymers.* 2014;102:416-425.
47. Brenna O, Pompei C, Ortolani C, Pravettoni V, Farioli L, Pastorello EA. Technological processes to decrease the allergenicity of peach juice and nectar. *J Agric Food Chem.* 2000;48:493-497.
48. Pastorello EA, Pompei C, Pravettoni V, et al. Lipid-transfer protein is the major maize allergen maintaining IgE-binding activity after cooking at 100 degrees C, as demonstrated in anaphylactic patients and patients with positive double-blind, placebo-controlled food challenge results. *J Allergy Clin Immunol.* 2003;112:775-783.
49. Pravettoni V, Primavesi L, Piantanida M, et al. Tomato industrial derivatives: Maillard reaction and residual allergenicity. *Clin Transl Allergy.* 2011;1(Suppl 1):P19.
50. Asero R, Mistrello G, Roncarolo D, Amato S. Detection of some safe plant-derived foods for LTP-allergic patients. *Int Arch Allergy Immunol.* 2007;144:57-63.
51. Ballmer-Weber BK, Wangorsch A, Bohle B, et al. Component-resolved in vitro diagnosis in carrot allergy: does the use of recombinant carrot allergens improve the reliability of the diagnostic procedure? *Clin Exp Allergy.* 2005;35:970-978.
52. Gandolfo-Cano M, Bartra J, González-Mancebo E, et al. Molecular characterization of contact urticaria in patients with melon allergy. *Br J Dermatol.* 2014;170:651-656.
53. Palacin A, Quirce S, Sanchez-Monge R, et al. Sensitization profiles to purified plant food allergens among pediatric patients with allergy to banana. *Pediatr Allergy Immunol.* 2011;22:186-195.
54. Gomez F, Bogas G, Gonzalez M, et al. The clinical and immunological effects of Pru p 3 sublingual immunotherapy on peach and peanut allergy in patients with systemic reactions. *Clin Exp Allergy.* 2017;47:339-350.

How to cite this article: Asero R, Piantanida M, Pinter E, Pravettoni V. The clinical relevance of lipid transfer protein. *Clin Exp Allergy.* 2018;48:6-12. <https://doi.org/10.1111/cea.13053>