IgE-Mediated Reactivity to Non-Specific Lipid Transfer Protein (nsLTP): Clinical Implications and Management. Consensus Document of the Association of Italian Territorial and Hospital Allergists and Immunologists (AAIITO)

Riccardo Asero[1], Valerio Pravettoni[2], Danilo Villalta[3], Lorenzo Cecchi[4], Enrico Scala[5]

[1] Ambulatorio di Allergologia, Clinica San Carlo, Paderno Dugnano, Milan, Italy

[2] Department of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[3] S.C. di Immunologia e Allergologia di Laboratorio, PO S. Maria degli Angeli, Pordenone, Italia

[4] SOS Allergology and Clinical Immunology, USL Toscana Centro, Prato, Italy

[5] Clinical and Laboratory Molecular Allergy Unit, IDI-IRCCS, Rome, Italy

Abstract

The primary cause of adult-onset food allergy in Mediterranean countries is IgE-mediated reactivity to non-specific Lipid Transfer Protein (nsLTP), with a prevalence of 9.5% in Italy. nsLTP is heat- and pepsin-stable due to its 3D structure, causing severe allergic reactions, even anaphylaxis. It's conserved across plants and a "panallergen" due to homologous forms in various vegetable foods. Found in Rosaceae fruits' skin, it's categorized into $nsLTP_1$ (9 kDa) and nsLTP2 (7 kDa), representing 93% and 7% of the molecules described to date, respectively. Pru p 3 ($nsLTP_1$) from peach is a primary sensitizer, binding more epitopes than other homologs. Cross-reactivity varies in sensitized patients, influenced by IgE levels. Clinical manifestations range from none to various symptoms. Managing patients sensitized to nsLTP without clinical allergy is a challenge. Sensitization hierarchy usually starts with peach, then expands through Prunoideae, Rosaceae, and other foods. Clinical symptoms don't always expand across LTPs. Patients can tolerate some nsLTP-containing foods and consuming them may maintain tolerance. The absence of guidelines led to the Associazione Allergologi Immunologi Italiani Territoriali e Ospedalieri (AAIITO) creating a consensus-based document. Strategies involve avoidance, self-injectable adrenaline, verification through in vivo and in vitro testing, considering cofactors, and peeling fruits. In localized reactions, abstinence is recommended if specific IgE is high. Concurrent pollinosis may complicates diagnosis, but may help management since symptoms are often less severe. Asymptomatic

patients are advised to continue normal diets while considering cofactors and total IgE levels. Management strategies should be case-specific, based on expert Consensus Document.

Consensus document

IgE-mediated reactivity to non-specific Lipid Transfer Protein (nsLTP) stands as the main cause of primary food allergy in adults in Mediterranean countries (1-3), with a prevalence of 9.5% Pru p 3 reactivity observed in Italy(4). The heat- and pepsin-stability due to its three-dimensional structure featuring 4 α-helices linked by 4 disulfide bridges(5) make it an allergen capable of inducing severe allergic reactions, even leading to anaphylaxis(6). nsLTP is a highly conserved protein from a phylogenetic standpoint(7) and is widely distributed throughout the plant kingdom, playing a defensive role against fungi and bacteria(8). As a consequence, homologous forms of nsLTP are present in a broad range of foods, often botanically unrelated to each other, warranting its classification as a "panallergen"(9-12). (Figure 1)

This protein is primarily found in the skin of Rosaceae fruits, encompassing numerous fruit-bearing trees (apple, pear, cherry, peach, plum, almond, medlar, rowan, apricot, quince, and more-13). Based on the molecular weight, two subfamilies have been identified: nsLTP1 (9 kDa) and nsLTP2 (7 kDa-8) (14), though 51 out of the 55 molecules officially registered in the WHO/IUIS database (www.allergen.org) belong to nsLTP1 (see Table 1). Examples of nsLTP1s include Pru p 3 from peach (15), Mal d 3 from apple(16), Cor a 8 from hazelnut(17), Ara h 9 from peanut(18), Jug r 3 from walnut(19), and Tri a 14 from wheat(20) (Figure). Pru p 3 is regarded as the most likely primary sensitizer to the nsLTP family showing the largest repertoire of IgE-binding epitopes(21), in contrast to other homologous proteins found in different plant sources(22-23). This view is supported by in-vitro experiments showing that the pre-absorption of sera of LTP hypersensitive patients with peach LTP almost invariably completely inhibits IgE reactivity to other plant food sources(22). Pollen allergens such as Par j 1 and Par j 2 from Parietaria and Ole e 7 from olive tree do not cross-react with either nsLTP1 from plant foods or with each other (24), although they frequently score positive in peach-allergic patients(25–27). LTP2 proteins are cross-reactive with each other but have low sequence identity when compared to LTP1. The widespread presence of nsLTP in nature leads to a long list of foods linked to anaphylactic reactions(28).

For sensitized patients, the risk of cross-reactivity varies significantly from case to case, primarily depending on specific IgE levels for Pru p 3(29-22-30). Another unique characteristic of nsLTP sensitization is the variable spectrum of clinical manifestations resulting from the ingestion of foods containing this protein. Symptoms can range from complete absence to oral allergy syndrome, contact urticaria, asthma, hives/angioedema, and food-dependent exercise-induced anaphylaxis(31).

In daily clinical practice, problems arise where a patient sensitized to nsLTP presents without a history of adverse reactions following the consumption of plant-based foods. Similarly, a patient reporting allergic reactions triggered by nsLTP (often to peach, a key allergenic food for this protein) (22) may show cross-sensitization to a wide array of plant-based foods that are tolerated

and commonly consumed. It has been demonstrated that some patients allergic to peach but positively reacting in skin tests and specific serum IgE to other Prunoideae tolerate the ingestion of these fruits, suggesting sensitization without clinical allergy(32). Similar findings have been observed in a pediatric population where sensitization to specific plant nsLTPs did not necessarily correlate with symptoms upon food ingestion (33).

Furthermore, the clinical expression of nsLTP sensitization may sometimes require cofactors. Concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) alongside nsLTP-containing foods can exacerbate adverse reactions (25, 34). nsLTP is the primary cause of exercise-induced anaphylaxis triggered by food in Italy (31). Reactivity may also depend on the simultaneous presence or absence of different foods in the digestive tract (35). Conversely, co-sensitization to PR10 and Profilin, or both, appears to play a protective role, resulting in a lower frequency of severe systemic reactions (25, 36), despite an increased prevalence of first-degree oral allergy syndrome(27). Another protective factor is the presence of atopic dermatitis, where despite very high IgE levels and multiple LTP recognition, the frequency of severe reactions is significantly lower than observed in allergic patients without atopic eczema. (25)

Sensitization to LTP appears to follow precise hierarchical pathways, starting from peach, progressing through other Prunoideae (apricot, plum, cherry), Rosaceae (apple, pear), then moving on to walnut, hazelnut, peanut, and subsequently rice, maize, and a wide variety of botanically unrelated plant foods(37). There is also a correlation between specific IgE levels and the likelihood of systemic allergic reactions(36-38). It should also be emphasized that such hierarchy is not rigid but may vary depending on the cases and patients (37).

It has been clinically observed that patients do not tend to progressively expand their clinical symptoms across different LTPs, but rather exhibit the development of clinical allergy either to Prunoideae and/or tree nuts, or to certain vegetables, or cereals that were formerly tolerated albeit scoring positive on SPT or specific IgE measurement(39). Managing sensitized patients who are clinically non-allergic or only exhibit minimal allergic symptoms represents a significant medico-legal and ethical challenge. Recommending a patient to continue consuming well-tolerated foods or advising them to abstain from foods that tested positive in vivo and/or in vitro investigations due to the risk of unpredictable allergic reactions upon accidental ingestion, requires careful consideration. It is worth noting that, akin to strategies employed in other types of food allergies where oral tolerance induction is attempted through repeated oral administration, consuming tolerated foods by nsLTP-sensitized individuals might contribute to maintaining a natural state of tolerance. Conversely, eliminating nsLTP-containing foods could potentially disrupt the tolerance state, leading to systemic reactions after ingestion of previously tolerated but now removed foods (39). The Associazione Allergologi Immunologi Italiani Territoriali e Ospedalieri (AAIITO)

recognized the need to address the absence of international and national guidelines on this subject and created this document which seeks to provide clinical guidance based on expert consensus.

Case-by-Case Indications for LTP Sensitization Management

1 | Patient with a history of systemic reaction to one or more plant foods

- Complete avoidance of the responsible food, even if subjected to food industry processing (e.g., commercial fruit juices, jams, desserts), due to nsLTP's resistance to such treatments. Prescription of self-injectable adrenaline only in case of anaphylactic events, especially considering the potential for accidental ingestion (hidden food) and risk factors, following the current Italian legislation.
- In skin prick testing, you can use commercial extracts or fresh foods. When using fresh foods, it's important to pay specific attention to the testing site since Lipid Transfer Proteins (LTPs) are mainly found under the skin's surface, especially under the peel. Peach, apple, peanut, walnut, hazelnut, wheat, tomato, and almond must be tested in all cases. Other plant foods (corn, celery, kiwi, rice, barley, fennel, cabbage, lettuce, legumes, citrus, mustard, pomegranate, etc.) can be tested based on clinical history.
- Positively reacting foods that were previously regularly consumed and tolerated can be ingested with the recommendation to avoid them in combination with known cofactors (physical exertion, NSAIDs, alcoholic beverages), to avoid consuming more of them within the same meal or day, and to peel them whenever possible.
- Positively reacting foods that previously induced mild local symptoms (oral allergy syndrome) are preferable to be avoided, especially in the presence of high specific IgE levels and in the absence of a positive reaction to PR-10 and/or profilin. Foods testing negative in both in vivo and in vitro investigations can be consumed, given the low likelihood of an allergic reaction.
- Given the predominant localization of the protein in the superficial layers of foods, peeling Rosaceae fruits is a preventive measure that allows the introduction of minimal allergenic amounts to maintain gastrointestinal tolerance. Peeling should be done with a very sharp knife to prevent carrying nsLTP into the fruit pulp. Additionally, it's important not to use the same knife for peeling the fruit and cutting the slices to eat, as this can risk transferring LTPs into the pulp. Note that certain fruits (e.g., tomato(40), kiwi, and orange) contain LTP not only in the skin but also in pulp and seeds.

2 | Patient with a history of localized reaction (oral allergy syndrome) to one or more plant foods

- In the presence of high specific IgE levels and in the absence of a positive reaction to PR-10 and/or profilin, abstinence from consuming the food in question is recommended due to the risk of systemic reactions. If the food has been previously tolerated, it can be continued to be consumed, paying particular attention to the cofactors already described.
- In cases of low specific IgE levels, consuming that specific food can continue, with the recommendation to peel it, to avoid known cofactors (physical exertion, NSAIDs, alcoholic beverages), and to avoid consuming it in combination with other LTP-containing foods within the same meal or day.

3 | Patient with localized reaction (oral allergy syndrome) to one or more plant foods with concurrent pollinosis

- Patients with peach LTP allergy, when sensitized to PR-10 and/or profilin, show protection from severe symptoms induced by plant foods (36). This suggests that measuring these two proteins could be beneficial (27). Similar results have been observed in patients allergic to any type of nsLTP, whether from food or pollen (27), and in patients sensitized to LTP in different geographic areas of Italy. In the North-East, co-sensitization to profilins and PR-10 is more common, while in the South, higher Pup 3 levels and monosensitization to LTP are prevalent (41).
- The role of airborne sensitization to LTP is debated. While this route of sensitization is established for peach fuzz(42) or peach field workers(43), the significance of two other pollen nsLTPs, Pla a 3 from plane tree and Art v 3 from mugwort, is less certain. IgE reactivity to these proteins, which present cross-reactive epitopes with Pru p 3, might account for weak Pru p 3 reactivity (especially in vitro) without necessarily causing clinical symptoms upon LTP ingestion. Nevertheless, recent studies have observed that sensitization to Ole e 7(26) or Pla a 3(44) is significantly associated with potential systemic food reactions, suggesting their utility as markers of LTP-related reactivity(45). Furthermore, there has been a suggestion that marijuana may play a role in potential contact or airborne sensitization.
- The presence of concurrent pollinosis can thus easily lead to incorrect conclusions in cases of positive reactions to food extracts containing nsLTP. In such cases, to establish an accurate allergological profile, simultaneous determination of specific IgE for nsLTP (Pru p 3), PR-10 (Bet v 1), profilin (Bet v 2 or Phl p 12), and CCD (MUXF3) is suggested if positivity is found via in vitro testing.

4 | Occasional identification of LTP sensitization in entirely asymptomatic patients

Patients are advised to maintain their current lifestyle and continue consuming tolerated foods. Particularly for patients with high specific IgE levels, it might be prudent to avoid cofactors such as physical exertion, NSAID intake, and alcohol consumption. It should also be emphasized that elevated levels of total IgE may lead to higher levels of specific IgE antibodies against a particular allergen, without necessarily being linked to an increased risk of adverse reactions (46).

Disclosure of Funding | This study was funded, in part, by the Italian Ministry of Health, Current Research Program 2018-2020.

Author contribution statement | All authors reviewed, edited and approved the final manuscript. All Authors consent for publication, and confirm that this manuscript is original, has not been published before, is not currently being considered for publication elsewhere, and has not been posted to a preprint server.

Data Availability | The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Conflict of interest | ES has received consultant arrangements and speakers' bureau participation from Stallergenes, Thermo Fisher Scientific, and non-financial support from Microarray Diagnostics, Vienna, all outside the submitted work. LC has received honoraria from Malesci, Menarini, Mylan and Thermo Fisher Scientific. DV and RA received honoraria from Thermo Fisher Scientific.

Funding information | This study was funded, in part, by the Italian Ministry of Health, Current Research Program 2021-2023.

References

(1) Skypala IJ, Bartra J, Ebo DG, Antje Faber M, Fernández-Rivas M, Gomez F, et al. The diagnosis and management of allergic reactions in patients sensitized to non-specific lipid transfer proteins. Allergy: European J. Allergy Clin. Immunol. 2021;76(8):2433–46. doi: 10.1111/all.14797.

(2) Asero R, Antonicelli L, Arena A, Bommarito L, Caruso B, Crivellaro M, et al. EpidemAAITO: Features of food allergy in Italian adults attending allergy clinics: A multi-centre study. Clin. Exp. Allergy. 2009;39(4):547-55. doi: 10.1111/j.1365-2222.2008.03167.x.

(3) Flores E, Cervera L, Sanz ML, Diaz-Perales A, Fernández J. Plant food allergy in patients with pollinosis from the mediterranean area. Int. Arch. Allergy. Immunol. 2012;159(4):346–54. doi: 10.1159/000338282.

(4) Scala E, Alessandri C, Bernardi ML, Ferrara R, Palazzo P, Pomponi D, et al. Cross-sectional survey on immunoglobulin E reactivity in 23 077 subjects using an allergenic molecule-based microarray detection system Clin. Exp. Allergy. 2010:40(6):911-21. doi: 10.1111/j.1365-2222.2010.03470.x.

(5) Skypala IJ, Asero R, Barber D, Cecchi L, Diaz Perales A, Hoffmann-Sommergruber K, et al. Non-specific lipid-transfer proteins: Allergen structure and function, cross-reactivity, sensitization, and epidemiology. Clin. Transl. Allergy. 2021;11(3):e12010. doi: 10.1002/clt2.12010.

(6) Asero R, Antonicelli L, Arena A, Bommarito L, Caruso B, Colombo G, et al. Causes of food-induced anaphylaxis in italian adults: A multi-centre study. Int. Arch. Allergy. Immunol. 2009;150(3):271–7. doi: 10.1159/000222679.

(7) Hauser M, Roulias A, Ferreira F, Egger M. Panallergens and their impact on the allergic patient. Ann. Allergy Asthma Immunol. 2010;6(1):1–14. doi: 10.1186/1710-1492-6-1.

(8) Douliez JP, Michon T, Marion D. Steady-state tyrosine fluorescence to study the lipid-binding properties of a wheat non-specific lipid-transfer protein (nsLTP1). Biochim. Biophys. Acta Biomembr. 2000;11467(1):65-72. doi: 10.1016/S0005-2736(00)00197-8.

(9) Díaz-Perales A, Sanz ML, García-Casado G, Sánchez-Monge R, García-Selles FJ, Lombardero M, et al. 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. 2003;111(3):628-33. doi: 10.1067/mai.2003.75.

(10) Lauer I, Miguel-Moncin MS, Abel T, Foetisch K, Hartz C, Fortunato D, et al. Identification of a plane pollen lipid transfer protein (Pla a 3) and its immunological relation to the peach lipid-transfer protein, Pru p 3. Clin. Exp. Allergy. 2007;37(2):261-9. doi: 10.1111/j.1365-2222.2007.02653.x.

(11) Lombardero M, García-Sellés FJ, Polo F, Jimeno L, Chamorro MJ, García-Casado G, et al. Prevalence of sensitization to Artemisia allergens Art v 1, Art v 3 and Art v 60 kDa. Cross-reactivity among Art v 3 and other relevant lipid-transfer protein allergens. Clin. Exp. Allergy. 2004;34(9):1415-21. doi: 10.1111/j.1365-2222.2004.02053.x.

(12) Asero R. Lipid transfer protein cross-reactivity assessed in vivo and in vitro in the office: Pros and cons. J. Investig. Allergol. Clin. Immunol.2011;21(2):129-36.

(13) Fernández-Rivas M, Cuevas M. Peels of Rosaceae fruits have a higher allergenicity than pulps. Clin. Exp. Allergy. 1999;29(9):1239-47. doi: 10.1046/j.1365-2222.1999.00628.x.

(14) Richard C, Leduc V, Battais F. Plant lipid transfer proteins (LTPS): biochemical aspect in panallergen--structural and functional features, and allergenicity. Eur. Ann. Allergy. Clin. Immuno. 2007;39(3):76-84.

(15) Pastorello EA, Monza M, Pravettoni V, Longhi R, Bonara P, Scibilia J, et al. Characterization of the T-cell epitopes of the major peach allergen Pru p 3. Int. Arch. Allergy. Immunol. 2010;153(1):1-12. doi: 10.1159/000301573.

(16) Diaz Perales A, Garcia Casado G, Sanchez Monge R, Garcia Selles FJ, Barber D, Salcedo G. cDNA cloning and heterologous expression of the major allergens from peach and apple belonging to the lipid-transfer protein family. Clin. Exp. Allergy. 2002;32(1):87-92. doi: 10.1046/j.0022-0477.2001.01257.x.

(17) Schocker F, Lüttkopf D, Scheurer S, Petersen A, Cisteró-Bahima A, Enrique E, et al. Recombinant lipid transfer protein Cor a 8 from hazelnut: A new tool for in vitro diagnosis of potentially severe hazelnut allergy. J. Allergy Clin. Immunol. 2004;113(1):141-7. doi: 10.1016/j.jaci.2003.09.013.

(18) Krause S, Reese G, Randow S, Zennaro D, Quaratino D, Palazzo P, et al. Lipid transfer protein (Ara h 9) as a new peanut allergen relevant for a Mediterranean allergic population. J. Allergy Clin. Immunol. 2009;124(4):771-8.e5. doi: 10.1016/j.jaci.2009.06.008.

(19) Roux KH, Teuber SS, Sathe SK. Tree nut allergens. Int. Arch. Allergy. Immunol. 2003;131(4):234-44. doi: 10.1159/000072135.

(20) Palacin A, Varela J, Quirce S, Del Pozo V, Tordesillas L, Barranco P, et al. Recombinant lipid transfer protein Tri a 14: A novel heat and proteolytic resistant tool for the diagnosis of baker's asthma. Clin. Exp. Allergy. 2009;39(8):1267-76. 10.1111/j.1365-2222.2009.03280.x.

(21) Asero R, Pravettoni V, Scala E, Villalta D. Lipid transfer protein allergy: A review of current controversies Clin. Exp. Allergy. 2022:52(2):222-230. doi: 10.1111/cea.14049.

(22) Schulten V, Nagl B, Scala E, Bernardi ML, Mari A, Ciardiello MA, et al. Pru p 3, the nonspecific lipid transfer protein from peach, dominates the immune response to its homolog in hazelnut. Allergy. 2011;66(8):1005-13. doi: 10.1111/j.1398-9995.2011.02567.x.

(23) 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(5):326-35. doi: 10.1007/s11882-010-0128-9.

(24) Tordesillas L, Sirvent S, Díaz-Perales A, Villalba M, Cuesta-Herranz J, Rodríguez R, et al. Plant lipid transfer protein allergens: No cross-reactivity between those from foods and olive and Parietaria pollen. Int. Arch. Allergy. Immunol. 2011;156(3):291-6. doi: 10.1159/000323503.

(25) Scala E, Abeni D, Villella V, Villalta D, Cecchi L, Pravettoni V, Giani M, Caprini E, Asero R. The pleomorphic syndrome of Lipid Transfer Protein: a decision algorithm among cofactors and comorbidities. Eur Ann Allergy Clin Immunol. 2023 Sep 15. doi: 10.23822/EurAnnACI.1764-1489.314

(26) Scala E, Abeni D, Pomponi D, Paganelli R, Locanto M, Giani M, et al. Ole e 1, Ole e 7, and Ole e 9: Identifying distinct clinical subsets of olive tree–allergic patients. J. Allergy Clin. Immunol. 2016;137(2):629-631.e3. doi: 10.1016/j.jaci.2015.07.009.

(27) Scala E, Till SJ, Asero R, Abeni D, Guerra EC, Pirrotta L, et al. Lipid transfer protein sensitization: Reactivity profiles and clinical risk assessment in an Italian cohort. Allergy. 2015;70(8):933-43. doi: 10.1111/all.12635.

(28) 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(4):379-85. doi: 10.1097/ACI.0b013e32835f5b07.

(29) Asero R, Mistrello G, Roncarolo D, Amato S, Caldironi G, Barocci F, et al. Immunological cross-reactivity between lipid transfer proteins from botanically unrelated plant-derived foods: A clinical study. Allergy. 2002;57(10):900-6. doi: 10.1034/j.1398-9995.2002.t01-1-23541.x.

(30) 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(2):268-72. doi: 10.1016/S1081-1206(10)61559-1.

(31) Romano A, Scala E, Rumi G, Gaeta F, Caruso C, Alonzi C, et al. Lipid transfer proteins : the most frequent sensitizer in Italian subjects with food-dependent exercise-induced anaphylaxis Clin. Exp. Allergy. 2012;42(11):1643-53. doi: 10.1111/cea.12011.

(32) Pascal M, Vazquez-Ortiz M, Folque MM, Jimenez-Feijoo R, Lozano J, Dominguez O, et al. Asymptomatic LTP sensitisation is common in plant-food allergic children from the Northeast of Spain. Allergol. Immunopathol. (Madr) 2016;44(44):351–8. doi: 10.1016/j.aller.2015.10.003.

(33) Pastorello EA, Ortolani C, Farioli L, Pravettoni V, Ispano M, Borga A, Bengtsson A, Incorvaia, C, Berti CZC. 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(4):699-707. doi: 10.1016/0091-6749(94)90177-5.

(34) Romano A. Possible interaction among hypersensitivity to lipid transfer proteins, chronic urticaria, and hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. Eur. Ann. Allergy Clin. Immunol. 2011;43(1):3–4.

(35) Arena A. Anaphylaxis to apple: Is fasting a risk factor for LTP-allergic patients? Eur. Ann. Allergy Clin. Immunol. 2010;42(4):155–8.

(36) Pastorello EA, Farioli L, Pravettoni V, Scibilia J, Mascheri A, Borgonovo L, et al. Pru p 3-sensitised 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(4):362-72. doi: 10.1159/000324440.

(37) Asero R. In patients with LTP syndrome food-specific IgE show a predictable hierarchical order. Eur. Ann. Allergy Clin. Immunol. 2014;46(4):142–6.

(38) Rossi RE, Monasterolo G, Canonica GW, Passalacqua G. Systemic reactions to peach are associated with high levels of specific IgE to Pru p 3. Allergy: European J. Allergy Clin. Immunol. 2009;64(12):1795–6. doi: 10.1111/j.1398-9995.2009.02133.x.

(39) Asero R, Piantanida M, Pravettoni V. Allergy to LTP: To eat or not to eat sensitizing foods? A follow-up study. Eur Ann Allergy Clin Immunol 2018;50(4):156-162. doi: 10.23822/EurAnnACI.1764-1489.57.

(40) Pravettoni V, Primavesi L, Farioli L, Brenna O V., Pompei C, Conti A, 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(22):10749–54. doi: 10.1021/jf9022367.

(41) Uasuf CG, Villalta D, Conte ME, Di Sano C, Barrale M, Cantisano V, et al. Different co-sensitizations could determine different risk assessment in peach allergy? Evaluation of an anaphylactic biomarker in Pru p 3 positive patients. Clin. Mol. Allergy 2015;13:30. doi: 10.1186/s12948-015-0035-7.

(42) Asero R, Mistrello G, Roncarolo D, Amato S. PT with heat-processed apple peel extract to detect LTP hypersensitivity. Eur. Ann. Allergy Clin. Immunol 2006;38(10):351–4.

(43) Perez-Calderon, R; Gonzalo-Garijo, MA; Rodrıguez-Velasco, FJ; Sanchez-Vega, S; Bartolome-Zavala V. Occupational respiratory allergy in peach crop workers. Allergy. 2017;72(10):1556–1564. doi: 10.1111/all.13163.

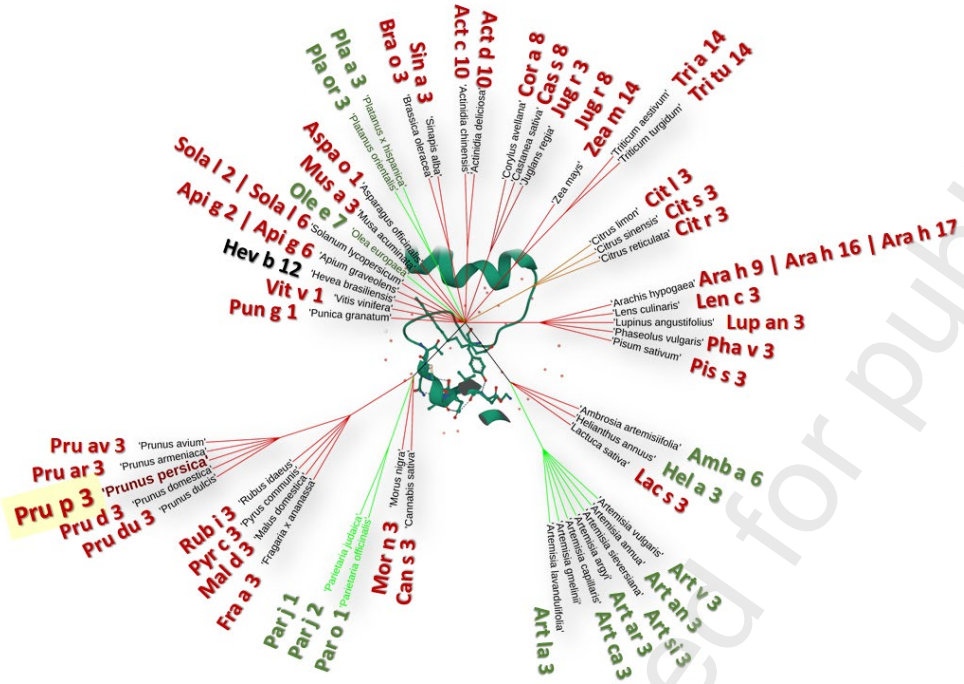
(44) Scala E, Cecchi, L, Abeni, D, Guerra EC, Pirrotta L, Locanto M, Giani, M, Asero R. Pla a 2 and Pla a 3 reactivities identify plane tree-allergic patients with respiratory symptoms or food allergy. Allergy. 2017;72(4):671–4. doi: 10.1111/all.13121.

(45) Asero R, Brusca I, Cecchi L, Pignatti P, Pravettoni V, Scala E, et al. Why lipid transfer protein allergy is not a pollen-food syndrome: novel data and literature review. Eur. Ann. Allergy Clin. Immunol. 2022;54(5):198–206. doi: 10.23822/EurAnnACI.1764-1489.206.

(46) Scala E, Abeni D, Guerra EC, Pirrotta L, Locanto M, Meneguzzi G, Giani M, Russo G, Asero R. β-1,3-glucanase rOle e 9 and MnSOD rAsp f 6 IgE reactivity are the signature of Atopic Dermatitis in the Mediterranean Area. Clinical and Experimental Allergy. 2020; 50:487-498 doi.org/10.1111/cea.13555.

Figure Legend

Figure 1 | The figure illustrates the taxonomic relationships among the non-specific Lipid Transfer Proteins (nsLTPs) currently documented in the literature, which are also catalogued in the International Union of Immunological Societies (IUIS) Database.



	Allergen	*nsLipid transfer protein*	PM (kDa)	Latin Name	Common Name
1	**Act c 10**	nsLTP1	10 kDa	*Actinidia chinensis*	Gold kiwi fruit
2	**Act d 10**	nsLTP1	10 kDa	*Actinidia deliciosa*	Green kiwi fruit
3	**Amb a 6**	nsLTP1	10 kDa	*Ambrosia artemisiifolia*	Short ragweed
4	**Api g 2**	nsLTP1	9 kDa	*Apium graveolens*	Celery
5	**Api g 6**	nsLTP2	7 kDa		
6	**Ara h 9**	nsLTP1	9.8 kDa	*Arachis hypogaea*	Peanut, groundnut
7	**Ara h 16**	nsLTP2	8.5 kDa		
8	**Ara h 17**	nsLTP1	11 kDa		
9	**Art an 3**	nsLTP1	10 kDa	*Artemisia annua*	Sweet Wormwood
10	**Art ar 3**	nsLTP1	10 kDa	*Artemisia argyi*	Silvery wormwood
11	**Art ca 3**	nsLTP1	10 kDa	*Artemisia capillaris*	Wormwood
12	**Art gm 3**	nsLTP1	10 kDa	*Artemisia gmelinii*	Russian wormwood
13	**Art la 3**	nsLTP1	10 kDa	*Artemisia lavandulifolia*	Mugwort
14	**Art si 3**	nsLTP1	10 kDa	*Artemisia sieversiana*	Sieversian wormwood
15	**Art v 3**	nsLTP1	12 kDa	*Artemisia vulgaris*	Mugwort, wormwood
16	**Aspa o 1**	nsLTP1	9 kDa	*Asparagus officinalis*	Asparagus
17	**Bra o 3**	nsLTP1	9 kDa	*Brassica oleracea*	Cabbage and others
18	**Can s 3**	nsLTP1	9 kDa	*Cannabis sativa*	Indian hemp
19	**Cas s 8**	nsLTP1	9 kDa	*Castanea sativa*	Chestnut
20	**Cit l 3**	nsLTP1	9.6 kDa	*Citrus limon*	Lemon
21	**Cit r 3**	nsLTP1	9 kDa	*Citrus reticulata*	Tangerine
22	**Cit s 3**	nsLTP1	9.46 kDa	*Citrus sinensis*	Sweet orange
23	**Cor a 8**	nsLTP1	9 kDa	*Corylus avellana*	Hazelnut
24	**Fra a 3**	nsLTP1	9 kDa	*Fragaria ananassa*	Strawberry
25	**Hel a 3**	nsLTP1	9 kDa	*Helianthus annuus*	Sunflower
26	**Hev b 12**	nsLTP1	9 kDa	*Hevea brasiliensis*	Para rubber tree | latex
27	**Jug r 3**	nsLTP1	9 kDa	*Juglans regia*	English walnut
28	**Jug r 8**	nsLTP2	9 kDa		
29	**Lac s 1**	nsLTP1	9 kDa	*Lactuca sativa*	Cultivated lettuce
30	**Len c 3**	nsLTP1	9 kDa	*Lens culinaris*	Lentil
31	**Lup an 3**	nsLTP1	11 kDa	*Lupinus angustifolius*	Narrow-leaved blue lupin
32	**Mal d 3**	nsLTP1	9 kDa	*Malus domestica*	Apple
33	**Mor n 3**	nsLTP1	10 kDa	*Morus nigra*	Mulberry
34	**Mus a 3**	nsLTP1	9 kDa	*Musa acuminata*	Banana
35	**Ole e 7**	*putative nsLTP1*	9.5 kDa	*Olea europaea*	Olive Tree
36	**Pha v 3**	nsLTP1	8.8-9.0 kDa	*Phaseolus vulgaris*	Green bean, French bean
37	**Pis s 3**	nsLTP1	9.5 kDa	*Pisum sativum*	Pea
38	**Pla a 3**	nsLTP1	10 kDa	*Platanus acerifolia*	London plane tree
39	**Pla or 3**	nsLTP1	11 kDa	*Platanus orientalis*	Oriental plane tree
40	**Pru ar 3**	nsLTP1	9 kDa	*Prunus armeniaca*	Apricot
41	**Pru av 3**	nsLTP1	10 kDa	*Prunus avium*	Sweet cherry
42	**Pru d 3**	nsLTP1	9 kDa	*Prunus domestica*	European plum
43	**Pru du 3**	nsLTP1	9 kDa	*Prunus dulcis*	Almond
44	**Pru p 3**	nsLTP1	10 kDa	*Prunus persica*	Peach
45	**Pun g 1**	nsLTP1	9 kDa	*Punica granatum*	Pomegranate
46	**Pyr c 3**	nsLTP1	9 kDa	*Pyrus communis*	Pear

47	**Rub i 3**	nsLTP1	11 kDa	*Rubus idaeus*	Red raspberry
48	**Sin a 3**	nsLTP1	12.3 kDa	*Sinapis alba*	Yellow mustard
49	**Sola l 3**	nsLTP1	9 kDa		
50	**Sola l 6**	nsLTP2	7 kDa	*Solanum lycopersicum*	*Tomato*
51	**Sola l 7**	nsLTP1	12.5 kDa		
52	**Tri a 14**	nsLTP1	9 kDa	*Triticum aestivum*	Wheat
53	**Tri tu 14**	nsLTP1	9.2 kDa	*Triticum turgidum*	Durum wheat
54	**Vit v 1**	nsLTP1	9 kDa	*Vitis vinifera*	Grape
55	**Zea m 14**	nsLTP1	9 kDa	*Zea mays*	Maize