

Lupin and Other Potentially Cross-Reactive Allergens in Peanut Allergy

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Abstract

Purpose of Review The presence of IgE cross-reactivity between peanut allergens and allergens from other legumes and tree nuts has been demonstrated, but the identification of the involved individual allergens is still limited. The aim of this review is to describe new allergenic findings, of potential relevance for cross-reactivity among peanut and lupin.

Recent Findings Seventeen allergens of peanut have been included in the official allergen nomenclature database to date. Lupin sensitization has been observed in 15–20% of individuals with known peanut allergy. The majority of lupin seed proteins are comprised of α -conglutins (legumin-like) and β -conglutins (vicilin-like), and to a lesser extent γ -conglutins (vicilin-like) and δ -conglutins (2S albumins).

Summary Several molecules may fuel peanut-lupin cross-reactivity. Awareness among physicians and general public could avoid unexpected allergic reactions. However, these do not appear frequent and no data suggest a precautionary labelling of lupin in foods.

Keywords Peanut allergy · Lupin · Cross-reactivity · Allergy · Food labelling · IgE

Introduction

Food allergy is defined as an IgE-mediated hypersensitivity response to ingested food with symptoms ranging from urticaria to life-threatening anaphylaxis [1, 2].

According to the United States National Center for Health Statistics, the prevalence of reported food allergies among children rose 18% from 1997 to 2007 [3]. More recently, the prevalence of food allergy in Australia peaked to 10% [4, 5], generating the fear of a new wave of allergic diseases [6]. Recent data from UK indicate a 7.1% of food allergy prevalence in the general population [7], largely exceeding that reported in the last epidemiological data from UK [8].

The current strategy to treat food allergies is strict allergen avoidance, but sometimes it is not enough to remove single incriminated food from the patient's diet. Cross-reactivity, an immune-mediated phenomenon due to an IgE antibody recognizing and binding, can induce an immune response to similar allergenic molecules (homologues) and may be responsible for unexpected reactions to different foods. IgE cross-reactivity often occurs between allergenic molecules in closely related species or well-preserved molecules with similar function present in widely different species, belonging to the same protein family [9]. The clinical relevance of cross-reactivity seems to be influenced by many factors including the host immune response against the allergen, exposure and the allergen itself [10].

The peanut is considered one of the main food allergens worldwide and in particular in the United States [11–14, 15]. Some studies have shown IgE cross-reactivity between peanut allergens and allergens from other legumes and tree nuts, but the identification of the involved individual allergens is still limited. Further studies are needed to answer the question whether allergic reactions to legumes and tree nuts in peanut-allergic individuals allergic to peanuts are a result of

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a primary allergy to peanut or cross-reactivity, in particular because it seems that the clinical hypersensitivity to one legume does not translate in allergy of all legumes [16]. These questions become important when considering if the rapid spread of some vegetables in the human diet warrants their inclusion in allergen-labelling lists. For example, lupin is now increasingly used in the bakery industry, and lupin allergy has been reported in patients who are already allergic to peanuts [17].

The aim of this review is to describe new findings, focused on research published within the past 5 years about cross reactivity in peanut allergy, with particular reference to that described between peanut and lupin.

Peanut Allergy

Peanuts are the seeds of the peanut plant (*Arachis hypogaea*), a member of the legume family (*Fabaceae*). The peanut is botanically related to peas and beans but not to tree nuts. The typical peanut seedpod, which usually contains two seeds, matures buried underground. Peanuts are very rich in nutrients and are one of the basic crops of India, China, the USA and West Africa. Peanuts contain 44–56% oil and 22–30% protein [18]. The total protein content of three of the most commonly used peanut cultivars (Valencia, Virginia, and Spanish) has been determined to be between 24 and 29% [19]. Seed storage proteins of the cupin or prolamin superfamilies make up most of the protein content. The cupin Ara h 1 has been determined to contribute between 12 and 16% of the total protein content of the peanut, and the 2S albumin Ara h 2 contributes between 5.9 and 9.3% to the total protein content of a peanut [19]. In a study by Hebling et al., all known peanut allergen classes were determined to comprise make up 85% of the total protein content of peanut, while Ara h 1, Ara h 2, and Ara h 3 together accounted for 75% [20]. The prevalence of peanut allergy ranges between 0.6 and 1% of the total population in the Western countries, but data from the developing world are lacking [21]. Recent data indicate that peanut allergy is on the rise. In England, children from the general population born on 2005–2007 were reported to develop peanut allergy in 0.7% [22], those born 2009–2012 in 2.5% cases [7]. In at-risk populations (infants with severe eczema and/or egg allergy), peanut allergy is reported at 17.2% [23•]. Before this steady increase, media, advocates, parents and institutions used to describe peanut allergy as a medical and public problem [24]. An analysis of epidemiology of peanut allergy underlined how the idea of this allergy as a population health risk and the social organization of the response to this risk were co-produced. According to this analysis, the “peanut panic”—which changed the way that people,

especially children, interacted with, and were governed within, the familiar social spaces of schools, airlines and medicine—anticipated the epidemiological trends [25•]. The author showed how for example seafood allergies in America are almost double that of peanut allergies, but that culturally, peanuts and peanut butter have long served as a staple snack for kids, especially in USA, and have been expectedly served in public spaces on a regular basis. With newfound awareness of peanuts as a health risk and problem, the social characteristics of this “normal” food are changing [26].

Making the correct diagnosis of peanut allergy is of paramount importance. A typical history of a hypersensitivity reaction to peanut following ingestion, in combination with a positive skin prick test or peanut specific IgE, would point towards a diagnosis of peanut allergy. If peanut has not been ingested, a positive test result to peanut will not automatically translate in a peanut allergy, as a significant proportion will produce specific IgE without clinical allergy [27]. A carefully conducted oral challenge may be required to clarify the situations of disagreement between the clinical picture and specific allergy tests [28•].

Patients and their families must be educated on how to recognize and treat peanut allergic reactions, when to ask for help and how to use their emergency medication. A single visit to an allergy specialist can improve families’ abilities to manage allergic reactions considerably and reduce the number of subsequent accidental reactions [29]. A comprehensive management plan including verbal and written advice on nut avoidance as well as training in recognition and treatment of allergic reactions, with the addition of a written management plan, can be effective in reducing both severity and number of future reactions [30].

Peanut Allergens and Possible Cross-Reactivity

Seventeen allergens of peanut have been included in the official allergen nomenclature database (<http://www.allergen.org>) to date.

They belong to the cupin (Ara h 1, Ara h 3), the prolamin (Ara h 2, Ara h 6, Ara h 7), the profilin (Ara h 5), the Bet v 1 (Ara h 8), the glycosyl transferase GT-C (Ara h 10, Ara h 11, Ara h 14, Ara h 15), the scorpion toxin-like knottin (Ara h 12, Ara h 13) superfamilies and non-specific Lipid Transfer Protein (Ara h 9, Ara h 16, Ara h 17).

Monosensitizations to a single peanut allergen is relatively rare [31]. Cross-reactivity relies on the presence of conserved antibody-accessible surface structures of peanut proteins and is hence observed in general between members of the same protein family. As protein evolution is linked to the evolution of species, the proteins that appeared very early in the

evolutionary process are distributed much wider than proteins that appeared later on.

Bet v 1-like proteins, as members of cupin superfamily, can be found in all three domains of life including birch pollen and peanut [32]. In contrast, the prolamin superfamily is of a later origin. Non-specific lipid transfer proteins (nsLTPs) have only been identified in seed plants but are not even present in algae [33].

In vitro IgE cross-reactivity of panallergens, such as Bet v 1 homologs, is not always associated with clinical manifestations. In peanut-allergic patients, a clinically relevant sensitization to other legumes such as soybean, lupin, lentil, or pea may occur. In a group of 39 peanut-sensitized patients, 87, 82 and 55% were also sensitized to soybean, lupin and pea, respectively, but based on DBPCFC, only 29–35% had symptoms after ingestion of these beans [34]. Peanut-allergic individuals may also have a co-existing allergy to taxonomically distantly related tree nuts, in 20–40% of cases [35]. IgE cross-reactivity has been shown among allergens present in peanut, almond, Brazil nut and hazelnut using protein extracts and sera from subjects with peanut and tree nut allergy in inhibition ELISA [36].

Peanut allergens such as Bet v-1 related Ara h 8, the peanut profilin Ara h 5 and the LTP Ara h 9 are considered as panallergens. Such allergens are responsible for allergic cross-reactivity across a wide variety of unrelated plants and are often associated with birch and grass pollinosis or involved in nsLTP-syndrome. The vicilin Ara h 1, the 2S albumins Ara h 2 and Ara h 6, and the legumin Ara h 3 represent major constituents of the peanut that frequently bind IgE.

Other authors observed cross-reactivity between unrelated allergens, indicating that simple comparison of amino acid sequences might be insufficient to predict cross-reactivity.

Among the legumes, one of the most used in the bakery industry and involved in the process of cross-reactivity with peanut is lupin.

Lupin Allergy

The interest to exploit alternative vegetable protein sources to soy has led to an increasing use of sweet lupin seed flour in bakery, confectionary, snack, and pastry products as an additive to wheat flour or as a substitute for soy flour. Some of the health benefits of consumption of lupin-enriched foods include increased satiety and reduced energy intake, decreased blood glucose level, hypolipidemic effect [37].

The frequency of allergic reactions to lupin in the general population is not clearly known, but it appears to be infrequent and probably depends on the dietary habits as well as the geographical differences [16, 38]. Lupin sensitization has been observed in 15–20% of individuals with known peanut allergy. The majority of lupin seed proteins are comprised of α -conglutins (legumin-like) and β -conglutins (vicilin-like), and to a lesser extent γ -conglutins (vicilin-like) and δ -conglutins (2S albumins). While Ara h1 most potently cross-reacted with β -conglutins and Ara h2 with δ -conglutins, Ara h 3 only displayed inhibition of IgE binding to α -conglutins at highest concentrations [39] (Fig. 1).

Sensitization as well as clinical manifestations of lupin allergy can occur after both ingestion as well as inhalation, is similar to those observed with other food or inhalant allergens and can be varied in severity from urticarial and vomiting to severe anaphylaxis. In a study on eight lupin-allergic patients, no-observed adverse effect level was 0.1 mg lupin flour for subjective symptoms and 1 mg for objective symptoms, of

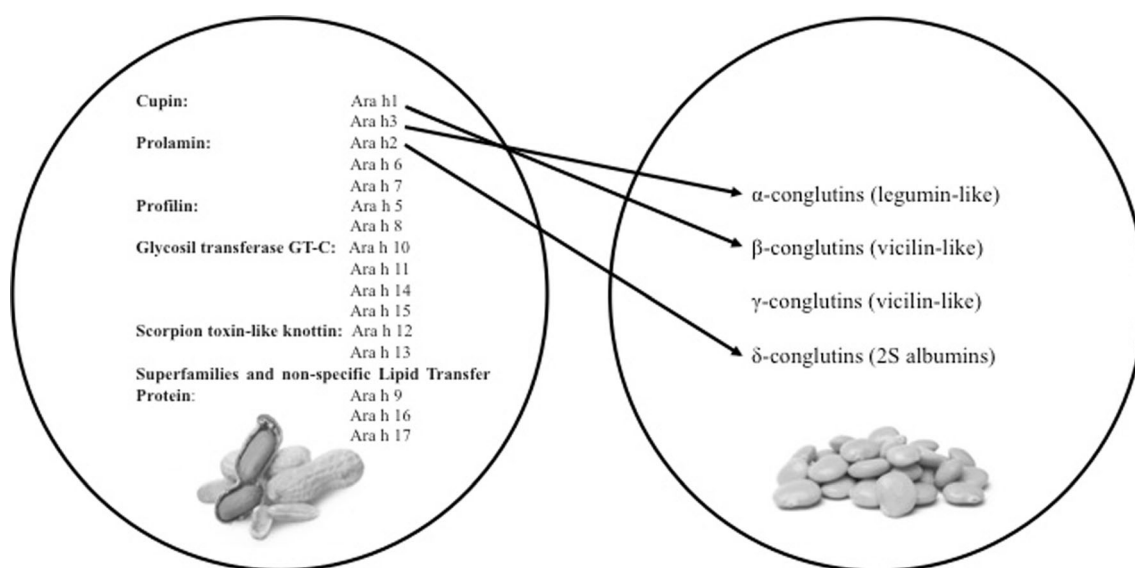


Fig. 1 Cross-reactivity between peanut and lupin allergens

whom three patients experienced only subjective responses at the highest dose of 3000 mg [40].

Three possible forms of clinical allergy to lupin have been reported: primary allergy to lupin; primary allergy to peanut with cross-reactivity to lupin; primary allergy by inhalation of lupin pollen or flour.

Cross-Sensitization Among Peanut and Other Legumes

Legumes are dicotyledonous plants belonging to the Fabales order. The main distinctive characteristic of which is their fruit. This botanical order is formed by three families: Mimosaceae, Caesalpinaceae and Papilionaceae or Fabaceae. The Papilionaceae family includes the most important allergenic species: *Lens culinaris* (lentil), *Cicer arietinum* (chick-pea), *Pisum sativum* (pea), *Arachis hypogea* (peanut), *Phaseolus vulgaris* (bean) and *Glycine max* (soy). Legumes are an important ingredient in the Mediterranean diet.

The major protein allergens responsible for legume allergy have been identified and characterized. Those potentially cross-reacting with peanut belong to the different families of vicilins (Ara h 1) [40], conglutins (Ara h 2, Ara h 6, and Ara h 7) [41], and glycinins (Ara h 3 and Ara h 4) [42]. Similar allergens also occur in the closely related edible legumes (pea, soybean, kidney bean, and lupine). However, seed proteins consist of an extremely complex mixture of individual proteins with particular properties (enzyme activity, sugar- or lipid-binding activity) besides participating in the protein bodies as seed storage proteins [43]. Among these proteins, lectins are known for a long time as a widespread group of plant proteins with interesting properties like their ability to trigger some non-specific lymphoblastic transformation in relation to their carbohydrate-binding properties [44].

Finally, lectins from currently consumed legume seeds (peanut, soybean, kidney bean, pea, and lentil) have been demonstrated to contain IgE-binding epitopes susceptible to specifically interact with IgE from peanut allergic patients. As shown in immunoblotting experiments performed with exhausted sera of allergic patients, IgE that specifically recognize legume lectins do not interact with IgE-binding epitopes of the major peanut allergens, e.g., Ara h 1, Ara h 2 or Ara h 3. In this respect, the question is still pending to discriminate between the ability of lectins to sensitize susceptible individuals or to simply trigger an allergic reaction in people previously sensitized to either vicilin (Ara h 1) or legumin (Ara h 2) or their homologous proteins from other edible legumes. However, the reported ability of various dietary lectins to induce in vitro release of IL-4 and IL-13 from human basophiles brings some credit to the first hypothesis that lectins could actually sensitize susceptible subjects.

Conclusions

The increase of the use of lupin generates the risk of cross-reactions among peanut-allergic patients. Such reactions, however, are not frequent nor—general speaking—serious. The molecular basis of cross-reactivity among legumes is very sound, but in this class, the clinical correlates are weaker than—for instance—in the class of nuts or fish. In this situation, although lupin should be declared among the ingredients of pre-packaged foods, it seems to us not opportune to label this food as potentially cross-reactive on the ground of a theoretical possibility only. We fear that this would add confusion among the consumers and health professionals who provide them with advice on how to manage their condition [45–47]. Nevertheless, the clinicians should warn peanut—allergic patients—in particular those with severe reactions—about risk of cross-reactions with legumes. Allergists employ the majority of their clinical work to prevent unnecessary elimination of foods, and PFAL type II would contradict their efforts [48, 49].

Compliance with Ethical Standards

Conflict of Interest Drs. Mennini, Dahdah, Mazzina, and Fiocchi declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, EAACI Food Allergy and Anaphylaxis Guidelines Group, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy*. 2014;69:1008–25.
2. Kulis M, Wright BL, Jones SM, Burks AW. Diagnosis, management, and investigational therapies for food allergies. *Gastroenterology*. 2015;148:1132–42.
3. Branum AM, Lukacs SL. Food allergy among U.S. children: trends in prevalence and hospitalizations. *NCHS Data Brief*; 2008. p. 1–8.
4. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol*. 2011;127:668–76.
5. Allen KJ. Food allergy: is there a rising prevalence and if so why? *Med J Aust*. 2011;195:5–7.

6. Prescott S, Allen KJ. Food allergy: riding the second wave of the allergy epidemic. *Pediatr Allergy Immunol*. 2011;22:155–60.
7. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med*. 2016;374:1733–43.
8. Xepapadaki P, Fiocchi A, Grabenhenrich L, Roberts G, Grimshaw KE, Fiandor A, et al. Incidence and natural history of hen's egg allergy in the first 2 years of life—the EuroPrevall birth cohort study. *Allergy*. 2016;71:350–7.
9. Ferreira F, Hawranek T, Gruber P, Wopfner N, Mari A. Allergic cross-reactivity: from gene to the clinic. *Allergy*. 2004;59:243–67.
10. Canonica GW, Ansotegui IJ, Pawankar R, Schmid-Grendelmeier P, van Hage M, Baena-Cagnani CE, et al. A WAO-ARIA-GA²LEN consensus document on molecular-based allergy diagnostics. *World Allergy Organ J*. 2013;6:17. **The official consensus of the World Allergy Organization emphasizes the role of molecular diagnostics in allergy food and its complex effects on the expression of clinical allergy.**
11. Nwaru B, Hickstein L, Panesar S, Muraro A, Werfel T, Cardona V, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy*. 2014;69:62–75.
12. Nwaru B, Hickstein L, Panesar S, Roberts G, Muraro A, Sheikh A. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy*. 2014;69:992–1007.
13. Urisu A, Ebisawa M, Ito K, Aihara Y, Ito S, Mayumi M, et al. Japanese guideline for food allergy 2014. *Allergol Int*. 2014;63:399e419.
14. Ebisawa M, Nishima S, Ohnishi H, Kondo N. Pediatric allergy and immunology in Japan. *Pediatr Allergy Immunol*. 2013;24:704e14.
15. Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011;128:e9e17. **The data show a steady increase in food allergies in the United States, by making people understand the social importance of the issue.**
16. Verma AK, Kumar S, Das M, Dwivedi PD. A comprehensive review of legume allergy. *Clin Rev Allergy Immunol*. 2013;45:30–46.
17. Ballabio C, Peñas E, Uberti F, Fiocchi A, Duranti M, Magni C, et al. Characterization of the sensitization profile to lupin in peanut-allergic children and assessment of cross-reactivity risk. *Pediatr Allergy Immunol*. 2013;24:270–5.
18. Sebei K, Gnouma A, Herchi W, Sakouhi F, Boukhchina S. Lipids, proteins, phenolic composition, antioxidant and antibacterial activities of seeds of peanuts (*Arachis hypogaea* L) cultivated in Tunisia. *Biol Res*. 2013;46:257–63.
19. Koppelman SJ, Vlooswijk RA, Knippels LM, Hessing M, Knol EF, van Reijssen FC, et al. Quantification of major peanut allergens Ara h 1 and Ara h 2 in the peanut varieties Runner, Spanish, Virginia, and Valencia, bred in different parts of the world. *Allergy*. 2001;56:132–7.
20. Hebling CM, Ross MM, Callahan JH, McFarland MA. Size-selective fractionation and visual mapping of allergen protein chemistry in *Arachis hypogaea*. *J Proteome Res*. 2012;11:5384–95.
21. Pawankar R, Canonica GW, Holgate ST, Lockey RF, editors. *WAO White Book on Allergy*; available at http://www.worldallergy.org/definingthespecialty/white_book.php. Accessed 29 Sept 2016.
22. Grimshaw KE, Bryant T, Oliver EM, Martin J, Maskell J, Kemp T, et al. Incidence and risk factors for food hypersensitivity in UK infants: results from a birth cohort study. *Clin Transl Allergy*. 2016;6:1.
23. Du Toit G, Roberts G, Sayre PH, LEAP Study Team, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015;372:803–13. **Recent RCT which conclude that the early introduction of peanuts significantly decreased the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts.**
24. Nettleton S, Woods B, Burrows R, Kerr A. Food allergy and food intolerance: towards a sociological agenda. *Health (London)*. 2009;13:647–64.
25. Waggoner MR. Parsing the peanut panic: the social life of a contested food allergy epidemic. *Soc Sci Med*. 2013;90:49–55. **This analysis compares medical literature to other textual sources, including media reports, legislation, and advocacy between 1980 and 2010 in order to examine how peanut allergies transformed from a rare medical malady into a contemporary public health problem. The authors argue that the peanut allergy epidemic was co-constructed through interactions between experts, publics, biomedical categories, and institutions, while social reactions to the putative epidemic expanded the sphere of surveillance and awareness of peanut allergy risk.**
26. Christakis NA. This allergies hysteria is just nuts. *BMJ*. 2008;337:a2880.
27. Sicherer SH, Sampson HA. Peanut allergy: emerging concepts and approaches for an apparent epidemic. *J Allergy Clin Immunol*. 2007;120:491–503.
28. Sicherer SH, Wood RA. Advances in diagnosing peanut allergy. *J Allergy Clin Immunol Pract*. 2013;1:1–13. **The authors review the utility of currently available tests and provide suggestions on how to best use them to accurately predict peanut allergy. Still, the physician-supervised oral food challenge remains the most definitive test available.**
29. Kapoor S, Roberts G, Bynoe Y, Gaughan M, Habibi P, Lack G. Influence of a multidisciplinary paediatric allergy clinic on parental knowledge and rate of subsequent allergic reactions. *Allergy*. 2004;59:185–91.
30. Ewan PW, Clark AT. Long-term prospective observational study of patients with peanut and nut allergy after participation in a management plan. *Lancet*. 2001;357:111–5.
31. Shreffler WG, Beyer K, Chu TH, Burks AW, Sampson HA. Microarray immunoassay: association of clinical history, in vitro IgE function, and heterogeneity of allergenic peanut epitopes. *J Allergy Clin Immunol*. 2004;113:776–82.
32. Radauer C, Lackner P, Breiteneder H. The Bet v 1 fold: an ancient, versatile scaffold for binding of large, hydrophobic ligands. *BMC Evol Biol*. 2008;8:286.
33. Edstam MM, Viitanen L, Salminen TA, Edqvist J. Evolutionary history of the non-specific lipid transfer proteins. *Mol Plant*. 2011;4:947–64.
34. Peeters KA, Koppelman SJ, Penninks AH, Lebens A, Bruijnzeel-Koomen CA, Hefle SL, et al. Clinical relevance of sensitization to lupine in peanut-sensitized adults. *Allergy*. 2009;64:549–55.
35. Sicherer SH, Muñoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol*. 2003;112:1203–7.
36. de Leon MP, Glaspole IN, Drew AC, Rolland JM, O'Hehir RE, Suphioglu C. Immunological analysis of allergenic cross-reactivity between peanut and tree nuts. *Clin Exp Allergy*. 2003;33:1273–80.
37. Lee YP, Mori TA, Sipsas S, Barden A, Puddey IB, Burke V, et al. Lupin-enriched bread increases satiety and reduces energy intake acutely. *Am J Clin Nutr*. 2006;84:975–80.
38. Fiocchi A, Sarratud P, Terracciano L, Vacca E, Bernardini R, Fuggetta D, et al. Assessment of the tolerance to lupine-enriched pasta in peanut-allergic children. *Clin Exp Allergy*. 2009;39:1045–51.
39. Shaw J, Roberts G, Grimshaw K, White S, Hourihane J. Lupin allergy in peanut-allergic children and teenagers. *Allergy*. 2008;63:370–3.

40. Peeters KA, Nordlee JA, Penninks AH, Chen L, Goodman RE, Bruijnzeel-Koomen CA, et al. Lupine allergy: not simply cross-reactivity with peanut or soy. *J Allergy Clin Immunol*. 2007;120: 647–53.
41. Burks AW, Williams LW, Helm RM, Connaughton C, Cockrell G, O'Brien T. Identification of a major peanut allergen, Ara h I, in patients with atopic dermatitis and positive peanut challenges. *J Allergy Clin Immunol*. 1991;88:172–9.
42. Burks AW, Williams LW, Connaughton C, Cockrell G, O'Brien TJ, Helm RM. Identification and characterization of a second major peanut allergen, Ara h II, with use of the sera of patients with atopic dermatitis and positive peanut challenge. *J Allergy Clin Immunol*. 1992;90:962–9.
43. Rabjohn P, Helm EM, Stanley JS, West CM, Sampson HA, Burks AW, et al. Molecular cloning and epitope analysis of the peanut allergen Ara h 3. *J Clin Invest*. 1999;103:535–42.
44. Shewry PR. Plant storage proteins. *Biol Rev Camb Philos Soc*. 1995;70:375–426.
45. Stavy L, Treves AJ, Feldman M. Effect of concanavalin A on lymphocyte-mediated cytotoxicity. *Nature*. 1971;232:56–8.
46. Ju SY, Park JH, Kwak TK, Kim KE. Attitudes and preferences of consumers toward food allergy labeling practices by diagnosis of food allergies. *Nutr Res Pract*. 2015;9:517–22.
47. Hefle SL, Furlong TJ, Niemann L, Lemon-Mule H, Sicherer S, Taylor SL. Consumer attitudes and risks associated with packaged foods having advisory labeling regarding the presence of peanuts. *J Allergy Clin Immunol*. 2007;120:171–6.
48. Fiocchi A, Dahdah L, Riccardi C, Mazzina O, Fierro V. Precautionary labelling of cross-reactive foods: the case of rapeseed. *Asthma Research and Practice*. 2016. doi:[10.1186/s40733-016-0028-4](https://doi.org/10.1186/s40733-016-0028-4).
49. Businco L, Bellanti J, Catassi C, Cavagni G, Corrias A, Fiocchi A, et al. Food Allergy in childhood. Hypersensitivity to cow's milk allergens. *Clin Experim Allergy*. 1993;23:481–83.