

Classification of Food Allergens and Cross-Reactivity

Ashley M. Kazatsky¹ · Robert A. Wood¹

Published online: 13 February 2016
© Springer Science+Business Media New York 2016

Abstract Patients with specific food allergies are commonly sensitized to related foods, for example, shrimp with other shellfish and peanut with other legumes. In some instances, this represents a true allergy to the related food, defined as cross-reactivity, while in other instances, it represents a positive skin or IgE test only, in a patient who can eat the related food without difficulty. This is defined as cross-sensitization. It is extremely important that the clinician recognize these patterns of cross-sensitization and cross-reactivity, both to counsel patients on foods that should be avoided and to make sure that foods are not unnecessarily restricted from the diet. In fact, it is very common for patients to be instructed to avoid entire food groups based just on positive tests, which leads to unnecessary dietary restrictions with effects on food choices, nutrition, and quality of life.

Keywords Food allergy · Food allergens · Sensitization · Cross-reactivity

Introduction

Concerns about possible cross-reactivity among foods is a common clinical issue in patients with food allergy. In fact,

for some food families, such as tree nuts, fish, and shellfish, true cross-reactivity is very common, while for other related foods, such as legumes and grains, cross-reactivity is less common even though cross-sensitization is frequently identified [1]. While there is some confusion in the literature, for this review, we will refer to cross-sensitization as a positive test, by either skin or IgE testing, to a related food to which the patient is clinically tolerant, while cross-reactivity will be used to define true clinical reactivity. This distinction is extremely important, both to be aware of foods that may pose a high risk of reaction and to avoid unnecessary food restrictions. For example, while the patient with cashew allergy is extremely likely to be allergic to pistachio, most patients with peanut allergy will test positive to other legumes but be able to eat them with no difficulty.

Here we will review specific food groups with the intent of providing a clinical perspective regarding cross-reactivity related to a variety of common food allergens, hopefully enabling the clinician to clearly distinguish cross-reactivity from cross-sensitization, with the ultimate goal of keeping patients safe without any unnecessary dietary restrictions. We will focus on food-to-food cross-reactivity and not discuss pollen-associated food allergies in any detail, aside from some discussion regarding the important relationship of peanut to birch pollen. A summary of each of the major food groups that will be discussed is presented in Table 1.

Mammalian Milks

Cow's milk allergy is the most common food allergy in early childhood, and many other mammalian milks have been shown to be highly cross-reactive with cow's milk due to significant homology between the antigenic milk proteins. For example, in a study by Restani of cow's milk allergic patients, all circulating IgEs recognized buffalo's and sheep's

This article is part of the Topical Collection on *Food Allergy*

✉ Robert A. Wood
rwood@jhmi.edu

Ashley M. Kazatsky
aaltman5@jhmi.edu

¹ Division of Allergy and Immunology, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Table 1 Cross-reactivity among specific food families

Food family	Overall risk of cross-reactivity	Specific considerations
Mammalian milks	High	Very high rate of CR between cow, goat, and sheep's milk; very low rate with mare, camel, and donkey's milk
Mammalian milks and meats	Low	10–20 % rate of CR between cow's milk and beef
Hen's egg and avian meats	Low	Estimated 5–10 % CR between egg and chicken
Fish	High	High frequency of CR among different species; OFCs to specific fish may be indicated based upon testing and importance to diet
Shellfish	Variable	High (>50 %) CR between different crustaceans and different mollusks; low between crustaceans and mollusks
Tree nuts	High	Most patients are allergic to >1 nut; nearly 100 % CR between walnut and pecan and between cashew and pistachio
Legumes	Variable	Low CR between peanut and other legumes except possibly lupine; higher CR between lentil and other legumes such as pea and chick pea
Wheat and cereal grains	Variable	High CR between wheat and rye, less so between wheat and barley; low between wheat and other grains

CR cross-reactivity

milk proteins, particularly for α -casein and β -lactoglobulin, and 50 % had IgEs that recognized goat's milk to the same affinity as cow's milk, while none showed a response to camel's milk or human milk proteins [2].

When considering clinical reactivity, the vast majority of patients with IgE-mediated cow's milk allergy do have true cross-reactivity to sheep, buffalo, and goat's milk, while very few demonstrate true reactivity to ass's (donkey) milk or mare's milk [3, 4]. In one study, of 26 cow's milk allergic patients, 23 had a positive oral food challenge (OFC) to goat's milk while only 1 was positive to ass's milk. Another safe option for children with cow's milk allergy appears to be camel's milk, although accessibility may be limited in the USA [5].

As an interesting side note in this food family—as the field of food allergen immunotherapy is emerging—one quarter to one half of children who underwent successful desensitization to cow's milk remained reactive to goat's milk [6–8]. These studies suggest that patients who do not tolerate goat's milk after cow's milk immunotherapy may be due to sensitization to specific goat's milk caseins that do not cross-react with cow's milk caseins. Therefore, there is sufficient homology to reliably induce reactions before treatment, but enough differences to permit ongoing reactivity even after successful cow's milk desensitization.

Mammalian Milk and Meat

Meat allergy is rare overall. The most commonly implicated meat is beef, and there is cross-reactivity between

different meats, such as beef and pork, as well as between milk and mammalian meats and between meat and animal danders [9].

The most common clinical concern in this area relates to possible cross-reactivity between cow's milk and beef, as these foods contain similar proteins, including but not limited to bovine serum albumin (BSA) and bovine gamma globulin [10, 11]. Among children with cow's milk allergy, cross-sensitization to beef is extremely common but true cross-reactivity occurs in only 10 to 20 % of patients, almost entirely in those with more severe cow's milk allergy [9, 10, 12, 13]. It has been shown that heating and processing can affect the allergenicity of beef and BSA [13, 14]. In the study by Fiocchi, ten beef-allergic children underwent detailed evaluation that revealed that all children had positive skin prick tests (SPT) to raw beef, cooked beef, and unheated BSA, while 7/10 had a positive SPT to heated BSA [14]. Interestingly, only 1/10 had a positive SPT to freeze-dried beef, and there were no positive SPTs to homogenized beef. When these children underwent OFCs, there were no positive challenges with ingestion of homogenized or freeze-dried beef, and half reacted to unheated BSA. This effect on allergenicity with heating was also seen in the study by Werfel in which 335 patients with atopic dermatitis were evaluated for beef allergy [13]. Of these patients, 11 were diagnosed with beef allergy, 3 of whom only reacted to lesser-cooked beef. These findings support the concept that cow's milk allergic patients who react to lesser cooked beef may not have to avoid all beef.

Egg and Avian Meats

Patients with egg allergy are at increased risk of allergic reactions to both chicken and other avian meats, as well as other types of eggs. Although neither of these topics has been systematically studied, from clinical experience, we find that 5–10 % of patients with egg allergy are reactive to chicken but that most are allergic to other types of eggs (e.g., goose and duck).

Another potential variety of cross-reactivity with egg is referred to as the “bird-egg syndrome,” a term used to describe a condition in which adults with allergic respiratory disease provoked by the inhalation of bird feathers or dander also develop allergic symptoms with egg ingestion [15–17]. Egg yolk α -livetin (also referred to as chicken serum albumin), a protein found in bird products and egg yolk, has been identified as a cross-sensitizer in the bird-egg syndrome.

Fish

The prevalence of fish allergy varies greatly between regions as well as between children and adults [18]. Among patients with fish allergy, the majority report reacting to multiple fish species [19]. The major cod allergen, Gad c 1, is a parvalbumin protein that has proven to be the major cross-reactive fish allergen [20]. While up to 90 % of fish-allergic patients react to Gad c 1, most fish have multiple parvalbumin lineages that can lead to sensitization to one fish but not another, and there also appears to be different binding epitopes with varied primary structure [21]. Cross-reactivity has been reported to be at least 50 % between different fish species, and children who are cod-allergic appear more likely to be sensitized to multiple fish species than non-cod-allergic children [22]. However, monosensitivity to individual fish species has been documented in a series of patients not sensitized to parvalbumin, which may be especially relevant to patients with allergy to tilapia [23].

Both SPT and serum-specific IgE have been widely used in the diagnosis and management of fish allergy; however, as with other foods, clinical reactivity does not correlate well with evidence of sensitization [24–27]. Bernhisel-Broadbent described a cohort of patients with suspected fish allergy. While a majority demonstrated positive skin testing to all fish, only 15/50 challenges elicited positive challenges [25]. Of note, this study also found a 21 % false negative challenge rate that was attributed to the lyophilization of the fish used in the double-blind challenge. This is important from a clinical perspective as fish allergenicity may be significantly altered by heating and processing, with very few fish allergic patients reacting to canned tuna or salmon [28].

Shellfish

The shellfish class of seafood is comprised of crustaceans and mollusks, and the major allergen responsible for allergic reactions is the muscle protein, tropomyosin [29]. In a US telephone survey, the prevalence of reported shellfish allergy was 2 % overall and the rate of reactions to multiple crustacean species was 38 %, 49 % for mollusks, and 14 % with crustacean allergy reported also having a mollusk allergy [19].

Cross-sensitization among shellfish species is extremely common, ranging from 70 to 100 % for crustaceans and from 17 to 100 % between crustaceans and mollusks [29–32]. Unfortunately, however, the incidence of true cross-reactivity is not clear due to a lack of comprehensive studies. Based upon the available data and clinical experience, we estimate that almost all patients with an allergy to one crustacean will be sensitized to other crustaceans, and at least half will react clinically upon ingestion. Similarly, among mollusk-allergic patients, approximately 50 % report reactions to more than one type of mollusk. Importantly, however, avoidance of all shellfish may not be necessary because the majority of patients—possibly as high as 80–90 %—with a crustacean allergy are not allergic to mollusks, and vice versa.

Tree Nuts

Tree nut allergy is estimated to occur in 0.5–1 % of the population, with wide variability in the prevalence of different nut allergies in different parts of the world [18]. Based upon a large telephone survey in the USA, it was shown that reported allergy to walnut, cashew, almond, pecan, and pistachio were most common, with hazelnut, Brazil nut, pine nut, and macadamia nut each attributed to <5 % of reactions [33].

The majority of tree nut allergens identified are seed storage proteins such as vicilins, legumins, 2S albumins, profilins, heveins, and lipid transfer proteins [34]. The latter three are categorized as pan-allergens, as they have high IgE-mediated cross-reactivity [31]. One study found that 37 % of tree nut allergic patients reported reacting to more than one variety of tree nut, and 92 % of patients allergic to peanut, tree nut, or both had elevated IgE to more than one tree nut [35]. However, the vast majority of the literature on this subject involves self-reported allergy, in vitro studies, and/or skin testing for sensitivity, and the correlation between positive test results and clinical cross-reactivity is not well documented.

With regard to in vitro testing, walnut has demonstrated in vitro cross-reactivity to multiple other nuts, including Brazil nut, hazelnut, and pecan [36–38]. Asero found that hazelnut, however, did not have an inhibitory effect on all walnut proteins in vitro and walnut only led to inhibition of a single protein band of Brazil nut. These studies have also shown strong cross-reactivity between walnut and pecan, which share a botanical family (*Juglandaceae*), while less

significant cross-reactivity was noted between walnut and other nuts, including almond, cashew, pistachio, and hazelnut. Significant cross-reactivity has also been demonstrated in vitro between cashew and pistachio nuts, which are also in the same botanical family, Anacardiaceae [38, 39•].

Most importantly, clinical cross-reactivity is very common among some tree nuts and not others. Cross-reactivity between pecan and walnut and between cashew and pistachio is virtually 100 % predictable. The latter pairing has been demonstrated in the study by Savvatanos of 100 cashew and/or pistachio allergic children, among whom there were no documented cases of selective cashew or pistachio allergy [39•]. Overall, it is safe to conclude that a majority patients with tree nut allergy are truly allergic to more than one nut, while very few patients are allergic to all tree nuts.

With regard to clinical management, while some clinicians recommend avoidance of all tree nuts for patients with any tree nut allergy, we advise an individualized approach depending on multiple factors, including the age of the patient, test results, the likelihood of cross-reactivity, and most importantly patient/family preferences. Some families simply prefer a “no nut policy” which they feel works best for them. If specific nuts are to be introduced to a patient with a known nut allergy, skin and IgE testing will help guide this process, and OFCs will be needed for most patients to allow for the safe introduction of specific nuts [40].

Legumes

It is common to find positive skin or IgE antibody tests to multiple legumes in individuals who are allergic to peanut. However, despite the high rate of cross-sensitization, cross-reactivity is uncommon and most patients with peanut allergy do not need to avoid other legumes, much less the entire legume family as had been recommended in the past. For example, in one study, 31 % (10 of 32) of children with peanut allergy had a positive skin test to soy, but only 3 % (1 of 32) had a clinical reaction to soy [41]. In another study, OFCs were performed in 69 children with at least one positive skin test to a legume [42]. Challenges were conducted to five legumes (peanut, soybean, pea, lima bean, green bean), which resulted in 43 reactions in 41 patients (59 %). However, while 52 % (36 of 69) reacted to two or more legumes on prick skin testing, only 5 % (2 of 41) of patients reacted to more than one legume when challenged.

Particular legumes may be more associated with cross-reactivity to other legumes, and there appear to be regional differences in this regard. For example, in a study from Spain, where allergy to lentil and other legumes is more common than allergy to peanut, 35 of 43 children with allergy to lentil also reacted to at least one other legume, most commonly chickpea ($n=8$), pea ($n=6$), or both chickpea and pea ($n=23$) [43, 44].

A final concern with regard to legume cross-reactivity relates to a potentially higher incidence of allergy to lupine, compared to other legumes, in patients with peanut allergy. While data are still limited and the true rate of cross-reactivity is not known, studies to date do suggest that this may be the case. For example, a study from France reported that 11 of 24 children with peanut allergy had positive skin tests to lupine, and seven of eight children who underwent OFCs to lupine reacted [45].

Wheat and Cereal Grains

Wheat allergy is one of the most common food allergies in childhood and has been estimated to affect up to 1 % of children. There are many clinical manifestations of wheat allergy, including classic IgE-mediated wheat allergy; wheat-dependent, exercise-induced anaphylaxis; Baker's asthma; and delayed reactions, such as atopic dermatitis and eosinophilic esophagitis. Wheat is comprised of a variety of proteins, many of which have been implicated in clinical manifestations of allergy. The term gluten refers to the component that is comprised of equal parts of glutenin and gliadin. The gluten proteins are the major determinants of the processing properties of wheat flour and are responsible for celiac disease. Alpha-amylase inhibitors have been identified as the major proteins in Baker's asthma [46]. However, while IgE reactivity to many wheat components has been identified, ω -5 gliadin (Tri a 19) has been identified as the major allergen associated with immediate type hypersensitivity reactions [46, 47, 48•, 49].

From a clinical perspective, cross-sensitization is very common among wheat, other cereal grains, and related grasses. True cross-reactivity is most common between wheat and rye, less so for wheat and barley, and far less so for wheat and other grains, including oat, rice, and corn. In a study by Jones, 145 patients had a positive SPT to one or more cereal grain (wheat, rye, oat, barley, rice corn), and all underwent OFCs [50]. Less than 25 % had a positive OFC and 80 % of those children only reacted to one grain. Additionally, 67 % of patients with positive SPT to wheat had negative OFC. In a study by Pourpak, over half of 18 children with wheat allergy had a positive challenge to barley, but all corn and rice challenges were negative [51].

Pollen–Food Allergy Syndrome (Oral Allergy Syndrome)

Pollen–food allergy syndrome (PFAS), or oral allergy syndrome (OAS), describes reactions typically localized to the oropharynx that occur with ingestion of fresh fruits, vegetables, or nuts in patients who are sensitized to pollens [52]. The majority of these reactions are caused by proteins that cross-react to the major birch pollen allergen, Bet v 1. These foods include those in the Rosaceae group, including apple, cherry,

apricot, pear, and plum, as well as Apiaceae vegetables such as celery and carrot [53, 54]. However, tree nuts, most commonly almond and hazelnut, and legumes, including peanut and soy, can be a cause of PFAS as well [55–57].

The issue of peanut and pollen cross-sensitization and cross-reactivity is a topic of particular interest. We have learned in recent years that cross-sensitization between peanut and birch pollen is very common. It is very important to recognize this from the clinical standpoint, as many patients with birch and other pollen allergies are misdiagnosed with peanut allergy due to a positive skin or IgE test [58•]. In reality, a positive test to peanut may represent one of several clinical conditions, including a false positive test due to cross-sensitivity with another legume or birch pollen, a true positive test with OAS symptoms only, or true peanut allergy with a risk of severe reactions. Aside from the history, which is always the most important diagnostic tool, component-resolved diagnostics, which detects IgE sensitization to individual peanut allergens, is extremely helpful above and beyond standard skin and IgE testing. Patients with IgE directed at stable seed storage proteins (e.g., Ara h 1, Ara h 2, and/or Ara h 3) have a high risk of true peanut allergy, whereas predominant or exclusive sensitization to pollen cross-reactive Ara h 8 is more likely to be associated with mild oral symptoms or no reactivity at all [57, 58•].

Clinical Implications and Conclusions

As described above, the potential for cross-reactivity among related foods is a common clinical issue. In the end, the goal for every patient is to accurately identify their true allergies without imposing any unnecessary food restrictions. Achieving this balance can be far more difficult than it sounds, especially since allergy testing within food groups yields a high rate of positive tests, which are in many cases are far more likely to be falsely positive than representative of true clinical reactivity. It is clear that some related foods, for example, tree nuts, fish, shellfish, and mammalian milks, are more commonly clinically cross-reactive, while others are less likely to cause clinically relevant cross-reactions (e.g., grains and legumes). It is essential that each case be considered on an individual basis, making recommendations to each patient/family based on the likelihood of a true allergy and the importance of the food to the individual's diet. For example, detailed exploration of possible allergies to fish, tree nuts, and legumes may be very important to a family following a vegetarian diet, and rather unimportant to another family.

The evaluation should always begin with a careful history. Since skin and IgE testing is likely to yield confusing results due to cross-sensitization, no testing should be performed to foods the patient has clearly tolerated. If the history is not clear, or if the patient has never eaten the food, testing should be based on the likelihood of true cross-reactivity. For

example, we would not recommend routine testing to other legumes in patients with peanut allergy, while for patients with tree nut allergy, additional testing is usually warranted to any nut that the patient has not clearly tolerated, especially if there is interest in adding specific nuts to the diet.

If negative, skin and IgE testing is usually accurate. Positive tests, however, need to be carefully interpreted on an individual basis. Sometimes, the relative proportion of specific IgE of a related food to the true food allergen is helpful, with a very low ratio suggesting a higher chance of insignificant cross-sensitization (e.g., a soy IgE of 3.5 kU/l in a patient with a peanut IgE >100 kU/l). When the picture is not clear, which is frequently the case, oral food challenges are the best means of making a definitive diagnosis. While food challenges are time consuming and carry some risk, they should be offered on an individual basis to all patients based on the likelihood of success and the importance of the food to the diet.

Compliance with Ethical Standards

Conflict of Interest Dr. Wood reports grants from NIH, from DBV, and from Aimmune, and is an editor for Up to Date. Dr. Kazatsky reports a grant from NIH.

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

1. Sicherer SH. Clinical implications of cross-reactive food allergens. *J Allergy Clin Immunol*. 2001;108(6):881–90.
2. Restani P, Gaiaschi A, Plebani A, Beretta B, Cavagni G, Fiocchi A, et al. Cross-reactivity between milk proteins from different animal species. *Clin Exp Allergy*. 1999;29(7):997–1004.
3. Vita D, Passalacqua G, Di Pasquale G, Caminiti L, Crisafulli G, Rulli I, et al. Ass's milk in children with atopic dermatitis and cow's milk allergy: crossover comparison with goat's milk. *Pediatr Allergy Immunol*. 2007;18(7):594–8.
4. Bellioni-Businco B, Paganelli R, Lucenti P, Giampietro PG, Perbom H, Businco L. Allergenicity of goat's milk in children with cow's milk allergy. *J Allergy Clin Immunol*. 1999;103(6):1191–4.
5. Ehlayel MS, Hazeima KA, Al-Mesaifri F, Bener A. Camel milk: an alternative for cow's milk allergy in children. *Allergy Asthma Proc*. 2011;32(3):255–8.
6. Alonso-Lebrero E, Fuentes V, Zapatero L, Perez-Bustamante S, Pineda F, Martinez-Molero MI. Goat's milk allergies in children following specific oral tolerance induction to cow's milk. *Allergol Immunopathol (Madr)*. 2008;36(3):180–1.

7. Martorell Aragones A, Martorell Calatayud C, Pineda F, Felix Toledo R, Cerda Mir JC, de las Marinas MD. Persistence of allergy to goat's milk after specific induction of tolerance to cow's milk. *J Investig Allergol Clin Immunol*. 2012;22(4):301–2.
8. Rodriguez del Rio P, Sanchez-Garcia S, Escudero C, Pastor-Vargas C, Sanchez Hernandez JJ, Perez-Rangel I, et al. Allergy to goat's and sheep's milk in a population of cow's milk-allergic children treated with oral immunotherapy. *Pediatr Allergy Immunol*. 2012;23(2):128–32.
9. Restani P, Fiocchi A, Beretta B, Velona T, Giovannini M, Galli CL. Meat allergy: III—Proteins involved and cross-reactivity between different animal species. *J Am Coll Nutr*. 1997;16(4):383–9.
10. Martelli A, De Chiara A, Corvo M, Restani P, Fiocchi A. Beef allergy in children with cow's milk allergy; cow's milk allergy in children with beef allergy. *Ann Allergy Asthma Immunol*. 2002;89(6 Suppl 1):38–43.
11. Fiocchi A, Restani P, Riva E, Qualizza R, Bruni P, Restelli AR, et al. Meat allergy: I—specific IgE to BSA and OSA in atopic, beef sensitive children. *J Am Coll Nutr*. 1995;14(3):239–44.
12. Fiocchi A, Restani P, Bouygue GR, Martelli A. Beef allergy in adults and children. *Allergy*. 2005;60(1):126.
13. Werfel SJ, Cooke SK, Sampson HA. Clinical reactivity to beef in children allergic to cow's milk. *J Allergy Clin Immunol*. 1997;99(3):293–300.
14. Fiocchi A, Restani P, Riva E, Mirri GP, Santini I, Bernardo L, et al. Heat treatment modifies the allergenicity of beef and bovine serum albumin. *Allergy*. 1998;53(8):798–802.
15. Szepefalusi Z, Ebner C, Pandjaitan R, Orlicek F, Scheiner O, Boltz-Nitulescu G, et al. Egg yolk alpha-livetin (chicken serum albumin) is a cross-reactive allergen in the bird-egg syndrome. *J Allergy Clin Immunol*. 1994;93(5):932–42.
16. Anibarro B, Garcia-Ara C, Ojeda JA. Bird-egg syndrome in childhood. *J Allergy Clin Immunol*. 1993;92(4):628–30.
17. Bausela BA, Garcia-Ara MC, Martin Esteban M, Boyano Martinez TB, Diaz Pena JM, Ojeda Casas JA. Peculiarities of egg allergy in children with bird protein sensitization. *Ann Allergy Asthma Immunol*. 1997;78(2):213–6.
18. Sicherer SH. Epidemiology of food allergy. *J Allergy Clin Immunol*. 2011;127(3):594–602.
19. Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of sea-food allergy in the United States determined by a random telephone survey. *J Allergy Clin Immunol*. 2004;114(1):159–65.
20. Sharp MF, Lopata AL. Fish allergy: in review. *Clin Rev Allergy Immunol*. 2014;46(3):258–71.
21. Saptarshi SR, Sharp MF, Kamath SD, Lopata AL. Antibody reactivity to the major fish allergen parvalbumin is determined by isoforms and impact of thermal processing. *Food Chem*. 2014;148:321–8.
22. de Martino M, Novembre E, Galli L, de Marco A, Botarelli P, Marano E, et al. Allergy to different fish species in cod-allergic children: in vivo and in vitro studies. *J Allergy Clin Immunol*. 1990;86(6 Pt 1):909–14.
23. Ebo DG, Kuehn A, Bridts CH, Hilger C, Hentges F, Stevens WJ. Monosensitivity to pangasius and tilapia caused by allergens other than parvalbumin. *J Investig Allergol Clin Immunol*. 2010;20(1):84–8.
24. Schulkes KJ, Klemans RJ, Knigge L, de Bruin-Weller M, Bruijnzeel-Koomen CA, Marknell deWitt A. Specific IgE to fish extracts does not predict allergy to specific species within an adult fish allergic population. *Clin Transl Allergy*. 2014;4:27.
25. Bernhisel-Broadbent J, Scanlon SM, Sampson HA. Fish hypersensitivity. I. In vitro and oral challenge results in fish-allergic patients. *J Allergy Clin Immunol*. 1992;89(3):730–7.
26. Helbling A, Haydel Jr R, McCants ML, Musmand JJ, El-Dahr J, Lehrer SB. Fish allergy: is cross-reactivity among fish species relevant? Double-blind placebo-controlled food challenge studies of fish allergic adults. *Ann Allergy Asthma Immunol*. 1999;83(6 Pt 1):517–23.
27. Pascual C, Martin Esteban M, Crespo JF. Fish allergy: evaluation of the importance of cross-reactivity. *J Pediatr*. 1992;121(5 Pt 2):S29–34.
28. Bernhisel-Broadbent J, Strause D, Sampson HA. Fish hypersensitivity. II: Clinical relevance of altered fish allergenicity caused by various preparation methods. *J Allergy Clin Immunol*. 1992;90(4 Pt 1):622–9.
29. Leung PS, Chow WK, Duffey S, Kwan HS, Gershwin ME, Chu KH. IgE reactivity against a cross-reactive allergen in crustacea and mollusca: evidence for tropomyosin as the common allergen. *J Allergy Clin Immunol*. 1996;98(5 Pt 1):954–61.
30. Daul CB, Morgan JE, Waring NP, McCants ML, Hughes J, Lehrer SB. Immunologic evaluation of shrimp-allergic individuals. *J Allergy Clin Immunol*. 1987;80(5):716–22.
31. Waring NP, Daul CB, deShazo RD, McCants ML, Lehrer SB. Hypersensitivity reactions to ingested crustacea: clinical evaluation and diagnostic studies in shrimp-sensitive individuals. *J Allergy Clin Immunol*. 1985;76(3):440–5.
32. Vidal C, Bartolome B, Rodriguez V, Armisen M, Linneberg A, Gonzalez-Quintela A. Sensitization pattern of crustacean-allergic individuals can indicate allergy to molluscs. *Allergy*. 2015;70(11):1493–6.
33. Sicherer SH, Munoz-Furlong A, Burks AW, Sampson HA. Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey. *J Allergy Clin Immunol*. 1999;103(4):559–62.
34. Roux KH, Teuber SS, Sathe SK. Tree nut allergens. *Int Arch Allergy Immunol*. 2003;131(4):234–44.
35. Sicherer SH, Furlong TJ, Munoz-Furlong A, Burks AW, Sampson HA. A voluntary registry for peanut and tree nut allergy: characteristics of the first 5149 registrants. *J Allergy Clin Immunol*. 2001;108(1):128–32.
36. Asero R, Mistrello G, Roncarolo D, Amato S. Walnut-induced anaphylaxis with cross-reactivity to hazelnut and Brazil nut. *J Allergy Clin Immunol*. 2004;113(2):358–60.
37. Robotham JM, Hoffman GG, Teuber SS, Beyer K, Sampson HA, Sathe SK, et al. Linear IgE-epitope mapping and comparative structural homology modeling of hazelnut and English walnut 11S globulins. *Mol Immunol*. 2009;46(15):2975–84.
38. Goetz DW, Whisman BA, Goetz AD. Cross-reactivity among edible nuts: double immunodiffusion, crossed immunoelectrophoresis, and human specific IgE serologic surveys. *Ann Allergy Asthma Immunol*. 2005;95(1):45–52.
39. Savvatanos S, Konstantinopoulos AP, Borga A, Stavroulakis G, Lidholm J, Borres MP, et al. Sensitization to cashew nut 2S albumin, Ana o 3, is highly predictive of cashew and pistachio allergy in Greek children. *J Allergy Clin Immunol*. 2015;136(1):192–4. **This paper reports on the identification of a major cashew allergen and its utility in diagnosing cashew and pistachio allergy.**
40. Maloney JM, Rudengren M, Ahlstedt S, Bock SA, Sampson HA. The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. *J Allergy Clin Immunol*. 2008;122(1):145–51.
41. Bock SA, Atkins FM. The natural history of peanut allergy. *J Allergy Clin Immunol*. 1989;83(5):900–4.
42. Bernhisel-Broadbent J, Taylor S, Sampson HA. Cross-allergenecity in the legume botanical family in children with food hypersensitivity. II. Laboratory correlates. *J Allergy Clin Immunol*. 1989;84(5 Pt 1):701–9.
43. Martinez San Ireneo M, Ibanez MD, Fernandez-Caldas E, Carnes J. In vitro and in vivo cross-reactivity studies of legume allergy in a Mediterranean population. *Int Arch Allergy Immunol*. 2008;147(3):222–30.

44. Martinez San Ireneo M, Ibanez MD, Sanchez JJ, Carnes J, Fernandez-Caldas E. Clinical features of legume allergy in children from a Mediterranean area. *Ann Allergy Asthma Immunol*. 2008;101(2):179–84.
45. Moneret-Vautrin DA, Guerin L, Kanny G, Flabbee J, Fremont S, Morisset M. Cross-allergenicity of peanut and lupine: the risk of lupine allergy in patients allergic to peanuts. *J Allergy Clin Immunol*. 1999;104(4 Pt 1):883–8.
46. Tatham AS, Shewry PR. Allergens to wheat and related cereals. *Clin Exp Allergy*. 2008;38(11):1712–26.
47. Battais F, Pineau F, Popineau Y, Aparicio C, Kanny G, Guerin L, et al. Food allergy to wheat: identification of immunoglobulin E and immunoglobulin G-binding proteins with sequential extracts and purified proteins from wheat flour. *Clin Exp Allergy*. 2003;33(7):962–70.
48. Makela MJ, Eriksson C, Kotaniemi-Syrjanen A, Palosuo K, Marsh J, Borres M, et al. Wheat allergy in children - new tools for diagnostics. *Clin Exp Allergy*. 2014;44(11):1420–30. **This study provides new information on the major wheat allergens and their implications in making an accurate diagnosis of wheat allergy.**
49. Palosuo K, Varjonen E, Kekki OM, Klemola T, Kalkkinen N, Alenius H, et al. Wheat omega-5 gliadin is a major allergen in children with immediate allergy to ingested wheat. *J Allergy Clin Immunol*. 2001;108(4):634–8.
50. Jones SM, Magnolfi CF, Cooke SK, Sampson HA. Immunologic cross-reactivity among cereal grains and grasses in children with food hypersensitivity. *J Allergy Clin Immunol*. 1995;96(3):341–51.
51. Pourpak Z, Mesdaghi M, Mansouri M, Kazemnejad A, Toosi SB, Farhoudi A. Which cereal is a suitable substitute for wheat in children with wheat allergy? *Pediatr Allergy Immunol*. 2005;16(3):262–6.
52. Kazemi-Shirazi L, Pauli G, Purohit A, Spitzauer S, Froschl R, Hoffmann-Sommergruber K, et al. Quantitative IgE inhibition experiments with purified recombinant allergens indicate pollen-derived allergens as the sensitizing agents responsible for many forms of plant food allergy. *J Allergy Clin Immunol*. 2000;105(1 Pt 1):116–25.
53. Rodriguez J, Crespo JF. Clinical features of cross-reactivity of food allergy caused by fruits. *Curr Opin Allergy Clin Immunol*. 2002;2(3):233–8.
54. Rodriguez J, Crespo JF, Lopez-Rubio A, De La Cruz-Bertolo J, Ferrando-Vivas P, Vives R, et al. Clinical cross-reactivity among foods of the Rosaceae family. *J Allergy Clin Immunol*. 2000;106(1 Pt 1):183–9.
55. Berkner H, Neudecker P, Mittag D, Ballmer-Weber BK, Schweimer K, Vieths S, et al. Cross-reactivity of pollen and food allergens: soybean Gly m 4 is a member of the Bet v 1 superfamily and closely resembles yellow lupine proteins. *Biosci Rep*. 2009;29(3):183–92.
56. Mittag D, Vieths S, Vogel L, Becker WM, Rihs HP, Helbling A, et al. Soybean allergy in patients allergic to birch pollen: clinical investigation and molecular characterization of allergens. *J Allergy Clin Immunol*. 2004;113(1):148–54.
57. Mittag D, Akkerdaas J, Ballmer-Weber BK, Vogel L, Wensing M, Becker WM, et al. Ara h 8, a Bet v 1-homologous allergen from peanut, is a major allergen in patients with combined birch pollen and peanut allergy. *J Allergy Clin Immunol*. 2004;114(6):1410–7.
58. Sicherer SH, Wood RA. Advances in diagnosing peanut allergy. *J Allergy Clin Immunol Pract*. 2013;1(1):1–13. **This review provides a detail, up to date approach to the diagnosis of peanut allergy, including the use of component resolved diagnostics.**