



Food Cross-Reactivity

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Cox et al. Clinical Relevance of Cross-Reactivity in Food. J Allergy Clin Immunol Pract 2021;9:82-99



Milk

- Major allergens
 - Casein (Bos d 8)
 - Whey
 - Alpha-lactalbumin (Bos d 4)
 - Beta-lactoglobulin (Bos d 5)
 - Bos d 6 (bovine serum albumin)
- High cross-reactivity with goat's milk (92% cross reacted in DBPCFC)
- However, only 4% cross-reacted to mare's milk and in a small trial (n=15) none reacted to camel's milk in DBPCFC
- Does milk share proteins with beef?

Where's the beef?

- Cow's milk proteins are only present in milk
- However, beef and milk share some common allergenic proteins
 - Serum albumins (Bos d 6)
 - Immunoglobulins (Bos d 7)
 - In a series of 28 children with beef allergy, 26 (93%) also reacted to milk
 - The reverse is NOT true
 - In those with milk allergy, only 13-20% reacted to beef on challenge



Egg

- Hen's egg is by far the common consumed
 - Ovomucoid (Gal d 1) is the major allergen
 - Acid resistant
 - Heat stable
 - Ovalbumin (Gal d 2) also plays a role
 - Heat labile
- Quail (69%) and duck (66%) are the most commonly cross-reactive



Wheat

- Relevant allergens are gliadins and glutenins
- Rates of cross-reactivity with other grains
 - Barley (60%)
 - Other studies show that only 20% with wheat allergy will also react to barley or rye
 - Oat (33%)
 - Job's tears (20%)
- Safe products (gluten-free) for those with grain allergy, but also not useful in OIT dosing
 - Millet, corn, sorghum, teff, amaranth, and quinoa



Shellfish

- Allergens in crustaceans and mollusks include:
 - **Tropomyosin (also HDM/cockroach and may be initial sensitizing force and consider AIT)**
 - Arginine kinase
 - Myosin light chain
 - Sarcoplasmic calcium binding protein
 - Paramyosin
 - Troponin triose phosphate isomerase
- Crustaceans (shrimp/prawn, crab, lobster) have >88% amino acid sequence homology with tropomyosin and is generally >95%
- Within mollusks (oyster, mussel, scallops, etc) tropomyosin homology is 70-90%
- Homology between mollusk/crustacean tropomyosin is 55-65%
- Heating may play a role in clinically relevant cross-reactivity





Fish

- Major allergens include:
 - Parvalbumins (85% or higher homology for carp-barramundi, carp-yellowfin tuna, barramundi-yellowfin tuna, and rainbow trout-Atlantic salmon)
 - Aldolase & enolase (heat labile so more important in raw fish)
 - Collagen may be important in fish skin
- These fish share allergenic properties
 - Cod, salmon, Pollack, herring, wolffish
- These fish have low cross-reactivity
 - Halibut, flounder, tuna, mackerel
- Heating/canning reduces allergenicity by 20-60%
- Different parts of the fish may have different concentrations of allergen and there may be geographic differences as well
- Bottom line—there is a lot variables with fish and if you want to do OIT



Fruits

- Look for other treatable conditions before OIT
- Oral Allergy Syndrome, Food Pollen Syndrome (consider AIT)
- Latex Cross-reactivity
- LTP Syndrome
 - Potentially severe reactions
 - Unclear if sensitizing route is aeroallergens, oral exposure to food, or nonpollen environmental exposure to foods like peach fuzz
 - Prevalent in Mediterranean countries

Meats

- Most common allergens are serum albumins (highly conserved) and α -Gal
- Most common include beef, lamb, pork, and poultry
- High cross-reactivity to beef-lamb and venison-lamb, but not with poultry
- Chicken and turkey are highly cross-reactive





Special Considerations

- Special sensitization patterns giving meat co-allergy syndromes:
- Pork-cat (homology between Fel d 1 and porcine albumin)
- Bird-egg (secondary sensitization to poultry after inhalant exposure to feathers/droppings)
- Fish-chicken (homologous proteins include parvalbumin, enolase, aldolase)
- α -Gal (susceptible pts who get tick bites, react to red meats with delayed symptoms)

Seeds

Sesame, sunflower, mustard, poppy,
pumpkin, and flaxseed



Sesame: ses i3 shares 80% homology with ara H1, co-sensitivity with walnut, cashew, macademia, poppy, hazelnut, kiwi, peanut and rye

Sunflower seed: same botanical family as mugwort with rxn's from PFAS to anaphylaxis

Mustard: white/brown share major allergens, x-react birch, mugwort, ragweed

Poppy: cross reactivity reported with hazelnut, little data

Legumes

peanut, soybean, lupin chickpea, lentil and pea

- sensitization varies regionally
- lupin becoming more common in US
- lupine flour added to pasta, baked goods and gluten free products
- lentil/chickpea/pea ~70% cross reactivity, Mediterranean areas
- 30-60% peanut pts. have + soy ST, only 3-15% allergic to soy

Bottom line: ~90% peanut pts tolerate legumes



Allergens:

prolamins
cupins
profilin
Bet v-1 like pathogenesis-related (PR)-10
lipid transfer proteins (LTP)
defensins
oleosins

Contrasting Data

69 US kids sensitive to multiple legumes

Peanut + skin test in 60

DBOFC's only 2 were + to >1 legume

JACI 1989;83:435-40



39 Dutch adults sensitized to peanut

87% + test soy, 82% lupin, 55% pea

Peanut + OFC: 35% also + lupin, 33% soy,
and 29% pea

JACI 2018;141:41-58

More About Peanut Allergy



❑ 10-25% react to sesame

❑ 2/3's are sensitized to tree nuts

❑ 1/3 are allergic to tree nuts, yet no homology of allergens

Tree Nut Allergens

Vicilins, profilins, lipid transfer proteins (LTP), and hevein-related proteins are pan allergens, plant based foods

PR-10 proteins are heat labile, cross react with birch (hazelnut, almond, walnut, peanut, et al)

Vicilins, legumin-like proteins, LTP, and heveins are heat stable, account for severe reactions

Coconut is labeled a TN, but is a fruit, rarely allergenic





Tree Nut Families

Hamamelididae

walnut, pecan, hazelnut

Macademia reactors cluster with these nuts

Anacardiacea

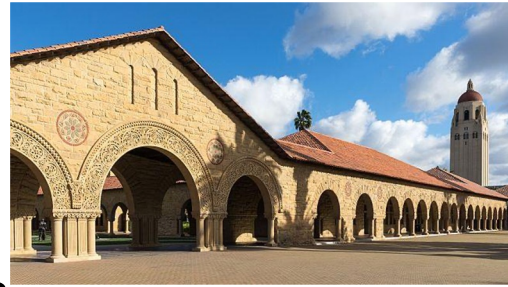
Cashew, pistachio

Can react to pink peppercorn, sumac spice,
citrus seed, pectin

Multiple tree nut allergy is common, increases with age

Nutcracker / Pronuts / Stanford / WW studies support dominant nut

Walnut & Cashew are Dominant Nuts



- 60 food allergic children at Stanford did multi-OFC's
- All pistachio allergic patients (42) reacted to cashew, whereas 4 of 46 cashew allergic patients tolerated pistachio
- All pecan allergic patients (29) reacted to walnut, whereas 3 of 32 walnut allergic patients tolerated pecan
- Epi used in 5 of 311 OFC's (1.6%)



Coexistent Nuts & Sesame Allergy

- 122 kids with one of more allergies to peanut, tree nuts or sesame (11 foods), 61% had >1 food allergy
- Tolerated a median of 9 foods
- Cashew and walnut dominant (97% pistachio allergic to cashew and pecan allergic to walnut; 83% and 75% opposite direction)
- Walnut and pecan also clustered with hazelnut and macademia



Impact of Walnut OIT

- 56 pts, 4-20 yo, reached 4 gm walnut protein OIT
- 86% were co-allergic to pecan, all passed post-OIT pecan OFC
- 15 co-allergic to hazelnut, 14 (93%) had either a 10-fold increase in threshold dose or reached 1 gm protein on hazelnut OFC
- Fewer cashew co-allergics succeeded

Leveraging Nut Cross Reactivity

- OIT patients completing cashew (n=88) or walnut (31)
- 94% post-cashew OIT pts passed pistachio OFC
- 97% post-walnut OIT pts passed pecan OFC
- Of the 5 pistachio OFC failures, only 1 reacted <5 nuts

Wasserman/Windom. Ann Allergy Asthma Immunol 2021;127:149-51



Summary



- To believe or not believe (food testing)
- Co-sensitization $\neq$ Co-allergy
- Goals: 1) Prevent over-avoidance of safe foods
2) Avoid exposure to offending foods
- Regional differences impact outcomes
- Even less known about cross-protection of OIT