Food Allergy Cross-Reactivity: What OIT Allergists Need to Know

Ruchir Agrawal, MD · Jacob Larison, DNP · Freedom Allergy

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Key Concepts: Not All Positive Tests Are Equal

Cross-Reactivity

- Sensitization to conserved, homologous proteins shared across foods
- Sensitivity (positive test) ≠ Clinical Reactivity (symptomatic allergy)
    - e.g. Peanut with Soy IgE but asymptomatic to Soy protein

Examples: Cashew and Pistachio, Walnut and Pecan

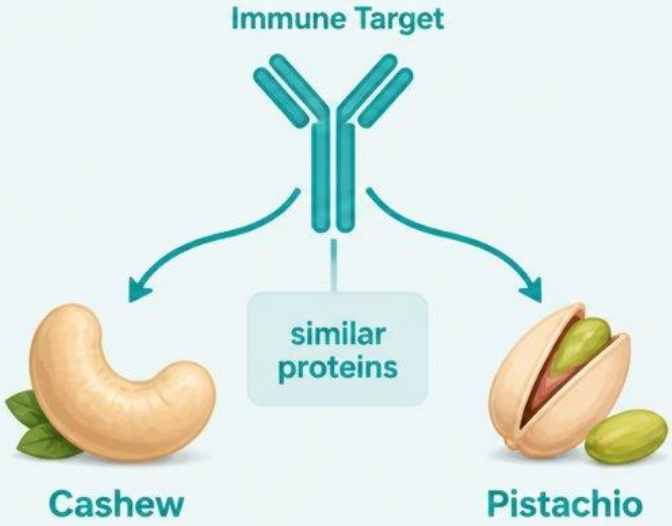
Co-Allergy

- Sensitization to two or more allergens — not necessarily structurally related
- One food's OIT may NOT cover the other — treat them as independent

- Examples:
    - Peanut and Tree Nut allergy
- Sesame in the Peanut+Tree nut patient

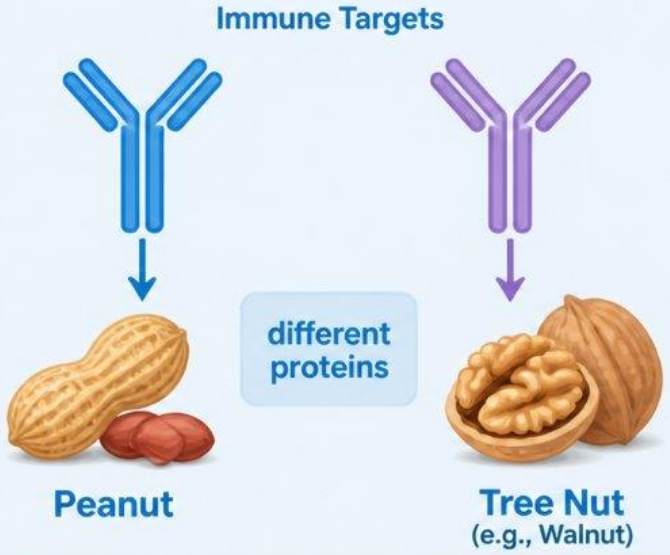
Understanding the Difference in Food Allergies

Cross-Reactivity



One antibody reacts to similar proteins in related foods.

Co-Allergy



Separate allergies to different foods in the same person.

3 Protein Families Drive Almost Everything

2S Albumins

Heat-STABLE | Highest systemic risk

- Ara h2/h6 (peanut)
- Ana o3 (cashew)
- Pis v1 (pistachio)
- Jug r1 (walnut)
- Ses i1 (sesame)

OIT note: Drives cashew/pistachio and walnut/pecan cross-reactivity

PR-10 / Bet v1

Heat-LABILE | Birch pollen bridge

- Cor a1 (hazelnut)
- Ara h8 (peanut)
- Mal d1 (apple)
- Bet v1 (birch pollen)

OIT note: Oral pruritus only — rarely needs OIT; allergy may appear worse than it is

Tropomyosin

Heat-STABLE | Environmental crossover

- Pen a1 (shrimp)
- Der p10 (dust mite)
- Bla g7 (cockroach)
- Myt e1 (mussel)

OIT note: if HDM primary sensitizer, may have less clinical relevance

F017-IgE Hazelnut (Filbert)	42.90	A	kU/L	F	Class V	02
Panel 604726:						
F428-IgE Cor a 1	46.20	A	kU/L	F	Class V	02
F425-IgE Cor a 8	0.15	A	kU/L	F	Class 0/I	02
F440-IgE Cor a 9	3.05	A	kU/L	F	Class III	02
F439-IgE Cor a 14	0.13	A	kU/L	F	Class 0/I	02
IgE Nut Prof. w/Component Rflx:						
F256-IgE Walnut	18.80	A	kU/L	F	Class IV	02
Panel 604721:						
F441-IgE Jug r 1	0.11	A	kU/L	F	Class 0/I	02
F442-IgE Jug r 3	0.18	A	kU/L	F	Class 0/I	02
IgE Nut Prof. w/Component Rflx:						
F202-IgE Cashew Nut	8.84	A	kU/L	F	Class IV	02
Panel 604239:						
F443-IgE Ana o 3	0.15	A	kU/L	F	Class 0/I	02
IgE Nut Prof. w/Component Rflx:						
F018-IgE Brazil Nut	3.94	A	kU/L	F	Class IV	02
Panel 604350:						
F354-IgE Ber e 1	0.11	A	kU/L	F	Class 0/I	02
IgE Nut Prof. w/Component Rflx:						
F013-IgE Peanut	29.60	A	kU/L	F	Class V	02
Panel 604845:						
F422-IgE Ara h 1	0.11	A	kU/L	F	Class 0/I	02
F423-IgE Ara h 2	0.12	A	kU/L	F	Class 0/I	02
F424-IgE Ara h 3	0.14	A	kU/L	F	Class 0/I	02
F447-IgE Ara h 6	<0.10		kU/L	F	Class 0	02
F352-IgE Ara h 8	19.50	A	kU/L	F	Class V	02
F427-IgE Ara h 9	0.13	A	kU/L	F	Class 0/I	02
IgE Nut Prof. w/Component Rflx:						
F345-IgE Macadamia Nut	23.30	A	kU/L	F	Class V	02
F201-IgE Pecan Nut	1.00	A	kU/L	F	Class II	02
F203-IgE Pistachio Nut	29.00	A	kU/L	F	Class V	02
F020-IgE Almond	14.60	A	kU/L	F	Class IV	02
Sesame, IgE w/Component Reflex:						
F010-IgE Sesame Seed	57.70	A	kU/L	F	Class V	02
F449-IgE Ses i 1:						
F449-IgE Ses i 1	<0.10		kU/L	F	Class 0	02
Immunoglobulin E, Total:						
Immunoglobulin E, Total	1723	H	IU/mL	F	22-1055	02

What Makes Cross-Reactivity Clinically Relevant?

Immune Factors

- IgE antibody concentration
- IgE specificity (proteins & epitopes)
- IgE affinity
- Effector cell reactivity

Protein / Food Factors

- Degree of protein homology
- Concentration in edible portion
- Stability to heat & digestion
- Preparation method (raw vs. cooked)

Patient Factors

- Amount consumed
- Augmentation factors (exercise, illness, alcohol)
- Age and prior exposure history
- Individual immune variability

Cow's Milk Cross-Reactivity

>90%

Sheep & Goat Milk

High clinical risk — same caseins & whey proteins

<5%

Camel & Mare Milk

Low risk — casein structure is sufficiently different

10–20%

Beef

Co-allergy; serum albumin (Bos d 6) is the bridge

Conflicting OIT data: Rodriguez del Rio 2012: ~26% of successfully treated CMA children remained goat/sheep milk allergic. BUT Nachshon 2020: 109/110 passed goat and 105/105 passed sheep milk challenge post-CM OIT.

OIT Takeaway: CM OIT usually (but not always) covers goat/sheep. Confirm with OFC post-maintenance. Camel milk is generally safe. Screen for beef allergy independently.

Tree Nuts: High-Value Cross-Reactive Pairs

Walnut → Pecan **~66–75%**

~100% of pecan-allergic patients are also walnut-allergic.
Relationship is asymmetric.

Pecan → Walnut **~100%**

If pecan-allergic → walnut nearly certain.
Walnut OIT cross-desensitizes pecan.

Cashew → Pistachio **64–100%**

Same 2S albumin family (Ana o3 / Pis v1) and 7S vicilin (o1/v3).
Strong OIT cross-desensitization evidence.

Pistachio → Cashew **~100%**

Always track pistachio sIgE throughout cashew OIT.

OIT Takeaway: Cashew OIT covers pistachio. Walnut OIT covers pecan. Select the dominant nut of each pair for OIT — but verify with labs. See next slide.

Source: NUT CRACKER Study (Elizur et al. Allergy 2018) • Wasserman & Windom, Ann Allergy 2021

Case: 4 Years on Cashew OIT — Did Pistachio Come Along?

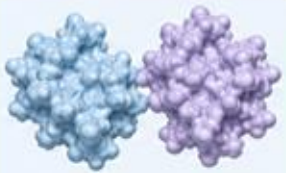
3 y/o started cashew + pistachio + sesame OIT (2022) with significant eczema. Pistachio dropped early — assumed covered by cashew. Labs rechecked 4 years later.

2022 — BEFORE OIT	
Total IgE	356 kU/L
Cashew (F202) sIgE	5.03
Pistachio (F203) sIgE	6.20

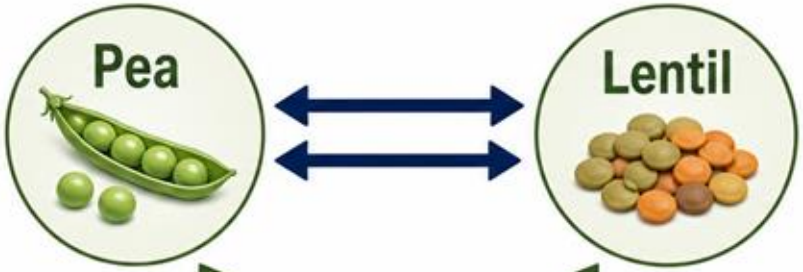
2025 — AFTER 4 YEARS CASHEW + SESAME OIT	
Total IgE	9809 kU/L
Cashew (F202) sIgE	**3.10 ↓**
Pistachio (F203) sIgE	**19.00 ↑**
Cashew IgG4	**28.0 (blocking Ab)**

Lesson: IgG4 is allergen-specific. A blocking antibody to cashew may NOT always cross-protect pistachio. Cross-desensitization must be verified. Track pistachio sIgE throughout cashew OIT.

Pea, Lentil, and Chickpea: A Cross-Reactive Cluster



7S Vicilin
+
11S Legumin



Stronger, two-way cross-reactivity

Weaker, asymmetric (from chickpea)

Weaker/less established

Cross-reactivity is real, but clinical allergy is narrower.

OIT Takeaway: Do not assume all legumes are covered. Test and challenge individually.

The Legume Triad (Lentil, Chickpea, Green Pea):

60–70%

of positive OFCs to one of the triad are positive to all three

>80%

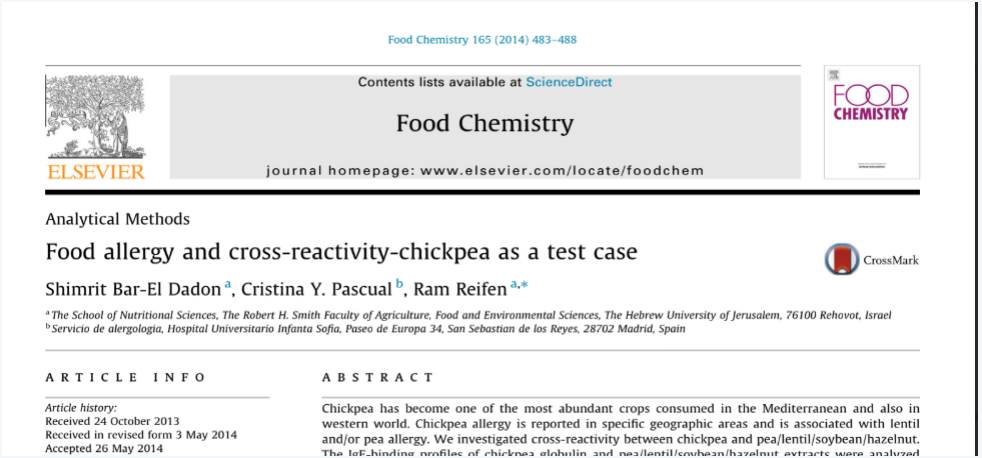
in-vitro cross-inhibition within the triad (100% inhibition of chickpea)

~64%

of peanut-allergic children sensitized to 1+ other legume

50%

of non-peanut legume reactions were "severe reactions"



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Analytical Methods

Food allergy and cross-reactivity-chickpea as a test case

Shimrit Bar-El Dadon[a], Cristina Y. Pascual[b], Ram Reifen[a,*]

[a] The School of Nutritional Sciences, The Robert H. Smith Faculty of Agriculture, Food and Environmental Sciences, The Hebrew University of Jerusalem, 76100 Rehovot, Israel
[b] Servicio de alergología, Hospital Universitario Infanta Sofía, Paseo de Europa 34, San Sebastian de los Reyes, 28702 Madrid, Spain

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ABSTRACT

Chickpea has become one of the most abundant crops consumed in the Mediterranean and also in western world. Chickpea allergy is reported in specific geographic areas and is associated with lentil and/or pea allergy. We investigated cross-reactivity between chickpea and pea/lentil/soybean/hazelnut. The IgE-binding profiles of chickpea globulin and pea/lentil/soybean/hazelnut extracts were analyzed

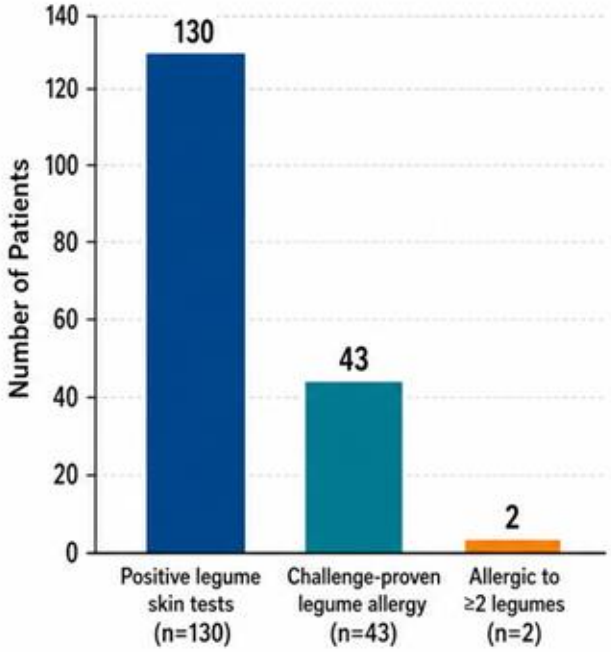
Co-sensitization between legumes is frequently seen, but variable and not always clinically relevant

Mark Smits[1,2,3]*, Kitty Verhoeckx[1,2], André Knulst[1,2], Paco Welsing[1,4], Aard de Jong[3,5], Marco Gaspari[6], Anna Ehlers[1,2], Paulien Verhoeff[1,2], Geert Houben[1,2,3] and Thuy-My Le[1,2]*

[1]Department of Dermatology/Allergology, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands, [2]Center for Translational Immunology, University Medical Center Utrecht, Utrecht, Netherlands, [3]Risk Analysis for Products in Development, Netherlands Organisation for Applied Scientific Research (TNO), Utrecht, Netherlands, [4]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands, [5]Fresh Food & Chains, Wageningen Food & Biobased Research, Wageningen University, Wageningen, Netherlands, [6]Research Centre for Advanced Biochemistry

Legume Cross-Allergy: Sensitization vs. True Allergy

Overall: Sensitization vs. True Allergy



Legume	Positive SPT (n)	Challenge-proven allergy (n)
Peanut	60	31 ✓
Soy	30	10 ✓
Pea	18	2 ✓
Green bean	9	0 —
Lima bean	13	0 —

Clinical takeaways

- Do not routinely eliminate all legumes for peanut-allergic children
- Positive SPTs to other legumes are often false positives
- Use oral food challenges to confirm suspected cross-reactivity when safe

Adapted from Sicherer SH, Sampson HA. J Allergy Clin Immunol. 2010;125(2):125-130.

Legumes: Immunologic vs. Clinical Cross-Reactivity

TABLE 1 The frequency of sensitization between 10 legumes in six different legume-allergic patient groups.

When allergic for		% sensitized									
	n	Peanut	Soybean	Green pea	Chickpea	Blue lupine	White lupine	Black lentil	Green lentil	Faba bean	White bean
Peanut	**30**	90%	76.7%	46.7%	53.3%	66.7%	56.7%	70%	63.3%	40%	60%
Soybean	**30**	63.3%	60%	53.3%	43.3%	46.7%	46.7%	50%	43.3%	36.7%	40%
Green pea	**30**	76.7%	83.3%	90%	86.7%	83.3%	80%	93.3%	90%	80%	66.7%
Lupine	**30**	83.3%	80%	70%	80%	93.3%	83.3%	93.3%	83.3%	70%	63.3%
Lentil	**17**	70.6%	82.4%	94.1%	82.4%	94.1%	82.4%	94.1%	88.2%	76.5%	58.8%
Bean	**9**	88.9%	100%	100%	100%	100%	88.9%	100%	100%	100%	77.8%

OIT Takeaway: Sensitization across the 10 legumes is significant, but does not correlate with clinical reactivity. e.g peanut and soybean are highly cross-reactive, but in most cases ~5% may be clinically relevant.

Legumes: Immunologic vs. Clinical Cross-Reactivity

TABLE 2 Odd ratios (OR) for allergy when sensitized for the 7S/11S globulin and 2S albumin fraction of the respective food.

			OR	
Allergic group	Co-allergy	Prevalence of co-allergy	7S/11S globulin	2S albumin
Peanut	Soybean	20% ($n = 6$)	6.7 (0.34–133.59)	1.68 (0.2–14.09)
$n = 30$	Green pea	13.3% ($n = 4$)	19.59 (0.94–406.44)	2.88 (0.31–26.44)
	Lupine	16.7% ($n = 5$)	6.33 (0.31–127.6)	**11.18 (1.41–88.95)**
	Lentil	3.3% ($n = 1$)	1.62 (0.06–43.25)	1.86 (0.07–49.77)
	Bean	0% ($n = 0$)	–	–
Soybean	Peanut	63.3% ($n = 19$)	**18.45 (2.57–132.64)**	**60.64 (3.03–1213.93)**
$n = 30$	Green pea	16.7% ($n = 5$)	**27.13 (1.33–554.23)**	6.69 (0.99–45.39)
	Lupine	16.7% ($n = 5$)	16.24 (0.81–325.88)	**11.18 (1.41–88.95)**
	Lentil	6.7% ($n = 2$)	5.74 (0.25–130.37)	8.81 (0.39–201.38)
	Bean	3.3% ($n = 1$)	4.83 (0.18–128.79)	10.85 (0.39–298.92)
Green pea	Peanut	73.3% ($n = 22$)	**12.89 (1.97–84.12)**	**94.71 (4.39–2041.83)**
$n = 30$	Soybean	50% ($n = 15$)	3.78 (0.51–28.05)	1.51 (0.25–9.11)
	Lupine	40% ($n = 12$)	0.36 (0.04–3.13)	2.62 (0.61–11.2)
	Lentil	46.7% ($n = 14$)	0.48 (0.06–4.18)	1.55 (0.18–13.4)
	Bean	23.3% ($n = 7$)	5.57 (0.28–112.01)	2.83 (0.52–15.46)
Lentil	Peanut	64.7% ($n = 11$)	6.84 (0.85–54.81)	**31.57 (1.37–725.23)**
$n = 17$	Soybean	64.7% ($n = 11$)	3.89 (0.39–39.02)	0.26 (0.03–2.58)
	Green pea	82.4% ($n = 14$)	3.00 (0.26–34.33)	0.6 (0.06–5.77)
	Lupine	64.7% ($n = 11$)	0.19 (0.01–4.29)	4.33 (0.51–36.57)
	Bean	35.3% ($n = 6$)	7.8 (0.35–173.98)	6.11 (0.71–52.5)

OIT Takeaway: ~90% of peanut-allergic patients tolerate all other legumes. But the lentil–chickpea–pea triad is a major exception — treat individually and sequence carefully.

Cicer arietinum (Same Species)

DESI TYPE
Small, dark seed coat

KABULI TYPE
Large, light seed coat

KALA CHANA (Whole)
Desi chickpea (with seed coat)

CHANA DAL (Split & Dehulled)
Split desi chickpea (hull removed)

BESAN (Flour)
Flour made from desi chickpea / chana dal

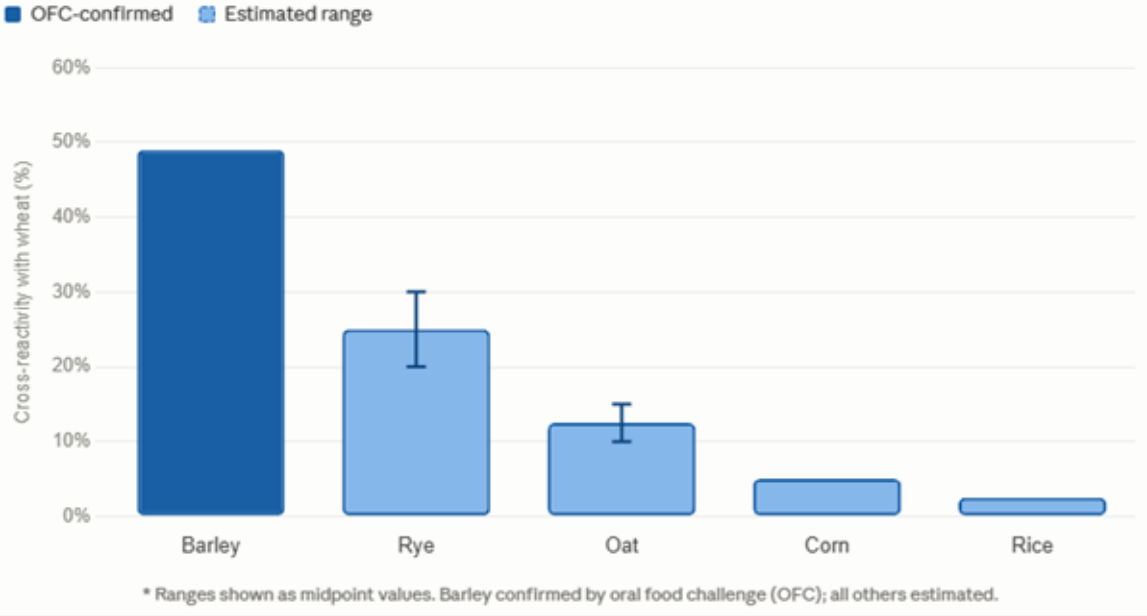
CHICKPEA / GARBANZO (Whole)
Kabuli chickpea (with seed coat)

KEY POINT

- Kala chana, chana dal and besan are different forms of the DESI type of chickpea.
- Chickpea / Garbanzo is the KABULI type.
- All are from the same species: *Cicer arietinum* → **High potential for cross-reativity.**

Note: Cross-reactivity occurs due to shared allergenic proteins.

Wheat & Grains: Cross-Reactivity Rates



Key Data Points

- Kubota 2022: 9/9 wheat-OIT patients passed barley challenge post-treatment
- Separate study: 5/5 passed rye challenge after wheat OIT
- Omega-5 gliadin (Tri a 19) predicts barley cross-reactivity

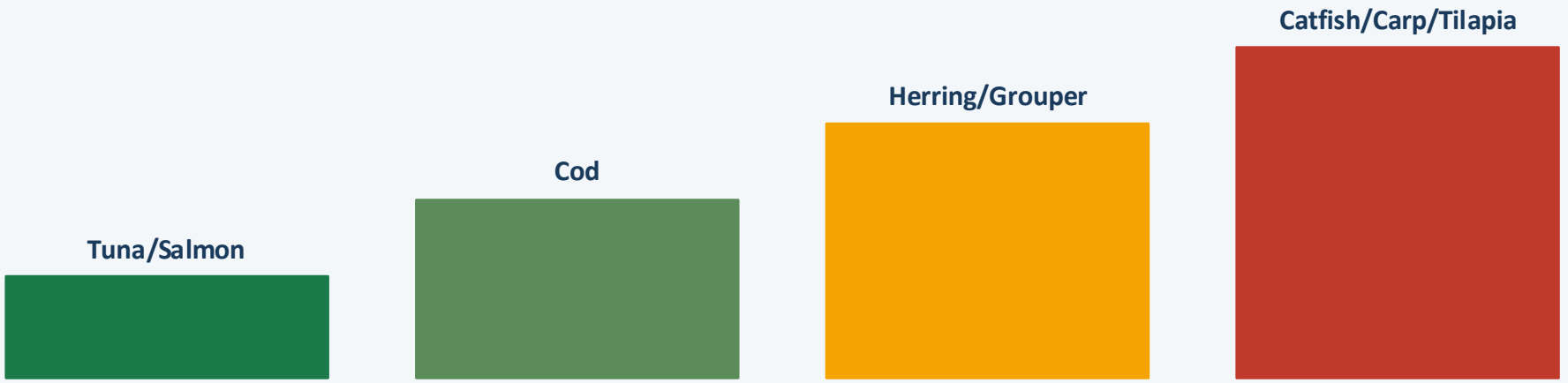
Grain taxonomy matters:
Wheat, barley & rye share Triticeae tribe — highest CR risk.
Oat, corn, rice — more distant, lower clinical CR.

OIT Takeaway: Wheat OIT appears to cross-desensitize barley (and likely rye). Wheat OIT may be the preferred treatment over isolated barley OIT.

Fish Allergy: Parvalbumin Is the Key Variable

β-Parvalbumin Content →

Leung et al. JACI Prac 2024 (n=249): 40% of fish-allergic patients were selectively tolerant to ≥1 fish species, typically those with lower β-parvalbumin. Allergenicity ladder: start tuna/salmon to cod.



Case: Fish Allergy

Case: Fish Allergy

Patient Overview

Age / Sex: 10-year-old female

Presenting Concern: Oral pruritus after eating salmon and white fish. Parents requested investigation of possible fish allergy.

Clinical Interpretation

Pattern consistent with **oligo-sensitized fish allergy:** strong reactivity to high-parvalbumin species; low reactivity/ tolerance to tuna (low parvalbumin)

Catfish/tilapia carry the highest parvalbumin load: strongly reactive species should be strictly avoided

Salmon codfish: low-moderate sensitization; clinical history of oral pruritus confirms relevance — avoid pending labs/OFC

Case Report: Fish Allergy – Species-Specific Reactivity & Selective Tolerance

Patient Overview

Age / Sex: 10-year-old female
Presenting Concern: Oral pruritus after eating salmon and white fish. Parents requested investigation of possible fish allergy.

Skin Prick Testing Results

Fish Species	Wheal (mm)	Reactivity
Catfish	20 mm	
Perch	12 mm	● Strongly Positive
Trout	12 mm	● Strongly Positive
Salmon	8 mm	● Moderately Positive
Codfish	8 mm	● Moderately Positive
Tuna	4 mm	● Low / Tolerated

Positive SPT threshold ≥3mm wheal; histamine control positive

Clinical Interpretation

Pattern consistent with **oligo-sensitized fish allergy** — strong reactivity to high-parvalbumin species; low reactivity + tolerance to tuna (low parvalbumin)

Catfish, perch, and trout carry the highest parvalbumin load — strongly reactive species should be strictly avoided

Salmon and codfish: moderate sensitization; clinical history of

Management & Next Steps

Continue tuna freely — clinical tolerance confirmed, no avoidance needed
Strict avoidance: catfish, perch, trout, salmon, and codfish
Consider supervised OFC for salmon/cod to clarify clinical threshold
Prescribe self-injectable epinephrine; educate on cross-contamination risk

Key Observation: SPT wheal size correlates with parvalbumin content. Tuna tolerance illustrates mono-/oligo-sensitization — blanket fish avoidance is not warranted for this patient.

Case: Shrimp or Dust Mite? The Tropomyosin Problem

Shrimp reaction age 5. Started HDM SLIT 2019. By 2023 shrimp sIgE rose from 20 → 71.6.

Sequence Homology vs. Crustaceans (Maug 2.0)

Crustaceans	91%	
Clinical Reactivity	38%	
Cockroach	82%	
Dust Mites	80%	
Mollusks	60%	
Clinical Reactivity	14%	

2023 Labs — Before Shellfish OIT Decision

Total IgE	2903 kU/L
Shrimp (F24) sIgE	**71.60**
Lobster (F80) sIgE	**66.80**
Clam (F207) sIgE	9.29
HDM D1 sIgE	**44.40**
HDM D2 sIgE	**81.20**

Outcome: Crustaceans: passed shrimp, crab, and lobster challenges — discharged from crustacean OIT. Mollusks: reacted repeatedly to clam and oyster. HDM + cockroach drove tropomyosin sensitization. Mollusk has only ~14% clinical cross reactivity — always challenge crustaceans and mollusks separately.

Atypical Cross Reactivities

Latex-Fruit Syndrome

Natural latex (Hevea brasiliensis) cross-reacts with class I chitinases.
30–50% of latex-allergic patients react to ≥1 fruit.
High risk: banana, avocado, chestnut, kiwi
Moderate risk: papaya, potato, bell pepper, peach, mango

Alpha-Gal Syndrome

IgE to galactose-α-1,3-galactose → delayed reactions (3–6 hrs) to all mammalian red meat, gelatin, and rarely dairy
Medications affected: Cetuximab, gelatin vaccines/capsules, heparin, pancreatic enzyme replacements

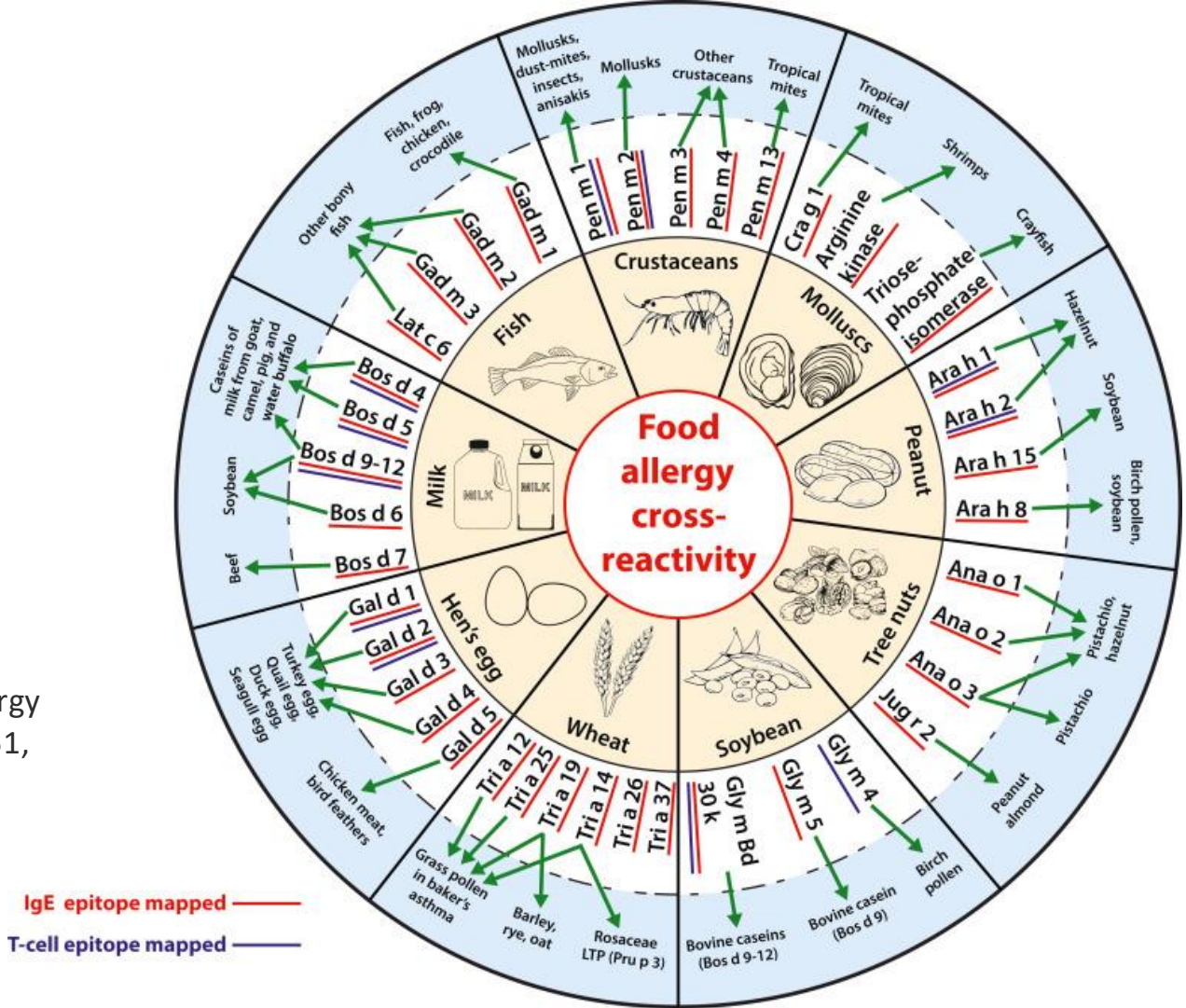
Cashew / Mango / Chironji: Anacardiaceae family

Shared family: urushiol-containing plants.
Unprocessed cashews contain anacardic acid, cardol, cardanol → allergic contact dermatitis.
Mango peel/sap: 4-alkenylresorcinol causes similar contact reactions.
~20% of cashew-sensitized children co-sensitized to other Anacardiaceae

Quick Reference: Cross-Reactivity & OIT Strategy

Primary Allergen	Cross-Reactive Food	Rate	OIT Action
Cow Milk	Sheep / Goat Milk	>90%	CM OIT usually covers — confirm with OFC post-maintenance
Walnut	Pecan	66-75%	Walnut OIT likely covers pecan — always confirm by OFC
Cashew	Pistachio	64-100%	Track pistachio sIgE throughout — do NOT assume coverage
Wheat	Barley	49%	Wheat OIT may desensitize barley; challenge to confirm
Crustacean	Other Crustaceans	38%	Shrimp OIT likely covers crab & lobster
Crustacean	Mollusks	14%	Challenge mollusks separately — NOT assumed covered
Lentil / Green Pea	Chickpea	64–73%	Sequence lentil/pea OIT first; chickpea may follow
Seeds	Other Seeds	Low	Each seed needs its own OIT — no cross-coverage shortcut

Kamath S, Bublin M, Kitamura K **Cross-reactive epitopes and their role in food allergy** Journal of Allergy and Clinical Immunology, 2023; 151, 1178-1190



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•Thermo Fisher Scientific. Allergen encyclopedia entries for relevant components and cross-reactivity summaries, used as supporting background only.