

Molecular insights and emerging therapies in shrimp & fish allergy: Contrasting perspectives from Asia and the West

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Abstract

Seafood allergy is a global health concern with substantial geographic variation in prevalence. This review examines molecular diagnostics and emerging therapies for shrimp and fish allergies, highlighting contrasting perspectives between Asian and Western populations in allergen sensitization profiles, clinical phenotypes, diagnostic performance, and therapeutic development.

In shrimp allergy, tropomyosin (TM) is a major allergen recognized by 50–80% of patients. TM's high structural conservation underlies IgE-mediated cross-reactivity among crustaceans, insects, and mites, complicating diagnostic testing. Non-TM allergens including Arginine Kinase (AK), Myosin Light Chain (MLC), Sarcoplasmic Calcium-Binding Protein (SCBP), and Hemocyanin (Hc) contribute substantially to sensitization, particularly in Asian pediatric cohorts. In contrast, Western populations demonstrate predominant TM sensitization.

In fish allergy, beta-parvalbumin is the predominant allergen, conferring extensive cross-reactivity across bony fish species. However, minor allergens such as beta-enolase, aldolase A, and collagen are clinically relevant, especially in parvalbumin-negative cases. Component-resolved diagnosis (CRD) is essential for diagnostic precision, particularly in selective fish allergies. IgE cross-reactivity with TM leads to false-positive results on skin prick tests (SPT) and specific IgE (sIgE) testing.

Immunotherapy is an emerging therapeutic option. Oral Immunotherapy (OIT) for shrimp and fish has demonstrated promising results. Sublingual Immunotherapy (SLIT) offers a potentially safer alternative approach. Omalizumab may facilitate OIT in high-risk patients.

Knowledge gaps remain regarding extract standardization, population-specific diagnostic algorithms and cutoffs, and the clinical relevance of emerging allergens, highlighting priorities for advancing personalized diagnosis and treatment across diverse global populations.

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Introduction

Seafood allergy is a global health concern and is among the most common food allergy triggers worldwide.¹ Unlike milk and egg allergies, which often remit in childhood, seafood allergy typically persists into adulthood and is associated with anaphylaxis.^{2,3} Geographic variation has been observed in both shellfish and fish allergy prevalence.⁴ This variation may be attributed to differences in per capita seafood consumption, dietary habits, seafood processing methods, and regional exposure to cross-reactive allergens.

Immunological cross-reactivity between seafood and environmental allergens, particularly house dust mites and cockroaches, poses significant diagnostic challenges. This cross-reactivity is especially problematic in regions with high exposure to environmental allergens, where sensitization patterns may not reflect true clinical allergy.^{5,6} Traditional testing methods show suboptimal performance in distinguishing genuine seafood allergy from cross-reactive sensitization, contributing to either underdiagnosis in truly allergic patients and overdiagnosis in those with clinically irrelevant sensitization.

Recent advances in component-resolved diagnostics (CRD) have revolutionized our understanding of individual allergen molecules and their clinical relevance, offering more precise diagnosis and personalized management. However, CRD application and interpretation may differ between Asian and Western populations because of differences in allergen exposure patterns and sensitization profiles. This review comprehensively examines the molecular characteristics of major seafood allergens and cross-reactive proteins, discusses how CRD can improve diagnostic accuracy across populations, and reviews emerging therapeutic approaches for seafood allergy.

Epidemiology of seafood allergies

Aquatic animals for human consumption are obtained from marine and inland waters through capture fisheries and aquaculture. Regional availability and consumption patterns influence the shrimp and fish species implicated in allergy. Seafood allergy prevalence differs across regions, with higher rates in coastal areas with substantial seafood consumption. Reported prevalence estimates vary by study method and case definition, with OFC-confirmed rates consistently lower than questionnaire- or sensitization-based estimates.

Shellfish allergy prevalence

Shellfish comprises crustaceans (shrimp, crab, lobster) and mollusks. In real-world clinical settings, oral food challenge (OFC) is underutilized, and challenge-confirmed prevalence is likely lower than clinically reported. In Europe, the point prevalence of self-reported shellfish allergy was 1.59% (95%CI 0.7-2.49), while the prevalence by positive OFC was lower at 0.1% (95%CI 0.03-0.35)⁷. A study from Northern Thailand report the OFC-confirmed prevalence of shellfish allergy was higher rate at 0.4-0.9%⁸ However, questionnaire-based

surveys demonstrated substantially higher prevalence estimates: 1.3% for shellfish allergy in the United States (1.2% for crustaceans and 0.5% for mollusks),⁹ 3.0% for doctor-diagnosed crustacean allergy among Vietnamese adults,¹⁰ and 0.84% for crustacean allergy in South Korean children.¹¹

This overestimation reflects asymptomatic sensitization rates. The EuroPrevall study found shrimp sensitization reached 13.1% in Shaoguan and 10.3% in India, yet probable allergy rates were only 0.65% and 0%, respectively.¹² Crucially, clinical OFC cohorts consistently show high tolerance. In Japan, 60.6% (40/66) of challenged children were fully tolerant, and among those with prior symptoms, 55.8% (24/43) were not allergic.¹³ Canadian adults show 0.71% confirmed shellfish allergy versus 1.91% perceived rate.¹⁴ This evidence demonstrates that most shellfish allergy labels, particularly for crustaceans, are not corroborated by objective challenge. Overall, shellfish allergy appears more common in tropical and coastal Asia due to high seafood exposure and house dust mite sensitization, driving cross-reactive sensitization to shellfish tropomyosin.

Fish allergy prevalence

OFC-confirmed fish allergy prevalence ranges from 0.04% in Turkey¹⁵ to 0.2% in Thailand¹⁶ and 0.3% in Iceland.¹⁷ Recent European data indicate a point prevalence of self-reported fish allergy at 0.96% (95%CI 0.54-1.38), but the prevalence from OFC was 0.05% (0.01-0.27).⁷ Studies using specific IgE (sIgE) with clinical history report higher prevalence estimates, including Norway 1.1%.¹⁸ In contrast, prevalence in China was comparatively lower, ranging from 0.2% in Hong Kong¹² to 0.3-0.6% in Chongqing.¹⁹ Parent-reported prevalence was highest in the Philippines at 2.3% and Vietnam at 1.6%,²⁰ while substantially lower rates were documented in Canada,¹⁴ the United States,²¹ Singapore,²⁰ Thailand,²⁰ and South Korea.¹¹ These prevalence estimates are from heterogeneous studies with varied methods and age ranges, which limit direct comparison. Overall, the discrepancy between self-reported and OFC-confirmed allergy appears less pronounced for fish than for shellfish. Fish allergy prevalence appears higher in coastal regions with traditionally high fish consumption, particularly in Northern Europe (Finland, Norway) and Southeast Asia (Philippines, Vietnam).²²

Clinical manifestations

IgE-mediated reactions

The clinical manifestations of shellfish allergy range from mild cutaneous symptoms to severe anaphylaxis. Data from the Asia Pacific Registry on Anaphylaxis (APRA) indicate that shellfish is the most common cause of anaphylaxis in children aged 13-17 years in Hong Kong, Singapore, and Thailand.²³ Shellfish is also a common trigger for food-dependent exercise-induced anaphylaxis,²⁴ and aspirin can also trigger symptoms.²⁵

While anaphylaxis is the most severe manifestation, most shellfish-allergic patients experience milder symptoms, with notable regional variation in clinical phenotypes. Many patients, particularly in Asia, present predominantly with mild perioral symptoms. Studies from Thailand and Singapore reported that 70.9%²⁶ and 87.1%²⁷ of patients, respectively, had predominant perioral symptoms. In contrast, a study conducted in the USA, Brazil, and Spain found that only 6.8% of shrimp-allergic individuals had perioral symptoms.²⁸ This difference may be explained by a mechanism similar to that of oral allergy syndrome, triggered by pollen-food cross-reactivity. In Asia, many patients are primarily sensitized to house dust mites, which may subsequently lead to the development of shellfish allergies through cross-reactive allergens.

Fish allergy similarly presents with a spectrum of IgE-mediated symptoms ranging from urticaria to anaphylaxis. Patients may also present with respiratory symptoms due to inhalation of aerosolized proteins generated by cooking or processing of fish,²⁹ which can cause occupational asthma. Contact urticaria may occur after handling raw fish.²⁹

Some conditions can clinically mimic IgE-mediated fish allergy and warrant consideration in the differential diagnosis.

- **Scombroid poisoning** is a non-immune histamine toxicity resulting from bacterial decomposition of fish, which can clinically mimic IgE-mediated fish allergy. When the clinical history suggests scombroid poisoning, such as rapid-onset flushing, headache, and gastrointestinal symptoms after consuming dark-fleshed fish that may have been improperly stored, prick-to-prick testing with the suspected culprit fish and with fresh fish of the same species can be informative. A positive reaction to spoiled fish but a negative reaction to fresh fish indicates scombroid poisoning rather than true fish allergy.
- **Anisakis allergy identification:** *Anisakis simplex*, a parasitic nematode found in marine fish, can cause IgE-mediated allergic reactions that may be misattributed to fish proteins. Clinical history suggestive of *Anisakis* allergy includes reactions primarily to raw or undercooked fish, particularly in regions with high consumption of such preparations (e.g., sushi, ceviche). For these patients, sIgE testing to *Anisakis* should be included to identify parasitic sensitization and differentiate it from primary fish protein allergy.

Food protein-induced enterocolitis syndrome (FPIES)

Finned fish is among the most common triggers of FPIES in Spain and Italy, which may reflect the earlier introduction of fish into their diets.³⁰ The Spanish and Italian cohorts reported that resolution of fish-induced FPIES occurred around 5.5 years of age. A study from Italy showed that 81.4% of FPIES cases were caused by fish alone, 12.9% by shellfish alone, and 5.7% by both fish and shellfish.

The typical clinical presentations include vomiting associated with pallor and lethargy.³¹ Cases of Adult-Onset FPIES to crustaceans have also been reported. The mean age was 34 years, with symptoms such as emesis occurring 3 minutes to 6.5 hours after ingestion of crustaceans.³² These findings highlight that FPIES, although predominantly a pediatric diagnosis, can occur in adulthood and should be considered in adults presenting with gastrointestinal symptoms after seafood consumption.

Natural history

The natural history of seafood allergies varies considerably between shellfish and fish. Although shellfish allergies are generally considered lifelong, evidence suggests that tolerance can develop over time. A 10-year follow-up study of patients with non-anaphylactic shrimp allergy found that 46% achieve tolerance to shrimp.³³ Patients who developed tolerance to shrimp had low sIgE to arginine kinase and myosin light chain.³⁴ In contrast, fish allergy tends to persist longer. A study from Singapore showed that only 25.9% of children acquired tolerance to the index fish at a median age of 60 months.³⁵

Molecular insight

Shrimp allergens

Several shrimp allergens have been reported over the past two decades (**Table 1, Figure 1**). Tropomyosin (TM) has long dominated research on shrimp allergens. However, recent studies highlight a more diverse allergen repertoire, including arginine kinase (AK), myosin light chain (MLC), sarcoplasmic calcium-binding protein (SCBP), hemocyanin (Hc), troponin C (TnC), and several newly described components. Multiple groups have demonstrated that non-TM allergens contribute substantially to sensitization, particularly in Asian pediatric cohorts. However, their clinical relevance has rarely been confirmed by double-blind placebo-controlled food challenges (DBPCFC) or oral food challenges.^{36,37} This review focuses on shrimp allergens evaluated in DBPCFC or OFC studies and on the prevalence of allergen-sIgE across various cohorts.

Tropomyosin (TM)

Tropomyosin is a heat-resistant acidic glycoprotein with a molecular weight of approximately 34–38 kDa.^{38–41} Specific IgE to TM is detected in about 50–80% of shrimp-allergic patients. To date, TM from eight shrimp species is listed in the Allergen.org “Allergen Nomenclature” database, which is approved by the World Health Organization and the International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-Committee. Additional TMs from species not listed in the WHO/IUIS database, such as TM from *Macrobrachium nipponense*, have also demonstrated IgE reactivity.⁴² As a component of actin filaments, TM regulates muscle contraction through its interaction with myosin.⁴³ Thermal or pressure processing can modestly reduce IgE binding and basophil activation *in vitro*.⁴⁴

Table 1. Shrimp allergens from various species as reported on the Allergen.org website ‘Allergen Nomenclature’

Biochemical name	Shrimp species	IUIS Allergen	Molecular mass
Tropomyosin	Crangon crangon (North Sea shrimp)	Cra c 1	~38 kDa
	Exopalaemon modestus (White legged freshwater shrimp)	Exo m 1	38 kDa
	Litopenaeus vannamei (White shrimp)	Lit v 1	36 kDa
	Metapenaeus ensis (Shrimp)	Met e 1	34 kDa
	Pandalus borealis (Northern shrimp)	Pan b 1	37 kDa
	Penaeus aztecus (Brown shrimp)	Pen a 1	36 kDa
	Penaeus indicus (Shrimp)	Pen i 1	34 kDa
	Penaeus monodon (Black tiger shrimp)	Pen m 1	38 kDa
Arginine Kinase	Crangon crangon (North Sea shrimp)	Cra c 2	~45 kDa
	Litopenaeus vannamei (White shrimp)	Lit v 2	40 kDa
	Penaeus monodon (Black tiger shrimp)	Pen m 2	40 kDa
Myosin, light chain 1	Artemia franciscana (Brine shrimp)	Art fr 5	~17.5 kDa
	Crangon crangon (North Sea shrimp)	Cra c 5	~17.5 kDa
Myosin, light chain 2	Litopenaeus vannamei (White shrimp)	Lit v 3	20 kDa
	Penaeus monodon (Black tiger shrimp)	Pen m 3	20 kDa
Sarcoplasmic calcium-binding protein (SCBP)	Crangon crangon (North Sea shrimp)	Cra c 4	~25 kDa
	Litopenaeus vannamei (White shrimp)	Lit v 4	20 kDa
	Penaeus monodon (Black tiger shrimp)	Pen m 4	20 kDa
Troponin C	Crangon crangon (North Sea shrimp)	Cra c 6	~21 kDa
	Penaeus monodon (Black tiger shrimp)	Pen m 6	16.8 kDa
Hemocyanin	Penaeus monodon (Black tiger shrimp)	Pen m 7	76 kDa
Triosephosphate isomerase	Crangon crangon (North Sea shrimp)	Cra c 8	~28 kDa
	Penaeus monodon (Black tiger shrimp)	Pen m 8	27 kDa
Cytosolic fatty acid binding protein	Litopenaeus vannamei (White shrimp)	Lit v 13	15 kDa
Cytoplasmic fatty acid binding protein	Penaeus monodon (Black tiger shrimp)	Pen m 13	20 kDa
Glycogen phosphorylase-like protein	Penaeus monodon (Black tiger shrimp)	Pen m 14	95 kDa

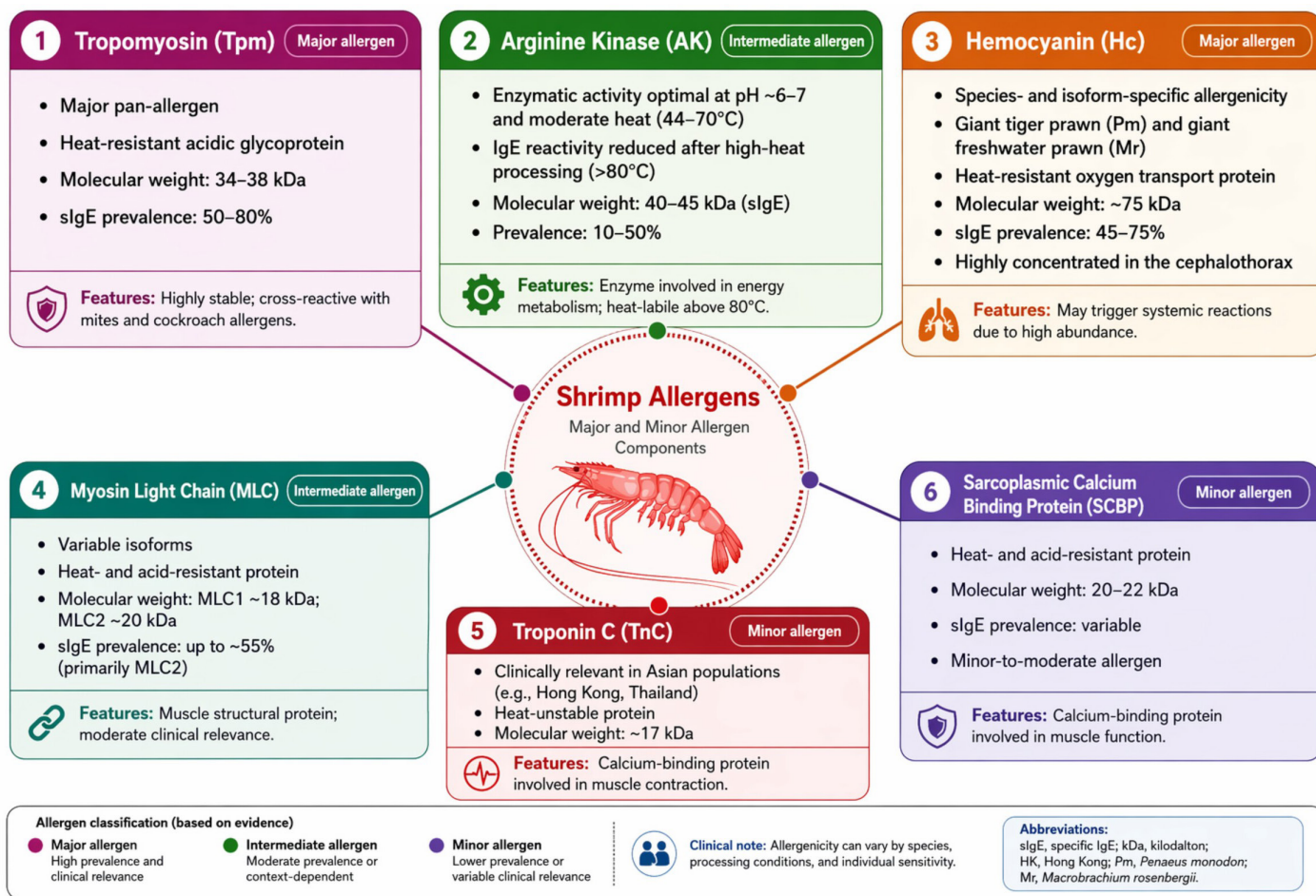


Figure 1. Shrimp allergens.

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Arginine kinase (AK)

Arginine kinase (AK) is a glycoprotein enzyme with a molecular mass of approximately 40–45 kDa. Across different cohorts, approximately 10–50% of shrimp-allergic patients have sIgE to AK.⁴⁵ Several factors affect its structure, and IgE reactivity has been reported.⁴⁶ For instance, increased IgE reactivity is observed under acidic conditions (pH 1.0–3.0) and at temperatures between 44°C and 70°C, whereas IgE reactivity decreases markedly above 80°C.⁴⁶

Myosin Light Chain (MLC)

Myosin light chain (MLC) is a cytoskeletal protein involved in muscle contraction, intracellular transport, and cell division.^{46,47} It is heat-stable and resistant to acid and digestive enzymes. Two isoforms have been characterized: the essential light chain (MLC1, 18 kDa) and the regulatory light chain (MLC2, 20 kDa). The sIgE prevalence to MLC2 is approximately 55%, whereas MLC1 has not been as extensively studied.^{47,48} The structural and immunological differences between MLC1 and MLC2 may contribute to variability in patient sensitization profiles.

Sarcoplasmic Calcium-Binding Protein (SCBP)

Sarcoplasmic calcium-binding protein (SCBP) is a water-soluble Ca²⁺-binding protein with a molecular weight of 20–22 kDa, primarily localized in the muscle tissues of invertebrates.^{49,50} SCBP plays a key role in muscle relaxation by regulating intracellular calcium levels. Its conformation and IgE-binding epitopes depend on Ca²⁺ binding; Ca²⁺ depletion can induce structural changes that reduce IgE reactivity.^{44,50} SCBP exhibits high stability under heat and extreme pH conditions, making it resistant to common food processing and digestive degradation.^{44,46}

Hemocyanin (Hc)

Hemocyanin (Hc) is a large, oxygen-carrying, heat-stable protein abundant in the hemolymph of crustaceans, comprising 75–95% of total protein in some species.⁵¹ In shrimp, Hc is highly concentrated in the cephalothorax, a portion commonly consumed in certain regions, including Thailand.⁵¹ Hc exhibits species-specific subunit composition, suggesting limited cross-reactivity between shrimp species, such as *Penaeus monodon* (Pm) and *Macrobrachium rosenbergii* (Mr) in Thai cohorts.⁵¹ The prevalence of sIgE to Hc varies across cohorts, ranging from 45% to 75%.⁵¹

Additionally, Hc from northern shrimp (*Pandalus borealis*, Pb) has also been reported as a cross-reactive inhalant allergen with house dust mites in Italian cohorts,⁵² likely due to conserved phylogenetic regions that retain allergenic activity. The observed discrepancies in Hc subunit composition between shrimp species and between shrimp and insects highlight a significant knowledge gap that warrants further investigation.

Troponin C (TnC)

The 17-kDa troponin C (TnC) is a Ca²⁺-binding protein that forms part of the troponin complex.⁵³ Heat treatment induces structural instability, and Ca²⁺ depletion reduces IgE reactivity.⁴⁶ Across regions, TnC was identified as one of the major shrimp allergens in Hong Kong and Thai cohorts.³⁶ In contrast, only 17.2% of individuals from Brazil, Spain, and the USA exhibited sIgE to TnC, suggesting regional variation in its allergenic significance.²⁸

Other shrimp allergens

Recent studies have identified additional shrimp allergens, including triosephosphate isomerase (Pen m 8),³⁶ cytosolic fatty acid-binding protein (FABP, Lit v 13),⁵⁴ cytoplasmic fatty acid-binding protein (Pen m 13),³⁶ and glycogen phosphorylase-like protein (Pen m 14).³⁶ Pen m 14 has been reported as one of the major shrimp allergens in the Hong Kong cohort and may predict the OFC outcomes.³⁶ Pen m 8 and Pen m 13 were shown to be minor shrimp allergens in the Hong Kong and Thai cohorts,³⁶ while Lit v 13 is a minor allergen in the Colombian population.⁵⁴

Cross-reactivity of TM

Shrimp allergens are structurally conserved across other crustaceans, insects, and house dust mites (HDM), creating complex patterns of IgE-mediated cross-reactivity that complicate diagnosis and prediction of clinical severity (Table 2, Figure 2). Approximately 91% of IgE epitopes are conserved in other crustaceans, 56% in cockroaches, and 48% in HDM species. IgE recognition by allergic patients

of identical or highly similar homologous peptides of allergen epitopes forms the molecular basis of cross-reactivity.⁵⁵ Moreover, changes in a few amino acids within conserved IgE-binding peptides may alter IgE reactivity, resulting in variability in hypersensitivity to different shrimp species. Several factors have been proposed to predict clinical cross-reactivity in allergic patients. Both epitope conservation and structural similarity have been identified as key determinants of clinical cross-reactivity.⁵⁶ Because conformational epitopes are degraded in acidic environments such as the gastrointestinal tract, sequential epitopes appear crucial for clinical cross-reactivity.⁵⁶ Sequential epitope conservation between crustaceans and mollusks, as well as between HDM and cockroaches, may be a key factor predicting clinical cross-reactivity.⁵⁶

TM is an alpha-helical coiled-coil dimeric protein, and this structure is highly conserved across various invertebrates, including insects and HDM. The IgE-binding epitopes located at the N- and C-terminal regions of TM are highly conserved.⁵⁶ Twenty-two of 97 shrimp TM IgE-binding epitopes are pan-epitopes among invertebrates, and 19 epitopes are shared among crustaceans, cockroaches, and HDM.⁵⁶ Moreover, 11 of these 19 epitopes are shared between crustaceans and cockroaches, while 6 are shared between crustaceans and HDM.⁵⁶ Thus, sensitization may arise from ingestion, inhalation, occupational exposure, or cross-sensitization from TM of cockroaches and HDM. IgE cross-reactivity between shrimp and edible insects, including mealworms, has been reported in adult participants from Dutch, German, and USA cohorts.⁵⁷⁻⁵⁹ Due to its stability during thermal processing and digestion, IgE reactivity to TM, but not SCBP, from both shrimp and the edible cricket (*A. domesticus*) has been observed.⁵⁷ Recently, a report of IgE cross-reactivity between shrimp and 3 edible insects using sera of Spanish adults to quantify sIgE to specific allergens on a multiplex immunoassay also confirmed TM as a major pan-allergen for (63%) subjects sensitized to at least 1 edible insect.⁶⁰

Table 2. A list of cross-reactive shrimp allergens with crustaceans, mollusks, and insects, including edible insects and mealworms.

Allergen	MW (kDa)	Stability	sIgE Prevalence (%)	Cross-reactivity	Representative References
Tropomyosin (TM)	34–38	Heat-resistant; acid-stable	50–80	Crustaceans, cockroach, HDM, edible insects	1-11
Arginine Kinase (AK)	40–45	Variable, pH & temp-dependent	10–50	Crustaceans, field cricket, minor pan-allergen	8, 12-15
Myosin Light Chain (MLC1/MLC2)	18–20	Heat-stable; acid & digestion resistant	55 (MLC2)	Cockroach (minor), edible insects (6–8%)	13-14, 16-18
Sarcoplasmic Calcium-Binding Protein (SCBP)	20–22	Heat-stable; acid-stable; Ca ²⁺ -dependent	Variable	None with HDM; minor cross-reactivity with edible insects	7, 13-14, 19-20
Hemocyanin (Hc)	75	Heat-stable; oxygen carrier	45–75	Northern shrimp Pb with HDM; some insects	21-22
Troponin C (TnC)	17	Ca ²⁺ -binding; heat-unstable	17–major in Hong Kong/Thai; 17.2 minor in Brazil/Spain/USA	Minor pan-allergen	13-14, 23-25

Table 2. (Continued)

Allergen	MW (kDa)	Stability	sIgE Prevalence (%)	Cross-reactivity	Representative References
Triosephosphate Isomerase (TPI)	27–30	Data limited	Minor	Crustaceans, insects, mollusks	23, 26
Fatty Acid Binding Protein (FABP, Lit v 13)	14–15	Heat-stable	Minor	HDM, edible insects	14, 27
Glycogen Phosphorylase-like Protein (Pen m 14)	~70	Data limited	Major in HK cohort	Unknown	23

Notes:

1. sIgE prevalence varies across cohorts and regions.
2. Cross-reactivity is largely based on epitope conservation and immunological studies.
3. Stability refers to resistance to heat, pH, and digestion as reported

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Allergens		Other Crustaceans	Cockroach	House dust mite	Edible insect	Mollusk
MAJOR ALLERGENS	Tropomyosin	● ● ●	● ● ●	● ● ●	● ● ●	● ●
	Arginine kinase	● ●	● ●	● ●	● ● ●	○
MINOR ALLERGENS	Hemocyanin	● ●	●	●	● ●	○
	Myosin light chain	●	● ●	○	●	○
	Sarcoplasmic calcium binding protein (SCBP)	●	○	○	●	○
	Triosephosphate isomerase (TPI)	● ●	○	○	● ●	●
	Fatty acid binding protein (FABP)	○	○	●	●	○

● ● ● Strong evidence
(IgE reactivity and clinical relevance)

● ● Moderate evidence
(IgE reactivity and/or limited clinical data)

● Limited evidence
(Some IgE reactivity, limited clinical data)

○ No significant evidence
(No IgE reactivity or clinical relevance)

REMARKS

- Tropomyosin is the dominant pan-allergen driving cross-reactivity across arthropods.
- High cross-reactivity exists among crustaceans, mites, cockroaches, and edible insects due to conserved protein homology.
- Cross-reactivity with mollusks is less consistent and generally weaker.
- Minor allergens contribute variably and have lower clinical relevance compared to major allergens.

Note: Evidence levels reflect currently available data from molecular, immunological and/or clinical studies.

Figure 2. Cross-Reactivity of Shrimp Allergens Across Arthropods and Mollusks.

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Cross-reactivity of AK, MLC, SCBP, Hc, and other shrimp allergens





Unlike TM, only five of the 39 shrimp AK IgE-binding epitopes are conserved across crustaceans, cockroaches, HDM, and mollusks (Figure 2).⁵⁶ AK has also been reported as a cross-reactive allergen between shrimp *Macrobrachium* spp. and the field cricket (*Gryllus bimaculatus*).⁶¹ Shrimp MLC shares only two epitopes with cockroach MLC, whereas shrimp SCBP has no conserved shared epitopes with cockroaches or HDM.⁵⁶ However, a study using sIgE from HDM-allergic infants in an Australian cohort found no binding to either shrimp MLC or SCBP, suggesting that these allergens do not cross-react with HDM in this population.⁶² In contrast, 6–8% of adult participants in German and USA cohorts sensitized to three edible insects exhibited IgE cross-reactivity to MLC (Pen m 3) and SCBP (Pen m 4).⁶⁰ Moreover, 26–28% of the same cohort exhibited IgE cross-reactivity to AK (Pen m 2) and TnC (Pen m 6), suggesting that both allergens are minor pan-allergens.⁶⁰ AK has also been reported as a cross-reactive allergen between shrimp *Macrobrachium* spp. and the field cricket (*Gryllus bimaculatus*) in Thai cohorts.⁶¹

Beyond TM and AK, other shrimp allergens demonstrated IgE cross-reactivity with insects, including fatty-acid-binding protein (FABP, Lit v 13), triosephosphate isomerase (TPI), and Hc. FABP (Lit v 13) has been shown to exhibit high cross-reactivity with HDM FABPs (Blo t 13 and Der p 13),

sharing two epitopes (amino acids 40–85 and 107–136).⁵⁴ TPI also displays cross-reactivity between shrimp, insects, and mollusks based on epitope mapping and proteomics.⁶³ Additionally, Hc of northern shrimp (*Pandalus borealis*) has been identified as a cross-reactive inhaled allergen linking HDM and shrimp in Italian cohorts.⁵² Collectively, TM, AK, and other shrimp allergens have been demonstrated to cross-react with allergens from crustaceans, mollusks, and insects, including edible insects and mealworms (Table 2).

Fish allergens

Despite the diversity of fish consumed globally, parvalbumin remains the predominant allergen implicated in fish allergies, with the majority of individuals’ allergic reactions triggered by this allergen component (Figure 3). Parvalbumins are phylogenetically divided into two distinct lineages: α-parvalbumin and β-parvalbumin (β-PV). Beta-parvalbumin, a calcium-binding protein with a molecular mass of approximately 11-12 kDa, constitutes the major fish allergen and is recognized by the vast majority of fish-allergic individuals. Its high degree of sequence conservation across fish species confers extensive cross-reactivity, whereby IgE antibodies directed against beta-parvalbumin in one species frequently recognize homologous proteins in other species, thereby explaining the common clinical observation of multi-species fish allergy. Clinical evidence demonstrates substantial IgE reactivity rates: 100% for Baltic cod (Gad c 1)

Allergen		Bony fish (e.g., cod, salmon) 	Cartilaginous fish (e.g., shark, ray) 	Fish roe (e.g., salmon roe) 	Crustacean (e.g., shrimp, crab) 
Major allergens	β -parvalbumin	● ● ●	●	○	○
	α -parvalbumin	○	● ● ●	○	○
	Vitellogenin (roe proteins)	○	○	● ● ●	○
Minor allergens	Collagen	● ●	● ●	○	○
	Enolase / Aldolase A	●	○	○	○
	Tropomyosin	●	○	○	●

● ● ● **Strong evidence**
(IgE reactivity and clinical relevance)

● ● **Moderate evidence**
(IgE reactivity and/or limited clinical data)

● **Limited evidence**
(Some IgE reactivity, limited clinical data)

○ **No significant evidence**
(No IgE reactivity or clinical relevance)

Remark

- β -parvalbumin is the dominant allergen in bony fish and accounts for the majority of IgE cross-reactivity between fish species.
- Cartilaginous fish (e.g., shark, ray) predominantly express α -parvalbumin, resulting in reduced cross-reactivity with bony fish allergens.
- Fish roe allergy is typically mediated by vitellogenin-derived proteins and may occur independently of fish meat allergy.
- Cross-reactivity between fish allergens and crustacean allergens is limited, with the exception of tropomyosin, which may show some IgE cross-reactivity.

Note: Evidence levels reflect currently available data from molecular, immunological and/or clinical studies.

Figure 3. Cross-Reactivity of Fish Allergens Across Species.

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and Atlantic cod (*Gad m 1*), 75% for swordfish (*Xip g 1*), 71% for grass carp (*Cten i 1*), and 60% for yellowfin tuna (*Thu a 1*).

Unlike β -parvalbumin, which is ubiquitous in bony fish and constitutes the major allergen in fish allergy, α -parvalbumin is primarily found in cartilaginous fish (such as sharks and rays) and higher vertebrates, including mammals and birds, and is generally considered non-allergenic in the context of fish hypersensitivity. Structurally, α -parvalbumin and β -parvalbumin share similar three-dimensional folds and calcium-dependent stability; however, α -parvalbumin exhibits substantially lower IgE and IgG binding capacity compared to β -parvalbumin. Epitope mapping studies in turbot (*Scophthalmus maximus*) have demonstrated that β -parvalbumin possesses epitopes characterized by higher IgE reactivity and greater hydrophobic residue content than those found in α -parvalbumin.⁶⁴ Additionally, α -parvalbumin epitopes display reduced sequence homology with known allergen sequences, which may account for their diminished allergenicity and limited cross-reactivity.

While β -parvalbumin is the predominant fish allergen, fish allergy presents a more complex immunological landscape, with several other proteins identified as minor allergens recognized by subsets of allergic individuals. These minor allergens demonstrate variable IgE reactivity rates and molecular characteristics across different fish species.

Beta-enolase (approximately 47-50 kDa) is a highly conserved glycolytic enzyme that catalyses the conversion of 2-phosphoglycerate to phosphoenolpyruvate in the glycolytic pathway.⁶⁵

Clinically, beta-enolase has been confirmed as a relevant fish allergen, identified in yellowfin tuna (*Thu a 2*), Atlantic salmon (*Sal s 2*), Atlantic cod (*Gad m 2*), and grass carp, among other species.⁶⁶⁻⁶⁹ It can trigger IgE-mediated allergic responses with recognition rates of 12% to 56% among fish-allergic patients. The high sequence conservation of beta-enolase across fish species facilitates cross-reactivity, though the extent of inter-species cross-reactivity requires further characterization in clinical populations.^{65,66}

Aldolase A (approximately 40 kDa), also known as fructose-bisphosphate aldolase, is a glycolytic enzyme that catalyses the reversible cleavage of fructose-1,6-bisphosphate into glyceraldehyde-3-phosphate and dihydroxyacetone phosphate. Aldolase A has been identified as an important fish allergen, with IgE recognition documented in up to 50% of fish-allergic patients in some studies.⁶⁶ It has been characterized in yellowfin tuna (*Thu a 3*), Atlantic salmon (*Sal s 3*), and Atlantic cod (*Gad m 3*), with IgE reactivity rates ranging from 13% to 37% of tested individuals. While inter-species cross-reactivity is present, it appears to be more limited compared to parvalbumin.

Tropomyosin (approximately 33-37 kDa), notably a major allergen in shellfish, functions as a minor allergen in fish, identified in Atlantic salmon (*Sal s 4*) and Mozambique tilapia (*Ore m 4*). This differential allergenic significance between fish and shellfish may have implications for cross-reactivity patterns and co-sensitization.

Collagen (130-140 kDa) is primarily type I collagen, composed of $\alpha 1$ and $\alpha 2$ chains, and is abundant in skin, scales, bones, and muscle tissues.^{70,71}

Clinically, fish collagen has emerged as an important allergen, with up to 50% of fish-allergic patients in some populations demonstrating IgE sensitization to collagen.^{72,73} It exhibits high cross-reactivity across fish species and can induce functional IgE crosslinking and mast cell activation.⁷² Notably, some patients are sensitized to collagen but not to parvalbumin, underscoring the clinical relevance of component-resolved diagnosis for fish allergy.⁷³ Collagen allergens from barramundi and Atlantic salmon are registered as *Lat c 6* and *Sal s 6*, respectively. This panallergen status, combined with its structural abundance in fish tissues, positions collagen as a critical component in comprehensive fish allergy diagnostics, particularly for patients with atypical or parvalbumin-negative presentations.

Additional minor allergens comprise various metabolic enzymes, including creatine kinase, triosephosphate isomerase, and lactate dehydrogenase, which have been particularly well-characterized in striped catfish (*Pan h 7* through *Pan h 11*).⁷⁴ The identification of these multiple minor allergens underscores the heterogeneity of fish allergy. It suggests that component-resolved diagnosis may be necessary for comprehensive evaluation in patients with complex or atypical presentations.

Diagnosis

Diagnosis of seafood allergy requires careful integration of clinical history with objective testing. The heterogeneity of clinical manifestations, ranging from oral allergy syndrome to systemic anaphylaxis, and immunological cross-reactivity with environmental allergens create interpretive challenges that distinguish seafood allergy diagnosis from other food allergies.

Shrimp

Conventional diagnostic approaches for shrimp allergy face significant challenges, particularly in regions with high environmental allergen exposure. Cross-reactivity with HDM and cockroaches complicates test interpretation; sensitization to shared allergens, such as tropomyosin, may yield positive results without clinical relevance. These factors likely contribute to the overestimation in survey-based prevalence studies.

Skin prick testing

Because the gold standard OFC consumes time and medical resources, several diagnostic tests, such as skin prick test (SPT) and prick-to-prick (PTP), and sIgE to shrimp or shrimp components, such as tropomyosin, are usually obtained before performing OFC. The main challenges of SPT for diagnosing shrimp allergy include the species of shrimp used in the extracts, the lack of standardized shrimp extracts, and the stability of the reagents.⁷⁵ Jirapongsananuruk et al. demonstrated that among shrimp-allergic children, some had isolated allergic reactions to seawater shrimp (*Penaeus monodon*, *Pm*), others to freshwater shrimp (*Macrobrachium rosenbergii*, *Mr*), and some reacted to both species.²⁶ OFC identified specific allergy to *Pm* and *Mr* in 17.65% and 23.53% of the subjects, respectively. Forty-seven percent of the subjects had reactions to both shrimp species, and 11.76% had negative challenges to both shrimp species. This study suggested that using an in-house *Pm* or *Mr* extract, or PTP to *Pm* or *Mr* meat, provided better sensitivity than using a commercial extract. In addition, using the same species of in-house shrimp extract for SPT and OFC provided a better discrimination of the OFC outcome.²⁶ The same group of investigators studied the storage of in-house shrimp extracts and suggested that the extracts could be kept at 4°C for 2 weeks and at -20°C for 4 weeks.^{76,77} Asero et al. evaluated 5 commercial crustacean and fresh shrimp extracts for SPT in shrimp allergic patients.⁷⁵ Three of these extracts were made from shrimp, one from lobster, and one from crustaceans. Compared with fresh shrimp extract, commercial extracts showed a frequent absence of proteins at molecular weights corresponding to the major shrimp allergens. Thus, selecting a high-quality extract from the same shrimp species to which the patients are allergic is a crucial step for SPT. A meta-analysis including 3 studies on SPT to shrimp in shrimp-allergic patients reported a pooled sensitivity of 62% and a specificity of 90% at the median 3 mm cutoff.⁷⁸

Specific IgE and component-resolved diagnosis (CRD)

Similar to SPT, the diagnostic accuracy of sIgE testing for shrimp allergy is limited by the quality of shrimp extracts and the species of shrimp used in the solid phase of the test system.⁷⁵ Tropomyosin (*Pen a 1*) is commercially available in a singleplex system. Isoforms of tropomyosin have been identified in several shrimp species, including *Penaeus aztecus* (*Pen a 1*), *Penaeus indicus* (*Pen i 1*), *Penaeus monodon* (*Pen m 1*), *Metapenaeus ensis* (*Met e 1*), and *Litopenaeus vannamei* (*Lit v 1*), with sequence homology ranging from 93-99%.⁷⁹ Specific IgE to other shrimp components can be tested by microarray or macroarray systems, such as arginine kinase (*Pen m 2*), myosin light chain (*Pen m 3*), sarcoplasmic calcium-binding protein (*Pen m 4*), and Troponin C (*Cra c 6*). A study in Spain investigated the role of SPT, sIgE to shrimp, and recombinant shrimp tropomyosins (*rPen a 1*) in challenged, proven red shrimp (*Solenocera melanthero*) allergic or tolerant subjects.⁷⁹ The SPT and sIgE to shrimp extract provided the specificity of 0.50 and 0.54, respectively.

The sIgE to rPen a 1 yielded specificity of 0.77.⁷⁹ In a study from the USA, subjects who had a positive shrimp challenge more frequently had sIgE to tropomyosin and sarcoplasmic calcium-binding proteins than those with a negative challenge.²⁸ Specific IgE to tropomyosin and sarcoplasmic calcium-binding proteins were positive in 82% and 29.3% of shrimp allergic subjects. A study in Hong Kong reported the performance of SPT, sIgE to shrimp, and multiple shrimp components, as measured by the area under the curve (AUC), in black tiger shrimp (*P. monodon*) allergic or tolerant subjects. The AUC of SPT to shrimp was 0.74, sIgE 0.75, sIgE Pen m 1 0.70, sIgE Pen m 4 0.77, sIgE Pen m 6 0.78.³⁶ Of note, the Pen m 1 was positive in 41% of shrimp allergic patients. This data was supported by a Singapore study, which reported that only 36% of shrimp-allergic subjects (to grass prawn, *L. vannamei*, or black tiger shrimp, *P. monodon*) had detectable sIgE to shrimp tropomyosin on a microarray assay.²⁷ These data may imply that tropomyosin was not a major allergen in the Asian population who have shrimp allergy.

Impact of Dust Mite Sensitization on Diagnostic Accuracy

A meta-analysis including 4 studies of shrimp-sIgE in shrimp-allergic patients reported a pooled sensitivity of 96% and a specificity of 63% at a median cutoff of 1.2 kUA/L.⁷⁸ For sIgE to Pen m 1, a meta-analysis including 3 studies in shrimp allergic patients reported a sensitivity of 62% and specificity of 89%.⁷⁸ However, these pooled estimates should be interpreted cautiously, given the significant regional variations and confounding factors described above. Comparative studies examining the diagnostic performance of shrimp sIgE and recombinant Pen a 1 (rPen a 1) in shrimp-allergic patients, stratified by dust mite sensitization status, have yielded important insights.⁸⁰ These investigations demonstrated that the diagnostic performance of both shrimp sIgE (AUC = 0.94) and rPen a 1 (AUC = 0.80) was significantly superior in shrimp-allergic patients without concomitant dust mite sensitization compared to those with dust mite sensitization. In a cross-sectional study conducted in mite-endemic Hong Kong, patients with clinically suspected shellfish allergy were evaluated based on clinical history and serological evidence of IgE sensitization to shellfish.³⁶ The investigation revealed a notably high false-positive rate for shellfish-sIgE testing. Among individuals who demonstrated clinical tolerance to 100 g of tiger prawn during double-blind, placebo-controlled food challenge (DBPCFC), 72% exhibited positive skin prick tests (SPT) to shellfish extract, and 65% demonstrated IgE sensitization to shellfish extract. The diagnostic performance, as measured by AUC, was 0.77 for shellfish SPT and 0.69 for shrimp sIgE, indicating suboptimal discriminatory capacity for both diagnostic modalities. These findings underscore the substantial confounding effect of dust mite sensitization on the accurate diagnosis of shrimp allergy, likely attributable to IgE cross-reactivity between homologous allergens, particularly tropomyosin, present in both crustaceans and dust mites.

Basophil activation tests (BAT), and IgE-crosslinking-induced luciferase expression (EXiLE) tests

The basophil activation test (BAT) is a flow-cytometry-based functional assay that measures basophil activation (CD203 and/or CD63 expression) upon allergen stimulation. However, its routine clinical use remains limited by short basophil lifespan, response variability, and high cost.⁸¹ A recent study in Vietnam compared the diagnostic performance of BAT, SPT, and sIgE by Euroimmune system, to distinguish shrimp allergy, as defined by OFC. The CD63 expression-based BAT was better than SPT or sIgE at discriminating subjects with shrimp allergy from those with shrimp tolerance.⁸²

The IgE-crosslinking-induced luciferase expression (EXiLE) uses the same principle as BAT, which measures IgE crosslinking with a specific allergen. In this assay, a rat basophilic leukemia (RBL) cell line is transfected with human IgE receptor FcεRI α/β/γ-subunits and luciferase reporter gene (RS-ATL8). Crosslinking of FcεRI induces nuclear factor of activated T cells (NFAT), which regulates the expression of the luciferase reporter gene. The luciferase signal reflects the degree of IgE crosslinking.⁸¹ Wai et al evaluated the performance of SPT, sIgE to shrimp and rPen a 1 by ImmunoCAP, BAT, and EXiLE tests to diagnose shrimp allergy confirmed by DBPCFC.⁸³ The authors concluded that BAT using shrimp extract provided the highest AUC (0.88), Youden Index of 0.81, likelihood ratio of 14.73, sensitivity of 0.87, specificity of 0.94, positive predictive value (PPV) of 0.93, and negative predictive value (NPV) of 0.89, when compared with other assays.

Oral food challenge

OFC is the gold standard for diagnosing food allergy.^{84,85} A recent consensus guideline from the AAAAI-EAACI PRACTALL on standardizing oral food challenges emphasized preclinical assessment, challenge setting/safety, challenge schedules, OFC material, scoring/stopping criteria, and reporting results.⁸⁶ The dosing schedule ranges from 4 to 8 steps, depending on the risk assessment. In general, the suggested dosing schedule is as follows: 3, 10, 30, 100, 300, 1000, and 3000 mg of food protein, with doses increased every 20-30 minutes.⁸⁶ The estimated doses eliciting reactions in 10% of the allergic population (ED10) for shrimp is 2.5 g of protein (the estimated shellfish protein is 5 g/1 oz), which is much higher than other foods.⁸⁷ A Singapore study found threshold doses ranging from 2 g to 80 g of cooked shrimp, with a close correlation between species, 28 indicating that some individuals require a very high dose to elicit a reaction. Starting doses vary by reaction severity.⁸⁸ The maximum dose should match the age-appropriate serving size. For shellfish, the age-appropriate portion size is ½-1 oz for subjects 4-11 months, 1 oz for 1-8 years, 2-3 oz for 9-18 years, and 3-4 oz for 19 years and up.⁸⁸ Although the OFC is a gold standard for diagnosing food allergy, it carries the risk of severe reactions. It requires a physician's supervision in a fully equipped medical facility.

Fish

Fish allergy diagnosis shares core principles with shellfish allergy evaluation but presents distinct considerations related to the allergen repertoire, cross-reactivity patterns, and differential diagnoses unique to fish. The initial evaluation should clarify the species of fish consumed, the preparation method (raw versus cooked), the timing of symptom onset, and the nature of clinical manifestations to differentiate true IgE-mediated allergy from non-immune reactions and to identify sensitization patterns that may permit selective fish consumption.

Skin prick test

Currently, about 30 commercial fish SPT extracts are available, mainly from European species. In a study that tested 26 commercial fish extracts from five manufacturers, the total fish protein content, fish allergen concentrations, and IgE reactivity were found to vary up to 10-fold between different manufacturers and species,⁸⁹ indicating that the lack of standardization in protein and allergen content during the production of SPT reagents impacts the reproducibility and diagnostic value. Although several commercial SPT extracts are available, diagnosing fish allergy remains particularly challenging given the vast diversity of over 1,000 fish species consumed globally. PTP tests with region-specific fish species could be a reasonable alternative diagnostic test. Unlike SPT,⁹⁰ the PTP method lacks standardization owing to variability in food source, preparation, and protein composition. However, it remains a cost-effective and practical alternative in settings where commercial extracts are unavailable.

Specific IgE and component-resolved diagnosis (CRD)

Fish-specific IgE testing with fish extracts and/or components is a helpful tool for diagnosing fish allergy. Sampson et al. compared sIgE levels with OFC outcomes in 100 children with suspected food allergy. In Western populations, a codfish sIgE level ≥ 20 kUA/L provided a 100% PPV for fish allergy, with 100% specificity but only 25% sensitivity. In contrast, a threshold of ≥ 3 kUA/L yielded a 56% PPV, with 91% specificity and 63% sensitivity.⁹¹ In contrast, in South Korea, a study of 66 children with suspected codfish allergy determined that a codfish sIgE level of 6.0 kUA/L provided a sensitivity of 77.8%, a specificity of 42.4%, and an AUC of 0.54. However, a much lower alternative cutoff of 2.05 kUA/L yielded a sensitivity of 93.3%, a specificity of 88.2%, and an AUC of 0.91.⁹² These findings suggest that population-specific factors may influence the optimal diagnostic thresholds for fish allergy, and caution should be exercised when applying Western-derived cutoffs to Asian populations.

Given the recognition of multiple clinically relevant fish allergens beyond parvalbumin, initial diagnostic evaluation should ideally incorporate CRD when available. Heat-labile proteins, particularly glycolytic enzymes such as enolase and aldolase, may lose their allergenic potential upon cooking, whereas heat-stable proteins such as parvalbumin and collagen retain allergenicity. Patients sensitized primarily to enolase or aldolase may tolerate cooked fish while reacting

to raw preparations. When clinical history suggests differential tolerance based on preparation method, evaluation should include enolase and aldolase components in the sIgE testing panel, and consider a supervised oral food challenge with heated fish if enolase/aldolase sensitization is confirmed without concomitant parvalbumin sensitization. This phenotype may permit expanded dietary options with appropriate cooking methods. This approach should include assessment of sensitization to:

- **Parvalbumin** (e.g., Gad c 1, Gad m 1): The major fish allergen, present in most bony fish species
- **Beta-enolase** (e.g., Thu a 2, Sal s 2, Gad m 2): A glycolytic enzyme implicated in 12-56% of cases
- **Aldolase A** (e.g., Thu a 3, Sal s 3, Gad m 3): Another glycolytic enzyme recognized by 13-37% of patients
- **Collagen** (e.g., Sal s 6, Lat c 6): A structural protein with up to 50% sensitization rates in some populations

Selective Fish Tolerance: In patients with sensitization primarily to parvalbumin, certain fish varieties characterized by lower parvalbumin content may be tolerated. In a study evaluating 249 fish-allergic children in Hong Kong,⁹³ 40% reported selective tolerance to at least one fish, more commonly to lower beta-parvalbumin fish such as tuna and salmon, compared with beta-parvalbumin-rich fish such as catfish and grass carp. Further, the group investigated whether differences in fish allergenicity stem from variations in parvalbumin IgE-binding capacity or parvalbumin content. Analysis of 37 serum samples revealed no significant differences in IgE reactivity among parvalbumins from different fish species, despite an 11-fold difference in species-specific sIgE levels. However, parvalbumin content in fish muscle, determined by SDS-PAGE and western blot, strongly correlated with both sIgE reactivity ($r = 0.925-0.988$) and self-reported allergic reactions ($r = 0.855-0.89$), indicating that allergenicity differences are primarily attributed to parvalbumin quantity rather than differential IgE-binding capacity.⁹⁴

Oral food challenge

Supervised oral food challenges are the appropriate next step for selected patients to assess tolerance. Challenge protocols use incremental dosing up to a full age-appropriate serving to confirm tolerance at typical consumption levels. For children, this serving ranges from 28 to 85 g (1-3 oz), while a standard adult serving is typically 100-150 g (3-5 oz), or roughly a palm-sized portion. In the OFC setting, a cumulative 5.3 g codfish protein (21.2 g fish) was used in fish allergy diagnosis in adults.⁹⁵ In other studies, age-adjusted cumulative doses were applied in fish challenges, with 10 g of fish protein for children aged 0-3 years, 13.3 g for 3-6 years, 16.6 g for 6-10 years, and 21 g for those above 10 years of age.⁹⁶ Since performing OFCs for each fish species requires substantial time and clinical resources, systematic evaluation of inter-species cross-reactivity in fish-allergic patients remains challenging.

This standardized diagnostic algorithm, incorporating detailed clinical history, SPT, and fish-sIgE testing, including CRD, enables systematic evaluation of differential reactivity patterns, enhances diagnostic accuracy, and enables personalized management strategies that optimize nutritional adequacy while ensuring patient safety.

Management, emerging therapy, and future direction

Current best practice for seafood allergy management relies primarily on strict allergen avoidance and selective oral food challenges to broaden dietary options safely. This conservative approach aims to prevent allergic reactions. Nevertheless, advances in immunotherapy research raise hope that targeted therapies may provide transformative treatment options in the near future.

Oral immunotherapy (OIT)

Unlike peanut, milk, and egg allergies, shellfish and fish allergy currently lack evidence-based OIT protocols, with no randomized controlled trials or consensus guidelines specifically supporting OIT for shellfish or fish allergy.

Evidence for shrimp OIT remains limited (**Table 3**). In a pediatric case series, 17 shrimp-allergic children underwent an OFC to 300 mg of shrimp protein. Sixteen (94%) continued daily ingestion of 300 mg without OIT-related anaphylaxis.⁹⁷ A recently published phase 2 trial treated 12 participants with shrimp OIT for 52 weeks. Shrimp OIT induced desensitization to a cumulative tolerated dose of 4,043 mg shrimp protein in 87.5% of the per-protocol group, and sustained unresponsiveness was maintained at week 58. No severe adverse events were reported.⁹⁸

Table 3. Oral immunotherapy related to shellfish and fish (USA ClinicalTrial.gov and WHO International Clinical Trial Registry Platform).

Public Title	Registration ID	Country/Region	Age (year)	Time Frame	Sample size	Registration Date	Outcome
Shellfish							
ADP101 for Oral Immunotherapy in Food-Allergic Children and Adults	NCT04856865	USA	4-55	40 wks	73	2021	Advisor feedback resulted in a modification to the ADP101 formulation that positively impacted palatability
Food Allergen OIT for Shrimp and Cashew	NCT03504774	USA	7-55	58 wks	52	2018	Study discontinued due to slow enrollment during COVID-19 pandemic
Immunological Response After Shrimp Oral Immunotherapy Treatment	NCT04552522	Thailand	12-40	52 wks	20	2021	Completed study. No study result posted.
Fish							
Fish Oral Immunotherapy in Hong Kong Children	NCT05590299	Hong Kong	2-10	52 weeks	70	2022	Children received gradually increasing doses of codfish protein up to a maintenance dose of 1000 mg, which was continued until completion of the 52-week treatment period.
Clinical trials for food allergic children with oral immunotherapy with a very small amount of allergen	JPRN-UMIN000033254	Japan	1-15	3 years	60	2018	Egg: start dose ≤ 0.2 g Milk: start dose ≤ 0.2 g wheat: start dose ≤ 0.2 g Others (e.g. peanuts, fish) ≤ 0.2 g Start ingestion and gradually increase. Continue for 3 years.
ADP101 for Oral Immunotherapy in Food-Allergic Children and Adults	NCT04856865	A	4 to 55	40 weeks	177	2021	Participants received low dose/ high dose/ placebo of ADP101 (Oral formulation mixture of 15 individual foods: almond, cashew, chicken's egg, codfish, cow's milk, hazelnut, peanut, pecan, pistachio, salmon, sesame seed, shrimp, soy, walnut, and wheat).
Open-label Extension Study of ADP101	NCT05243719	USA	4 to 55	4-6 years	45	2022	Open-label long-term extension study of ADP101

A search of major clinical trial registries using “fish oral immunotherapy” identified only four registered trials on the WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov. The USA studies involve mixed food allergens, whereas the Japanese trial provides limited publicly available protocol details (Table 3). The Hong Kong trial is the only study focusing exclusively on fish OIT and has reported increased tolerance thresholds and favorable immunologic changes. Alternative approaches are also being explored, including subcutaneous immunotherapy with mCyp c 1, a modified hypoallergenic parvalbumin engineered with two mutations in the calcium-binding domain to reduce allergenicity (NCT02382718).^{99,100}

Sublingual immunotherapy (SLIT)

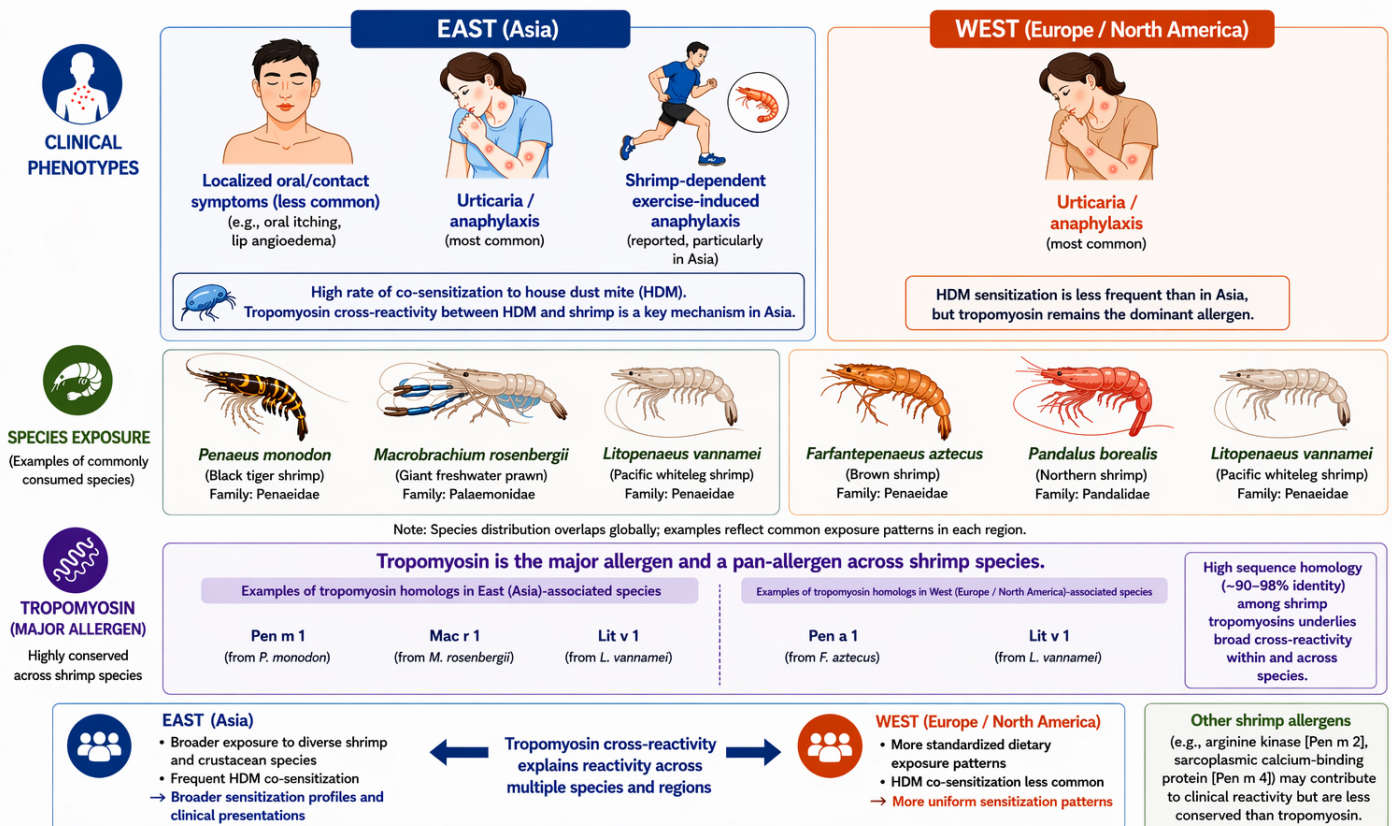
SLIT offers a potentially safer approach for food allergy treatment. In a study of 66 shrimp-allergic patients treated with gradually increasing doses of shrimp extract up to 0.5 mg/dose, 61% tolerated 42 grams of shrimp or more after a mean of 51 months, with no severe reactions reported.¹⁰¹ Another multi-food SLIT study, including patients with shrimp- and fish-allergies, showed no serious adverse events with a maintenance dose up to 2 mg protein.¹⁰² These findings support SLIT as a promising approach.

Biologics

Among biologics for food allergy treatment, omalizumab is the most widely used. Omalizumab can be used as monotherapy or as adjunctive therapy with OIT. When combined with OIT, omalizumab facilitates faster dose escalation and reduces adverse events from OIT.¹⁰³ In a multi-food OIT study, omalizumab was administered for 16 weeks, and multi-food OIT was initiated at week 8; among three shrimp-allergic participants, two tolerated 12,000 mg of shrimp protein by week 36, with no serious adverse events reported.¹⁰⁴ Although only a few studies have examined omalizumab-facilitated OIT specifically for seafood, its mechanism and cross-food efficacy suggest potential applicability in seafood allergies.

DNA vaccines and peptide-based therapy

Innovative therapies, such as DNA vaccines, are being investigated to induce tolerance through immunomodulation. DNA vaccines encoding hypoallergenic variants of shrimp allergens (MEM49, MED171) have shown preclinical efficacy, inducing regulatory T cells and reducing allergic responses in mouse models.¹⁰⁵ Likewise, peptide-based immunotherapy using synthetic peptides containing T cell epitopes that target shrimp tropomyosin and induce tolerance by stimulating regulatory T cells has demonstrated allergy reduction in animal studies.¹⁰⁶



Sources: 1. Lopata AL, O'Hehir RE, Lehrer SB. *Clin Exp Allergy*. 2010;40:850–858. 2. WHO/IUIS Allergen Nomenclature Sub-Committee. Allergen.org (Accessed May 2024). 3. FishStatJ. www.fao.org

Figure 4. Regional differences in Shrimp Allergy: Clinical Phenotypes, Species Exposure, and Tropomyosin (Major Allergen).

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Regional Difference in Fish Allergy: East and West

A Allergens Comparison

Allergens	East (Asia)	West (Europe, N. America)	Note
Parvalbumin	Major allergen	Major allergen	Heat-stable. Universal allergen across fish species
Collagen	Clinical relevant in East Asia, (notably in Japan)	Less common reported	Heat-stable
Enolase	Minor allergen	Minor allergen	Heat-labile
Vitellogenin	Roe-associated Allergen	Rarely reported	Fish egg allergy
Aldolase	Rarely reported	Minor allergen	Heat-labile

B Common Trigger Fish Species Comparison



Category	East (Asia)	West (Europe, North America)
Fresh-Water Fish 	<ul style="list-style-type: none"> Grass carp/common carp Tilapia Catfish 	Rarely reported
Marine Fish 	<ul style="list-style-type: none"> Mackerel Salmon Grouper Threadfin 	<ul style="list-style-type: none"> Mackerel Salmon Cod Tuna Herring Sardine

Figure 5. Regional differences in Fish Allergy: East and West.

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Other emerging new therapeutic approaches

Hypoallergen-based immunotherapy aims to maintain immunogenicity while improving safety. Allergenic epitopes can be modified by several methods, such as glycation (the binding of a protein to sugar molecules), enzymatic treatment, or epitope deletion. Although *in vitro* studies have demonstrated reduced allergenicity, clinical trials in humans are lacking. In addition, probiotics have reduced allergic reactions in mouse model,¹⁰⁷ warranting further investigation.

Gap of knowledge/Unmet need

Taken together, the data reviewed in this manuscript reveal several consistent contrasts between Asian and Western populations. In shrimp allergy, Western cohorts demonstrate predominant sensitization to tropomyosin, whereas Asian studies report substantially lower TM sensitization rates with greater contributions from non-TM allergens including Hc, TnC, and SCBP. Clinically, perioral symptoms predominate among shrimp-allergic patients in Asia, in contrast to more frequent systemic reactions in Western populations, a pattern potentially driven by house dust mite cross-sensitization (Figure 4). In fish allergy, population-specific diagnostic cutoffs appear necessary, as illustrated by the divergent optimal codfish sIgE thresholds between Western and

Korean populations (Figure 5). These contrasting perspectives underscore that a uniform approach to seafood allergy diagnosis and management is inadequate across diverse populations.

Despite these advances, significant gaps continue to limit diagnostic accuracy and patient management. Many studies did not report the species of shrimp used in the SPT extracts or OFC, limiting comparisons across populations. Similarly, fish allergy research often focuses on a limited number of species that may not reflect regional consumption patterns, particularly in Asia.

The lack of standardized shrimp or fish extracts, together with heterogeneous protocols for preparing fresh extracts, represents a major barrier to research comparability and makes it difficult to establish universal diagnostic cutoffs or compare prevalence data across studies. While TM dominates commercial diagnostic panels, emerging evidence suggests that allergens such as SCBP or Hc may be more relevant markers of true shrimp allergy in Asia, where HDM cross-reactivity complicates TM-based testing. Expanding current CRD platforms to include these allergens could improve diagnostic specificity and help distinguish primary sensitization from environmental cross-reactivity.

Furthermore, most studies rely on clinical history, SPT, or sIgE without OFC confirmation, likely contributes to prevalence overestimation. Development of *in vitro* biomarkers with higher positive predictive values could reduce OFC dependence while maintaining diagnostic accuracy.

The role of cofactors in seafood-induced allergic reactions also remains insufficiently studied. Exercise, nonsteroidal anti-inflammatory drugs, and alcohol consumption can augment allergic responses and lower the reaction threshold. Understanding these effects is essential for accurate risk assessment.

Future research directions emerge from these regional disparities. Asia-specific diagnostic cutoffs for shrimp and fish allergy should be established through multi-center studies in mite-endemic regions. Commercial CRD platforms should be expanded to include emerging allergens, which may better identify true shrimp allergy in populations where TM-based testing is confounded by HDM cross-reactivity. Multi-center validation studies across diverse Asian populations are also needed to define the clinical relevance of newly identified allergens and develop population-specific CRD panels. Finally, prospective immunotherapy trials specifically designed for seafood allergies are urgently needed, as currently only very limited trial data exist for both shrimp and fish.

AI and Software Disclosure

Scientific illustrations (Figures 1–5) were created with BioRender (BioRender.com). The AI image-generation tools (ChatGPT, OpenAI; Gemini, Google) were used to modify all figures based on author-specified data and parameters. No AI tools were used for manuscript drafting or statistical analysis.

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