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REVIEW

Diagnosis of fish and shellfish allergies

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Abstract: Seafood allergy is a hypersensitive disorder with increasing prevalence worldwide. Effective and accurate diagnostic workup for seafood allergy is essential for clinicians and patients. Parvalbumin and tropomyosin are the most common fish and shellfish allergens, respectively. The diagnosis of seafood allergies is complicated by cross-reactivity among fish allergens and between shellfish allergens and other arthropods. Current clinical diagnosis of seafood allergy is a complex algorithm that includes clinical assessment, skin prick test, specific IgE measurement, and oral food challenges. Emerging diagnostic strategies, such as component-resolved diagnosis (CRD), which uses single allergenic components for assessment of epitope specific IgE, can provide critical information in predicting individualized sensitization patterns and risk of severe allergic reactions. Further understanding of the molecular identities and characteristics of seafood allergens can advance the development of CRD and lead to more precise diagnosis and improved clinical management of seafood allergies.

Keywords: skin prick test, DBPCFC, component-resolved diagnosis, immunoCAP, ISAC

Introduction

IgE-mediated food allergy is a major global public health issue. A cross-sectional study in a United States cohort of 333,200 children reported a food allergy prevalence of 6.7%.[1] Sensitization usually occurs by exposure through ingestion, inhalation, or skin contact, and re-exposure to milligrams of allergens is sufficient to trigger life-threatening allergic responses.[2,3] Another survey in the United States on 38,480 subjects younger than 18 years of age reported a food allergy prevalence of 8.0%, where 38.7% of the cohort experienced severe allergic reaction, and 30.4% developed multiple food allergies.[4]

Fish and shellfish are among the most common culprits of food allergies. Fish allergy affects 0.2% of the general population.[5] In the USA, the lifetime prevalence rate for reported fish allergy was 0.4% while 0.2% of population experienced both fish and shellfish allergy.[6] In Asia, fish allergy prevalence was much higher in the Philippines (2.29%) than in Singapore (0.26%) and Thailand (0.29%).[7] Worldwide prevalence of shellfish allergy was found to be 0.6% with higher incidence reported in the Asia-Pacific region.[8] In the USA, the lifetime prevalence rate for reported shellfish allergy was 2%, with higher prevalence reported in adults (2.8%) compared to children (0.6%), and in women (3.6%) compared to men (2%).[6] Shellfish allergy is highly prevalent among teenagers in the Philippines (5.12%) and Singapore (5.23%) and is the leading cause of food anaphylaxis in Hong Kong and Taiwan.[9–11] The increasing incidence of fish and shellfish allergy may be attributed to the growing consumption of seafood worldwide. The

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2016 Food and Agriculture Organization of the United Nations report indicated that global fish consumption per capita has risen to over 20 kg year on year.[12] In 2014, the global capture fisheries production was 93.4 million tons, while crustacean and mollusks output from aquaculture amounted to 6.9 and 16.1 million tons, respectively.[12]

Considering the pervasiveness of fish and shellfish allergies, developing precise diagnostic protocols is essential for appropriate prevention and management strategies including avoidance of unnecessary dietary restrictions. Conventional first-line diagnostic approach includes clinical assessment, oral food challenge (open or blinded), skin prick test (SPT), and serum-specific IgE (sIgE) measurement. Fish and shellfish extracts are commonly used in these *in vivo* and *in vitro* tests. However, the presence of cross-reactive allergens and the varying allergen contents among commercial extracts may lead to over- or underdiagnosis of seafood allergy. Fortunately, our increasing understanding of seafood allergens and improvements in technology to produce recombinant allergens allow for the detection of allergen-specific IgE and the development of component-resolved diagnosis (CRD) to reduce the ambiguities of conventional tests.

Fish allergens and cross-reactivity

Twenty-one allergens from 15 fish species are officially recognized by the World Health Organization/International Union of Immunological Societies at present (Table 1). Parvalbumin was first identified as the major fish allergen in 1969.[13] It is a 10–12 kDa protein abundant in muscle and is physiologically important for calcium binding. Bugajska-Schretter et al characterized the IgE reactive proteins in fish with serum samples from 30 fish-allergic patients and demonstrated that all tested sera were IgE positive to parvalbumin from cod extract (Gad c 1).[14] Interestingly, calcium depletion reduced IgE binding to parvalbumin in most patient sera.[14] Fish parvalbumin is thermally stable[15] and maintains its allergenic activity and antigenicity even under acidic conditions and after pepsinolysis.[13,16] Short burst swimming in fish is powered by white muscles, which have a higher parvalbumin content than the dark muscles that drives continuous stroke.[17] It was, therefore, suggested that fish with more dark muscles such as tuna and mackerel is less allergenic than fish with more white muscle such as cod and haddock.[17] Based on amino acid sequences, the parvalbumin protein family can be classified into the less acidic alpha-subtype (nonallergenic) or the more acidic beta-subtype (allergenic).[18–20] Fish contain mainly beta-subtype parvalbumins while the alpha-subtype is found in other vertebrates.[21]

In 2000, fish gelatin was discovered as a fish allergen, and in 2013, Kuehn et al reported the 50 kDa beta-enolase and 40 kDa fructose-bisphosphate aldolase A from cod, salmon, and tuna as important fish allergens.[22–26] Specific IgE to enolases, adolases, and gelatin was detected in 62%, 50%, and 19.3% of fish-allergic subjects, respectively.[23] Fish gelatin was reported

Table 1 Fish allergens with approved nomenclature by the World Health Organization and International Union of Immunological Societies (www.allergen.org)

Allergen	Species	Allergen name	Molecular weight (kDa)	Reference
Beta-parvalbumin	*Clupea harengus*	Clu h 1	12	127
	Cyprinus carpio	Cyp c 1	12	128
	Gadus callarias	Gad c 1	12	14
	Gadus morhua	Gad m 1	12	129
	Lates calcarifer	Lat c 1	11.5	130
	Lepidorhombus whiffiagonis	Lep w 1	11.5	15
	Oncorhynchus mykiss	Onc m 1	12	131
	Rastrelliger kanagurta	Ras k 1	11.3	132
	Salmo salar	Sal s 1	12	133
	Sardinops sagax	Sar sa 1	12	134
	Sebastes marinus	Sub m 1	11	135
	Thunnus albacares	Thu a 1	11	34
	Xiphias gladius	Xip g 1	11.5	136
Beta-enolase	*G. morhua*	Gad m 2	47.3	23
	S. salar	Sal s 2	47.3	23
	T. albacares	Thu a 2	50	23
Aldolase A	*G. morhua*	Gad m 3	40	23
	S. salar	Sal s 3	40	23
	T. albacares	Thu a 3	40	23
Tropomyosin	*Oreochromis mossambicus*	Ore m 4	33	22
Beta-prime-component of vitellogenin	*Oncorhynchus keta*	Onc k 5	18	137

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to trigger positive response in SPT in 10% of fish-allergic patients but oral food challenge with a cumulative dose of 3.61 g of gelatin did not trigger adverse reactions in any of the allergic subjects, thus raising the question if gelatin is a clinically relevant fish allergen.[27] Furthermore, it was reported that a minority of fish-allergic patients developed sIgE to other fish allergens such as aldehyde phosphate dehydrogenase from cod fish,[28,29] triose-phosphate isomerase, and serum albumin from amago salmon[30] and creatine kinase from tuna.[31]

Clinical cross-reactivity among various fish species is common even in fishes from taxonomically distinct orders.[32–34] Parvalbumin from cod extract (Gad c 1) has been shown to cross-react with parvalbumin homologs from distantly related species such as wolffish or flounder.[14,34–37] Besides parvalbumin, cross-reactivity between fish muscle collagens from five fish species has also been reported.[25–29] However, in some cases, codfish-allergic patients may ingest other fish without triggering allergic symptoms.[32,35,38] In addition to the cross-reactivity among fishes, clinical cross-reaction of parvalbumin between fish and other vertebrate meats has been described. Serologic cross-reactions have been described between fish and frog beta-parvalbumins.[39] Cross-reactivity among fish and chicken allergens including parvalbumins, enolases, and aldolases have been reported,[40] and described as "fish-chicken syndrome" phenomenon.

Shellfish allergens and cross-reactivity

Compared with that of fish allergens, the spectrum of shellfish allergens is more diverse (Table 2).[41,42] Tropomyosin (TM) was identified as the major shrimp allergen in 1993.[43] TM is a protein of 38–41 kDa with coiled-coiled secondary structure and is highly conserved across invertebrates to regulate muscle contraction.[44] TM is a heat-stable allergen that can withstand high temperature and common food processing.[42] Usui et al examined the structural stability of shellfish TM and showed that the alpha-helical structure of TM collapsed easily upon heating to 80°C.[45] However, TM could regain its native circular dichroism pattern and retained its antigenicity after cooling to 25°C.[45] Furthermore, TM can be easily solubilized and can remain at high concentration even after thorough cooking, such as boiling and roasting.[46]

Other shellfish allergens have also been well characterized. Arginine kinase (AK) was identified as a shrimp allergen with IgE reactivity that induced immediate skin manifestation in sensitized patients.[47] Although AK is abundant in shrimp muscle, unlike TM, AK is physiochemically and thermally unstable.[48,49] Significant IgE reactivity to AK (Pen m 2) was reported in 27% of shrimp-allergic patients.[47] Myosin light chain (MLC) is a 20 kDa allergen displaying IgE reactivity in both raw and cooked shrimp extracts despite the alteration in its secondary structure under high temperature or acid treatment.[50,51] Sarcoplasmic calcium-binding protein (SCP) is an allergen recognized by serum IgE in 38% of patients with shrimp allergy.[52] Similar to other allergenic components, SCP is highly conserved among crustaceans (alpha chain: 90%–94% identity, beta chain: 80% identity).[53] IgE reactivity to shrimp hemocyanin, troponin C, paramyosin, troponin I, triose phosphate isomerase, myosin heavy chain, alpha-actinin, smooth endoplasmic reticulum Ca^{2+} ATPase, and GADPH has been reported, but their clinical significance in food allergies is less understood.[54–58] Although TM, AK, and SCP were well characterized as crab allergens, TM is the only allergen identified across multiple edible crustacean and mollusk species.[59,60] There remains a clear need to compile a comprehensive shellfish allergen panel.

The major shellfish allergen, TM, has been suggested as a pan-allergen, whose cross-reactivity is likely because of the high homology in amino acid sequence (69%–100%) among crustaceans and mollusks.[61] Although crustacean and cephalopod TMs share only 63%–64% sequence identity, their cross-reactivity is probably due to their highly conserved IgE-binding epitopes.[62] Nevertheless, there are also reports on species-specific allergies to marine shrimp (*Penaeus monodon*) or fresh water shrimp (*Macrobrachium rosenbergii*) through oral challenge.[63] Apart from the cross-reactivity observed among edible shellfish, Leung et al also reported significant IgE reactivity of sera from shrimp-allergic subjects to grasshopper, cockroach, and fruit fly.[64] Cross-reactivity between shrimp and cockroach is also experimentally demonstrated in other studies.[65,66] Reciprocally, subjects with house dust mite or cockroach allergy also showed substantial IgE reactivity to shrimp TM.[65–67] The IgE cross-reactivity among TMs might be attributed to the recognition of similar epitopes within the eight IgE binding epitopes in shrimp TM (Pen a 1), of which five are identical to cockroach TM (Per a 7), and four are identical to lobster TM (Hom a 1) and dust mite TM (Der p 10 and Der f 10).[65] Besides TM, Gámez et al also reported that ubiquitin, alpha-actinin, and AK are responsible for mite-seafood cross-reactivity,[41] and a similar study by Pascal et al also suggested that AK and hemocyanin may be the markers of cross-reactivity between shellfish and other arthropods.[68]

Cross-reactivity between fish and shellfish

To date, limited cases of cross-reactivity between fish and shellfish allergens have been reported,[69] with most of these studies suggesting TM as the possible cross-reactive allergen.

Table 2 Officially recognized shellfish allergens with approved nomenclature by the World Health Organization and International Union of Immunological Societies (www.allergen.org)

Allergen	Species	Allergen Name	MW	Reference[a]
Tropomyosin	*Charybdis feriatus*	Cha f 1	34	60
	Crangon crangon	Cra c 1	38	55
	Crassostrea gigas	Cra g 1	18	153
	Haliotis laevigata x Haliotis rubra	Hal l 1	33.4	
	Helix aspersa	Hel as 1	36	154
	Homarus americanus	Hom a 1	34	138
	Litopenaeus vannamei	Lit v 1	36	139
	Macrobrachium rosenbergii	Mac r 1	37	140
	Melicertus latisulcatus	Mel l 1	38	141
	Metapenaeus ensis	Met e 1	34	142
	Pandalus borealis	Pan b 1	37	87
	Panulirus stimpsoni	Pan s 1	34	138
	Penaeus aztecus	Pen a 1	36	143
	Penaeus indicus	Pen i 1	34	43
	Penaeus monodon	Pen m 1	38	144
	Portunus pelagicus	Por p 1	39	49
	Procambarus clarkii	Pro c 1	36	
	Saccostrea glomerata	Sac g 1	38	155
	Todarodes pacificus	Tod p 1	38	156
Arginine kinase	*Crangon crangon*	Cra c 2	45	55
	Litopenaeus vannamei	Lit v 2	40	145
	Penaeus monodon	Pen m 2	40	47
	Procambarus clarkii	Pro c 2	40	157
	Sylla paramamosain	Scy p 2	40	158
Myosin light chain 2	*Homarus americanus*	Hom a 3	23	146
	Litopenaeus vannamei	Lit v 3	20	50
	Penaeus monodon	Pen m 3	20	144
Sarcoplasmic calcium binding protein	*Crangon crangon*	Cra c 4	25	55
	Litopenaeus vannamei	Lit v 4	20	52
	Penaeus monodon	Pen m 4	20	147
	Pontastacus leptodactylus	Pon l 4	24	
	Sylla paramamosain	Scy p 4	20	159
Myosin, light chain 1	*Artemia franciscana*	Art fr 5	17.5	
	Crangon crangon	Cra c 5	17.5	55
	Procambarus clarkii	Pro c 5	18	51
Troponin C	*Crangon crangon*	Cra c 6	21	55
	Homarus americanus	Hom a 6	20	146
	Penaeus monodon	Pen m 6	16.8	160
Troponin I	*Pontastacus leptodactylus*	Pon l 7	30	148
Triosephosphate isomerase	*Archaeopotamobius sibiriensis*	Arc s 8	28	
	Crangon crangon	Cra c 8	28	55
	Procambarus clarkii	Pro c 8	28	161
	Sylla paramamosain	Scy p 8	28	
Ovary development-related protein	*Eriocheir sinensis*	Eri s 2	28.2	149

Note: [a]The corresponding allergens of the empty spaces remaining were approved by the World Health Organization and International Union of Immunological Societies with unpublished data.

In 2013, Liu et al demonstrated that sera from tilapia-allergic subjects (10/10) reacted to a 32 kDa protein that was later identified as TM.[69] Interestingly, there is 87.7% amino acid sequence homology between TM from tilapia and human but only 58.8% homology between the tilapia and northern shrimp (Pandalus borealis) TM. Further, this study also pointed out that antibodies against human TM isoform 5 could be present in patients with inflammatory bowel disease (IBD). It is intriguing that six out of ten of the tilapia-allergic subjects included in this study were diagnosed with IBD, bringing to question whether the detected reactivity was a consequence of allergy or autoimmunity.[22,70,71]

On the other hand, Peixoto et al illustrated IgE reactivity among TMs from hake, codfish, shrimp, and Indian prawn in the serum of an 11-year-old boy in Spain by IgE immunoblotting and competitive-inhibition immunoblotting. As the specific IgE level to crustaceans (>100 kUA/L) was markedly higher than to fishes (0.02–2.77 kUA/L) accord-

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ing to ImmunoCAP, the authors suggested shrimp TM as the primary sensitizer, while reaction with fish TM was a consequence of cross-reactivity in this subject. However, it was clearly reported in this study that this 11-year-old boy had previous experience of fish allergy that apparently occurred before the episode of shrimp anaphylaxis. It was also his first time consuming shrimp when he was admitted to hospital during an anaphylaxis.[69] Nevertheless, we cannot conclude yet whether cross-reactivity between fish and shellfish, and specifically among their TMs, exists based on these two studies.

Diagnosis of fish and shellfish allergies

The current clinical approaches to seafood allergy diagnosis include clinical assessment, SPT, sIgE testing, and oral food challenge. A suggested algorithm is illustrated in Figure 1. The emerging and promising strategy of CRD is also considered here.

Clinical assessment

Clinical assessment is the first step of allergy diagnosis. Clinical symptoms and medical history underpin the likelihood of seafood allergy. For accurate diagnosis, information is collected on allergic episodes, including the type and quantity of suspected seafood ingested, the time to onset of symptoms, whether previous exposure to suspected culprits elicited similar allergic responses, and when the last reaction to food occurred.[72] As shellfish is recognized as one of the major food groups to induce food-dependent exercise-induced anaphylaxis,[73] whether exercise was performed before an allergic episode should also be considered. Family history of food allergy is often considered during clinical assessment. However, the link between genetics and seafood allergy has not been thoroughly established, with only one report of an estimated heritability of 0.54 in a twin study on shellfish allergy.[74]

One major drawback with clinical assessments is that patients often cannot provide precise and detailed medical histories and may fail to identify the suspected food that trigger their allergic symptoms.[75] It is also crucial that the history is assessed by an allergist capable of differentiating other disorders with similar clinical presentations that might be misconstrued as food allergy. Additional tests, such as SPT, sIgE levels, and/or results of oral food challenge, are usually interpreted in conjunction before reaching a diagnosis.

SPT

SPT is a common *in vivo* screening procedure for IgE-mediated food hypersensitivity by examining skin reactivity to food extracts. It is a reliable method for patients to rapidly

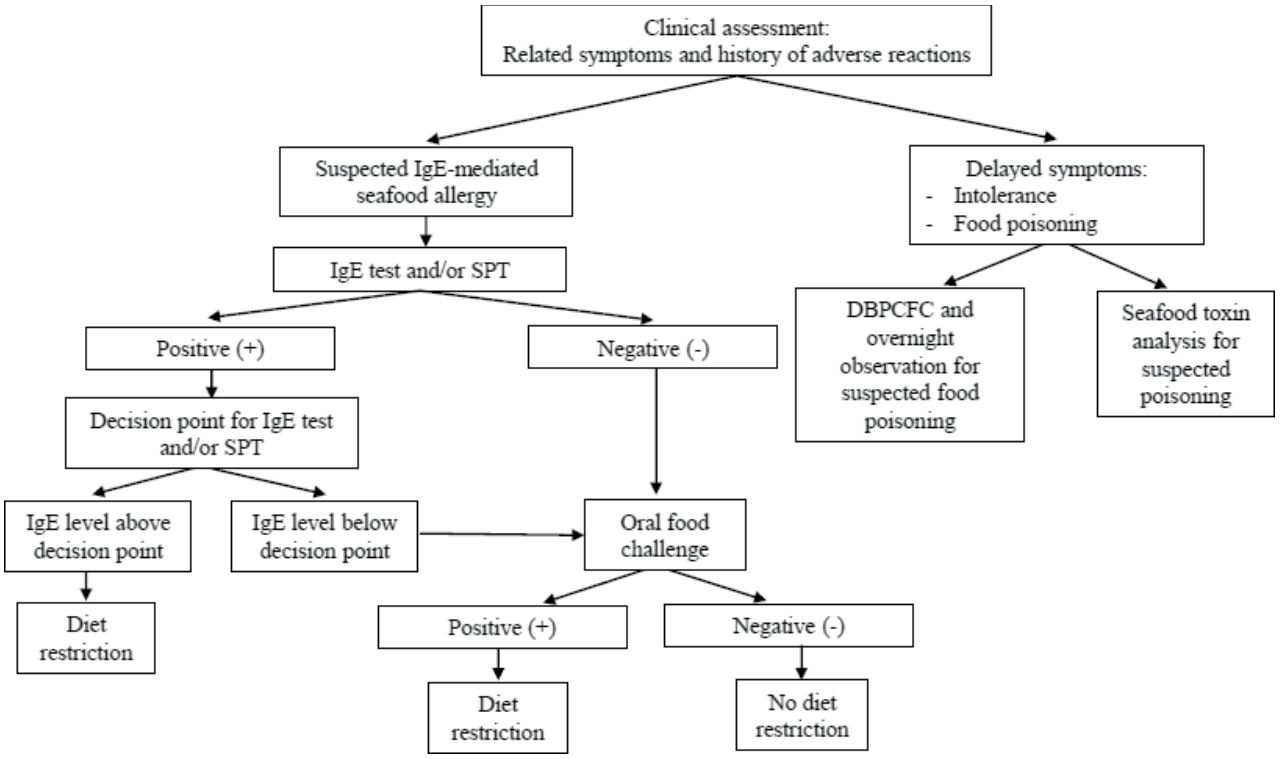

Figure 1 Diagnostic algorithm and clinical management for seafood allergy.
Note: Data from Niggemann and Beyer[150] and Lopata et al.[151]
Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; IgE, immunoglobulin E; SPT, skin prick test.

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determine their sensitization results and can be tested with uncommon allergens that are not available as commercial extracts. The cross-linking of specific IgE with allergens introduced into the skin triggers an immunologic milieu, leading to the release of various mediators including histamine, which is responsible for localized swelling around the prick area.

The procedure for SPT involves applying a drop of allergen test solutions to the forearm or back along with positive (histamine 1–10 mg/mL) and negative (50% glycerol saline) control drops. Modified methods may apply a lancet aid allergen penetration. Localized wheals are quantified by measuring the mean of the longest diameter and the length of the perpendicular line through its middle after 15–30 minutes of skin pricking. According to European standards, positive reactions are defined by wheal sizes from test drops that are more than 3 mm greater in diameter than those from the negative control.[76,77] SPT requires normal healthy skin with good patient cooperation. Drugs that may interfere with skin reactivity (eg, antihistamine, phenothiazines, and antidepressants) must be avoided before SPT. However, the safety of SPT for seafood allergy has not been fully evaluated. Cases of SPT-induced anaphylaxis and fatality have been reported after application of fish, egg, shellfish nut, and peanut allergens.[78,79] Although the risk associated with SPT is minimal, anaphylactic precautions must be in place.

Although SPT is a more sensitive test method for fish allergy than milk, egg, and peanut allergies,[80] commercially available fish and shellfish extracts are limited compared to the wide variety of dietary fish and shellfish. Prick-to-prick tests using fresh food could, in this regard, circumvent the obstacle.[81,82] The reliability of SPT could be greatly hampered by the method of SPT and measurement method, as well as the lack of allergen standardization and presence of preservatives in the extracts.[83–86] A study by Asero et al on five commercial crustacean SPT extracts found that these commercial extracts displayed a dramatic loss of protein bands compared to fresh shrimp extract on sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), which could cause heterogeneous SPT profiles. Attention should, thus, be drawn to the diagnostic sensitivity of SPT depending on the commercial extract used.

Recombinant allergens that can be standardized of its quantity and quality could be an alternative. For example, recombinant Pan b 1 was found to induce equivalent positive wheal sizes as natural Pan b 1 and commercial shrimp extract.[87] The drawback with these recombinant proteins, however, is that other potentially important allergens from natural extracts will be excluded. Recombinant allergens also do not address cross-reactivity when identifying a bona fide allergen. Future analyses evaluating the diagnostic utility of fish and other shellfish components in SPT are expected.

Specific IgE measurement

Serologic sIgE level is useful not only for diagnosis, but also for predicting the development of tolerance and persistence of seafood allergy, as well as monitoring allergy treatments.[88] Common clinically adopted sIgE measurement platforms include HYPEC-288 (Hycor-Agilent), Immunulite (Siemens), and the ImmunoCAP (Phadia).[89] In the ImmunoCAP system, 16 shellfish extracts and 28 fish extracts are readily available for routine sIgE quantification (Tables 3 and 4), but allergen components are scarce.

Table 3 Common crustacea and mollusca allergens included in the ImmunoCAP system (Phadia/Thermo Fisher Scientific) (http://www.phadia.com/en/Products/Allergy-testing-products/ImmunoCAP-Allergen-Information/Food-of-Animal-Origin/Shellfish/Shrimp/)

Taxa	Food groups (test code)	Commercial allergens	Source
Crustacea	Shrimp (f24)	*Metapenaeopsis barbata*	Boiled, frozen, or raw, frozen meat
		Metapenaus joyneri	Boiled, frozen, or raw, frozen meat
		Pandalus borealis	Boiled, frozen, or raw, frozen meat
		Penaeus monodon	Boiled, frozen, or raw, frozen meat
	Lobster	Crayfish (f320): *Astacus astacus*	Unknown
		Lobster (f80): *Homarus gammarus*	Unknown
		Langust (f304): *Palinurus* spp.	Boiled meat and shell
	Crab (f23)	*Chionocetes* spp.	Boiled meat
Mollusca	Abalone (f346)	*Haliotis* spp.	Unknown
	Blue mussel (f37)	*Mytilus edulis*	Canned meat
	Clam (f207)	*Clam*	Fresh frozen muscle
	Octopus (f59)	*Octopus vulgaris*	Fresh frozen muscle
	Oyster (f290)	*Ostrea edulis*	Fresh whole oyster
	Scallop (f338)	*Pecten* spp.	Squid muscle
	Pacific flying squid (f58)	*Todarodes pacificus*	Squid meat
	Squid (f258)	*Loligo edulis, Loligo vulgaris*	Unknown

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Table 4 Common fish allergens included in the ImmunoCAP system (Phadia/Thermo Fisher Scientific) (http://www.phadia.com/en/Products/Allergy-testing-products/ImmunoCAP-Allergen-Information/Food-of-Animal-Origin/Fish/Anchovy/)

Food groups (test code)	Commercial allergens	Source
Anchovy (f313)	*Engraulis encrasicolus*	Whole fish
Catfish (f369)	*Ictalurus punctatus*	Fish filet
Chub mackerel (f50)	*Scomber japonicas*	Fish muscle
Cod (f3)	*Gadus morhua*	Fish muscle
Eel (f264)	*Anguilla Anguilla*	Whole fish
Grouper (f410)	*Epinephelus* sp.	Fish filet
Gulf flounder (f147)	*Paralichthys albigutta*	Fish filet
Haddock (f42)	*Melanogrammus aeglefinus*	Whole fish
Hake (f307)	*Merluccius merluccius*	Fish muscle
Halibut (f303)	*Hippoglossus hippoglossus*	Fish muscle
Herring (f205)	*Clupea harengus*	Fish muscle
Jack mackerel/Scad (f60)	*Trachurus japonicas*	Fish muscle
Mackerel (f206)	*Scomber scombrus*	Fresh meat
Megrim (f311)	*Lepidorhombus whiffiagonis*	Whole fish
Orange roughy (f412)	*Hoplostethus atlanticus*	Fish filet
Plaice (f254)	*Pleuronectes platessa*	Fish muscle
Pollock (f413)	*Pollachius virens*	Fish filet
Red snapper (f381)	*Lutjanus campechanus*	Whole fish
Salmon, Atlantic (f41)	*Salmo salar*	Fish muscle
Sardine (Pilchard) (f308)	*Sardine pilchardus*	Whole fish
Sardine/Japanese pilchard (f61)	*Sardinops melanosticta*	Fish muscle
Sole (f337)	*Solea solea*	Fish muscle
Swordfish (f312)	*Xiphias gladius*	Fish muscle
Tilapia (f414)	*Oreochromis* sp.	Fish filet
Trout, Rainbow trout (f204)	*Oncorhynchus mykiss*	Fish muscle
Tuna or Yellow fin (f40)	*Thunnus albacares*	Fish muscle
Walleye pike (f415)	*Sander vitreus (Stizostedion vitreum)*	Fish filet
Whitefish (Inconnu) (f384)	*Stenodus* sp.	Fish filet

It is generally believed that the levels of sIgE and the severity of allergic symptoms,[73] or the outcome of food challenge, are closely associated.[90] Mekaroonkamol et al also showed that measuring shrimp sIgE could be a useful screening test with high sensitivity (90%) and high positive predictive value (PPV; 0.86),[91] while individuals with serologic cod sIgE levels higher than 20kUA/L would give at least 95% certainty of positive food challenge results.[92,93] However, the extensive IgE cross-reactivity among shrimp, cockroach, and dust mites could misrepresent the association between a positive shellfish SPT or positive sIgE results and clinical reactivity.[94] Children who were sensitized to cockroach through environmental exposure had higher levels of IgE to shrimp, but they did not manifest clinical symptoms of shrimp allergy, suggesting that such extract-based SPT and IgE tests indicate only IgE sensitization but not necessarily clinical allergy.[72,94] Another study also reported that all shellfish-allergic individuals with positive SPT or IgE test results passed the food challenge,[95] which was consistent with previous reports.[96]

Oral food challenge

Oral food challenge is by far the only diagnostic test reflecting clinical food allergy,[97] and positive food challenge usually correlates with strong SPT and IgE measurement results.[93] Currently, there are three types of oral food challenges: open food challenge (OFC), single-blind placebo-controlled food challenge, and double-blind placebo-controlled food challenge (DBPCFC).

In OFC, food is given in its ordinary form such that both the observer and patient recognize the tested food. The use of OFC is largely due to its convenience in clinical settings. Furthermore, OFC is also conducted when the load of food is too large to be effectively masked in a blinded challenge, for confirming a negative DBPCFC result and for children under 3 years of age.[98] The major flaw is obviously the high degree of bias by either the observer or the patient.

In single-blind placebo-controlled food challenge, only the patients are unaware of the kind of food administered, whereas the observer and patient are both unaware of the

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tested food in DBPCFC. For both types of challenges, the taste and smell of the suspected causal food are blinded by masking with other foods that are tolerated by the subjects (ie, active provocation). Placebos made with the same preparation without the allergic food are also included in both types of challenges to evaluate the allergic symptoms (both subjective and objective). The active and placebo provocations will be performed on separate days and both are given to subjects from low to increasing doses until the first incidence of observed reaction.[99] However, the methods for preparing blinded food for DBPCFC may vary among clinics, such as using chocolates for fish, and chocolate pudding or burgers for shrimp.[99]

While DBPCFC represents the gold standard in food allergy diagnosis, the major drawbacks limiting its applications in clinical practice are that it is time-consuming, labor-intensive, and expensive.[100] Oral food challenges also pose the risk of severe anaphylactic shock,[101,102] and thus should be optimized for safety by cautiously considering the subjects' age, anticipated symptoms, SPT and sIgE levels, as well as the doses of the suspected allergic food used in the challenge and food contaminations before conducting a food challenge.[103] It is also noteworthy that the allergenicity of seafood may be altered after thermoprocessing.[104] For instance, some cooked shrimp and mollusk species extracts have higher allergenicity than raw preparations,[105,106] whereas some other species were shown to induce higher IgE production when consumed raw.[107]

Component-resolved diagnosis

As discussed above, SPT and sIgE measurements only reflect IgE sensitization with suboptimal specificity, and do not predict the severity of allergic symptoms.[100] The high cost and safety issues of DBPCFC have limited its use in clinical practice. CRD has been developed recently as an emerging strategy to overcome the shortcomings of these traditional methods. CRD aims at measuring IgE antibodies to individual allergenic components in the form of proteins or peptides[108] to provide more details on the sensitizing profile of patients.[109] The working principle of CRD is depicted in Figure 2.

The utility of CRD has been well demonstrated in peanut allergy. False-positive SPT and sIgE results are common in peanut-tolerant subjects[110] that could be in part due to nonspecific IgE reactivity to carbohydrate determinants and/or pollen allergens in the preparation.[111] It was found that subjects who failed food challenges inadvertently had higher sIgE to peanut allergens Ara h 1, 2, and 3, while positive sIgE to Ara h 8 was found in patients passing OFCs. Compared to peanut extracts that have a diagnostic specificity of only 17% and PPV of 0.67, Ara h 2 is a better diagnostic marker with a specificity of 92% and PPV of 0.94. By adding the level of Ara h 2-specific IgE as a second diagnostic step after detecting positive sIgE to peanut extract, 91.1% Ara h 2-positive subjects failed a food challenge while 78.6% of Ara h 2-negative subjects passed. This suggests that Ara h 2 is a more specific marker than peanut extract for identifying challenge-proven peanut allergy, and that sIgE level to Ara h 2 can be an indicator to reduce the need for OFC.[112]

For fish and shellfish allergies, single-plex CRD can be performed on the ImmunoCAP system (Phadia/Thermo Fisher Scientific, Uppsala, Sweden) against fish parvalbumins rCyp c 1 and rGad c 1, as well as shrimp TM rPen a 1.[113–115] ImmunoCAP allows quantification of sIgE level at standard unit (ie, kUA/L) but requires a larger amount of sera for analysis as each allergen

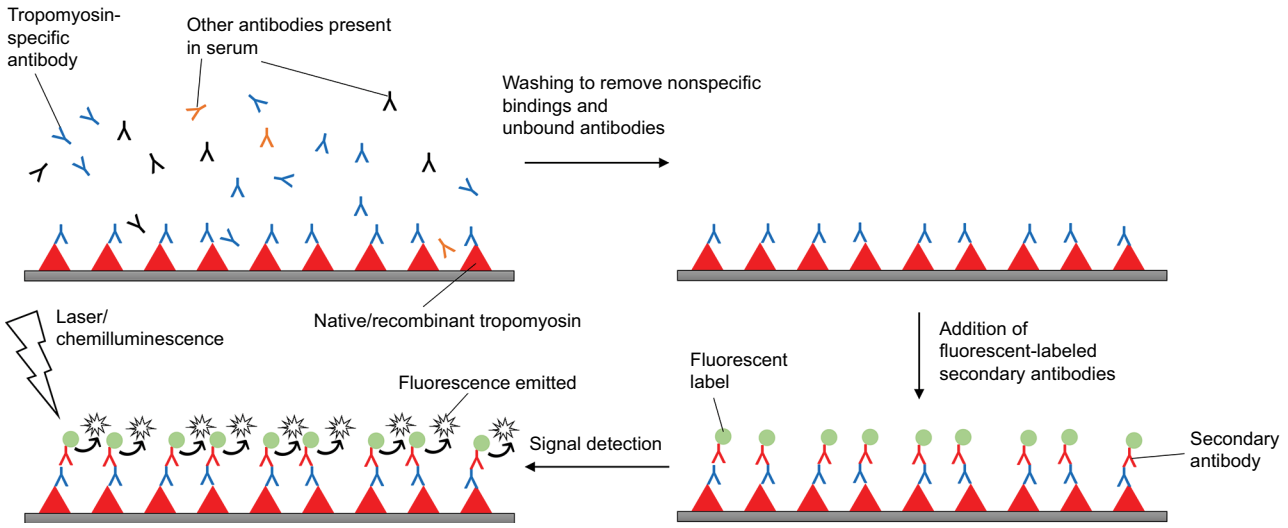

Figure 2 Working principle of component-resolved diagnosis, using shrimp tropomyosin as an example.

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component is tested individually. This might limit its application among pediatric subjects. Microarray-based ImmunoCAP ISAC system (Immuno-Solid Phase Allergen Chip; Phadia/Thermo Fisher Scientific) is also available, by which the allergen panel covers 112 inhalation and common food allergens that include cod (rGad c 1) and shrimp (nPen m 1, nPen m 2 and rPen m 4) allergens.[116,117] Although the results between the ImmunoCAP and ISAC platforms are closely correlated, the sensitivity of ISAC is lower than that of ImmunoCAP.[118]

Studies on the diagnostic utility of CRD in fish and shellfish allergies are lacking. Currently, *in vitro* assays of serologic IgE reactivity to recombinant fish parvalbumin are often used to assess for clinical cross-reactivity in fish allergy.[23,119] A few studies, however, revealed that there was IgE binding to other allergens other than parvalbumin in patients. Monosensitivity to some fish species including swordfish and cod was observed in some patients. For example, Kelso et al found allergy specific to swordfish and not to the other nine commercial fish extracts tested.[120] Kuehn et al also demonstrated the correlation of fish enolases- and aldolases-specific IgE with clinical sensitivity in three cod-sensitized but parvalbumin-nonreactive patients.[121] Inclusion of the minor fish allergens such as enolases, aldolases, and perhaps gelatin into the testing panel will likely enhance the resolution of fish allergy diagnosis.

On the other hand, for shellfish allergy, it was reported that IgE reactivity to shrimp TM rPen a 1 was detected in 98% of shrimp-allergic patients,[122] and shrimp TM-specific IgE level can better predict clinical reactivity than SPT and IgE to shrimp extract at a specificity of 92.8% compared to 75% and 64.2% only, respectively.[123] A more comprehensive study by Pascal et al included the proteins and peptides of TM (Lit v 1), AK (Lit v 2), MLC (Lit v 3), SCP isoform alpha (Lit v 4), hemocyanin (HM), fatty-acid-binding protein, SCP isoform beta, and troponin C to study the utility of CRD for shrimp allergy diagnosis.[68] The sensitization profile suggested that apart from TM, which accounts for the majority of allergic symptoms after shellfish ingestion, SCP was also highly associated with allergic manifestations and MLC was a predictive marker of positive oral food challenge. AK and hemocyanin were, on the other hand, markers of cross-reactivity with a recognition frequency higher than 60% in house dust mite- and/or cockroach-allergic patients. Furthermore, the study by Asero et al reported that shrimp-allergic subjects with strong Pen m 1 hypersensitivity showed positive SPT with extracts depleted of TM and they frequently reacted to other minor allergens such as Pen m 2 and Pen m 4 on ISAC, as well as other high-molecular-weight shrimp allergens.[81] These two independent studies, thus, highlight the uncomprehensiveness of the current shellfish allergen panel, and perhaps fish allergy as well, which intelligibly challenge our development of CRD.

Future perspectives

Advances in the molecular and physiochemical characterization of shellfish and fish allergens have facilitated the development of CRD that can lead to more precise diagnoses and better clinical management of these allergies. However, there are still significant areas that need to be refined regarding the diagnosis of shellfish and fish allergies:

1. Although many shellfish and fish allergens are identified at the molecular level to date, few of these recombinant proteins are employed in diagnostic assays. Thus far, TM is the only allergen identified across different edible crustacean and mollusk species. The report by Asero et al, however, pointed out that TM may not be the only allergen for shellfish allergy diagnosis and emphasizes the values of other clinically important shellfish allergens. Identifying and characterizing seafood allergens, especially species-specific allergens, may advance the resolution of fish and shellfish allergy diagnosis.[81]
2. Although CRD is an emerging method that could potentially reduce the need for oral food challenge and contribute to tailored treatment plans based on patients' sensitization profiles, it is yet to be considered as a routine diagnostic method.[97] The diagnostic utility of CRD for fish and shellfish allergies is also yet to be thoroughly investigated.
3. Other emerging diagnostic tests are also worth investigating, including epitope binding, T-cell response, basophil activation assays, and atopy patch test. It is worth noting that sIgE measurements to extracts or allergen components indeed reflect the affinity between IgE and the allergens but not necessarily their ability to trigger subsequent degranulation in the effector cells. This issue could be addressed by using basophil activation test, which has been suggested to differentiate between subjects allergic to or tolerant to peanut, milk, and egg.[124–126]

Conclusion

With the increasing worldwide prevalence of seafood allergy, the precise diagnosis of this disorder is crucial for appropriate management strategies and unnecessary dietary avoidance. The current diagnostic methods in clinical practice for food allergy are often held back by the suboptimal

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specificity and safety and economic issues, especially for oral food challenges and allergen cross-reactivity. Incorporating CRD into the diagnostic workup might increase the resolution to the severity of allergic symptoms, resolve clinical cross-reactivity, and circumvent the need for oral food challenge. However, we should always appreciate that precise diagnosis should be achieved through a stepwise approach incorporating different tests to complement both sensitivity and specificity. We note that diagnosis of fish and shellfish allergy indeed becomes complicated by the extensive cross-reactivity among fish allergens and between allergens in edible shellfish and other arthropods. Large-scale studies evaluating the diagnostic accuracy and utility of the conventional tests and other emerging strategies for these allergies are also lacking. Advances in validation studies, together with the development of next-generation diagnostic strategies, are needed to improve the specificity of diagnostic workups for food allergies.

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Disclosure

The authors report no conflicts of interest in this work.

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