Diagnosis and management of shrimp allergy

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Shrimp allergy, the most common food allergy in the United States, affects up to 2% of the population. Its etiology is multi-factorial with the combination of genetic predisposition and environmental exposures. This review summarizes the latest diagnosis and management strategies for shrimp allergy. Currently, the double-blind, placebo-controlled food challenge is the gold standard for diagnosis. Moreover, mainstream and experimental management strategies include food allergen avoidance, the FDA-approved omalizumab, and oral immunotherapy. Herein, we emphasize the urgent need to develop more effective diagnostic tools and therapies for shrimp allergy.

1 Introduction

1.1 Epidemiology

Food allergy (FA) involves complex immune responses to proteins and in some cases, carbohydrates, present in specific foods, approximately 10% of the world's population suffers from food allergies (1, 2). The exact prevalence rates depend on the method of diagnosis, geographic areas, and consumption habits. The prevalence of shellfish allergy has been reported as up to 10.3% and is observed in many parts of the globe (3). Pediatric shellfish allergy increased from 0.5% in 2004 to 1.3% in 2019 in the US (3, 4). Shrimp allergy (SA) is the second most common FA in the United States, affecting up to 1.3% of the population (2, 5). There are some variables of shellfish and shrimp allergy in different regions and ages that are summarized in Table 1 (2, 6–17). The possible symptoms of shrimp allergy range from mild to moderate, to severe, and even life-threatening anaphylaxis, accidental exposure to shrimp is a major cause of visits to the emergency room, with anaphylaxis occurring in up to 50% of those with shrimp allergy (2, 18, 19).

1.2 Shrimp allergens

Shrimp is popularly consumed shellfish because of its rich nutritional value, and particular protein content. However, many shrimp proteins (allergens) can cause allergic reactions in some people. Currently, a total of ten shrimp allergens have been registered based on the World Health Organization and International Union of

TABLE 1 The prevalence of shellfish, shrimp—area and age.

Continent	Shrimp				Shellfish			
	Region/Country/City	Prevalence %	Age	Refs	Region/Country/City	Prevalence %	Age	Refs
Asia	South Asia	3.4	3–7 yrs[a]	Lao-araya et al. (6)	Hong Kong, Philippines, Singapore	0.9–1.3	<7 yrs	Leung et al. (13)
	China	4.4	Preschool	Zeng et al. (7)		5.1–7.7	Adolescents, adult	
	Hong Kong, China	0.1	NA	Li et al. (8)	Singapore	1.2 (4–6 yrs); 5.23 (14–16 yrs)		Shek et al. (14)
	Guangzhou, China	0.18			Philippines	5.12	14–16 yrs	
	Shaoguan, China	0.7			Guangzhou, China	5.1	School children	Yang et al. (15)
	India	15.5[b]; 3.2[c]	Adult	Magesh et al. (9)	Shaoguan, China	1.8		
Europe	Northern, Central, Southern Italy	4, 13, 16	NA	Asero et al. (10)	Michigan	16	College students	Greenhawt et al. (16)
	Denmark	2		Ostertale et al. (11)	France	0–10.3	NA	Moonesinghe et al. (17)
Northern America	U.S.A	1.9	2.5% at 30–39[d]	Guputa et al. (2)		5.5	5–17 yrs	
Africa	Ghana	0.1	5–16 yrs	Obeng et al. (12)	U.S.A. (12)	2.9	3.6% at 30–39[d]	Gupta et al. (2), Wang et al. (3)
	Worldwide	0.3–0.6	NA	Wood et al. (20)		9	Adult	

[a]yrs: years old.
[b]overall weighted population.
[c]weighted population if total IgE <median.
[d]highest age with allergy between 18 and 60 yrs old.

Immunological Societies' Database (21, 22), including the major shrimp allergen tropomyosin (TM) and the minor allergens including arginine kinase, myosin light chain, sarcoplasmic calcium-binding protein, troponin C, hemocyanin, triosephosphate isomerase, fatty-acid-binding protein, and glycogen phosphorylase, plus two potential allergens, enolase, and aldolase (22). A few more potential shrimp allergens have been revealed: shock protein 70, α-tubulin, chymotrypsin, β-enolase, Eno, aldolase A, glyceraldehyde-3-phosphate dehydrogenase, and cyclophilin (22).

Shrimp TM is a ubiquitous structure muscle protein and is a cross-reactive invertebrate pan allergen because of a high homology with the TM from dust mites and cockroaches (23–28). Shrimp tropomyosin (Pen a 1), the muscle protein invertebrate pan-allergen functions in muscle contraction, and heat-stable (29, 30). However, there are conflicting reports on the IgE-binding to heat-stable allergens, such as TM and myosin light chain (31). The conflicting results of heat-treatment may reveal the importance of shrimp species and environmental influences on patient IgE profiles in determining allergenicity. Evidence has shown persistent certain allergenicity from shrimp tropomyosin under low pH conditions because of the conservation of its linear epitopes (32). This emphasizes the role of solubility and the isoelectric point of proteins in allergenicity.

A strong correlation between shellfish and HDM sensitization, most likely because there are 81% homologs of TM in amino acid sequence similarity between prawns and HDMs and 82% similarity between prawns and cockroach (33–36). The sequence identity of the HDM TM (Der p 10 and Blot 10) to the identified eight IgE epitopes of Pen a 1 was >80% (36, 37). More studies have indicated the association of exposure to house dust mites or cockroaches with peanut and shrimp allergy (38–40). Therefore, the IgE cross-reactivity with shellfish tropomyosins accounts for mild oral allergies when people consume shellfish (36).

1.3 Etiology and pathogenesis of shrimp allergy

Shrimp allergy, like other complicated diseases, is caused by several factors, including genetic and environmental exposures. Evidence shows that genetic and environmental factors are involved in shrimp allergy development, even though the exact causes of shrimp allergy are not fully understood (41–53).

1.4 Genetics in shrimp allergy

Genetics plays a crucial role in the manifestation of food allergy (41). Compared to fraternal twins, there exists a greater probability that identical twins are both allergic to peanuts, indicating that peanut allergy is at least partially heritable (42). Kivisto et al., (2019) found a similar trend for pistachio, walnut, sesame, and fish. Several associations of gene mutations, variants, and single nuclear polymorphisms have been found in genes associated with food allergy, but not necessarily as causative factors (43). For example, filaggrin (FLG) is a general food allergy risk gene, HLA has food-specific effects, and mucosa-associated lymphoid tissue lymphoma translocation 1 (MALT1) variants increase the risk of sensitization and the development of allergy (44). A few reports have unveiled specific genetic markers linked to an elevated risk of developing shrimp allergy (Table 2). These shrimp allergy-

associated genes include HLA-DQ (rs9275596), HLA-DRB1 (HLA-DRB1*04:05-HLA-DQB1*04:01), IL-13 (rs20541, and IL13 rs1800925) (45, 46), and food allergy -associated gene TLR4 rs4986790 (Asp299Gly) (47). Genome-wide association studies identified the causal effect of SA on the occurrence of major depressive disorder (48). All these studies suggested a strong association between genetic factors, and three out of four studies listed in Table 2 investigated shrimp allergy (Table 2).

Although current genetic studies have low statistical power and there is relatively small sample size as well as heterogeneity in the definition of shrimp allergy, studies reveal several genetic loci/genes, which implicate the importance of barrier and immune function genes in shrimp allergy. Furthermore, variations in genes responsible for the breakdown and metabolism of specific proteins in shrimp can impact an individual's susceptibility to allergic reactions. Integrative approaches, including genetics/genomics with transcriptomics, proteomics, and metabolomics, will be critical next steps to translating these genetic insights into practice. The biggest challenge in shrimp allergy genetics is elucidating specific mechanisms of action for shrimp allergy risk and pathogenesis for the loci.

The knowledge of the genetic underpinnings of shrimp allergy holds significant implications for diagnosis. Genetic testing aids in identifying individuals allowing for early interventions at higher risk individuals. In the future, by applying single nucleotide polymorphism (SNP) genotyping through whole genome amplification (WGA), candidate gene study (e.g., human leukocyte antigen, HLA region), whole exome sequencing (WES), or whole genome sequencing (WGS) of shrimp allergy patients, we can better identify clinical risk factors and genetic loci associated with shrimp allergy during screening to reduce its incidence. The genetic findings in shrimp allergy may shed light on the contribution of human genetics to the susceptibility to shrimp allergy.

1.5 Environmental exposures

Several environmental factors are involved in the pathogenesis of shrimp allergy development. A few hypotheses associated with shrimp allergy development with environmental variables such as mono-allergen and dual-allergens exposure, dietary, hygiene, intestinal microbiota, vitamin D, pollution, co-exposure to dust mites or cockroaches, and microbes (49–56). Here we discuss a few environmental exposures.

The hygiene hypothesis suggests that a post-natal environment lacking sufficient exposure to allergens and pathogens could lead to an undeveloped immune system or misdirection of the immune system towards otherwise tolerated allergens (49). Lynch and colleagues found that in the first year of life, "exposure to cockroach, mouse and cat allergens was negatively associated with recurrent wheeze ($p < 0.01$)" (50). The intestinal microbiota forms a barrier that may promote or suppress food allergies (51). For example, *Dorea* may reduce the allergic risk of shellfish, while *Ralstonia* may promote it and *Bacillus coagulans*, *Bifidobacterium infantis*, and *Bifidobacterium lactis* have been utilized as potential therapies (50, 52, 53).

This phenomenon extends beyond topical or respiratory allergens. Until 2008, the American Academy of Pediatrics recommended avoiding allergenic foods until 3 years of age, and the incidence of peanut and other allergies increased exponentially (53). A team led by Professor Gideon Lack of King's College in London, along with the Immune Tolerance Network and Food Allergy Research & Education, launched the Learning Early About Peanut Allergy study to probe whether early introduction of peanuts would be effective in preventing the development of peanut allergy in high-risk children. They found that introducing high-risk children to peanut foods early was associated with more than an 80% reduction in developing peanut allergy (54). This study showed young children's immune systems exhibit a high degree of plasticity and require some level of exposure to food allergens during early life to be able to modulate immune responses that can persist for the rest of their lives. The cause of this phenomenon is likely multi-factorial (55, 56).

Together, genetic susceptibility and environmental factors determine the complex etiology and pathogenesis of shrimp allergy.

2 Diagnosis of shrimp allergy

The diagnosis of shrimp allergy is based on history, skin prick test (SPT), and sIgE to shrimp allergens, as recommended by the guidelines for diagnosis and management of food allergy in the United States, and the European Academy of Allergy and Clinical

TABLE 2 Summary of the studies of host genetic susceptibility for shrimp allergy.

	Sample size	Populations	Genes Identified	Findings	Author
1	130 infants/110 controls	Turkish	rs1898830 & rs5743708—TLR2	rs4986790 (Asp299Gly) in TLR4 gene associated with children with food allergies.	(47)
			rs4986790 & rs4986791—TLR4		
2	30,206 participants with shrimp allergy based on two sample sets	East Asian population	44 shared by Shrimp Allergy (SA) and Major Depressive Disorder (MDD) at the genomic level; 17 shared by SA and MDD in brain tissue; 6 genes shared by SA and MDD in blood samples	GWA identified the causal effect of shrimp allergy on the occurrence of MDD,	(48)
3	532 participants	India	HLA-DQ rs9275596,	HLA-DQ and IL13 polymorphisms pose a major risk for shrimp-allergic patients	(45)
			IL13 rs20541, and IL13 rs1800925		
4	11,011 participants	Japanese	HLA-DRB1*04:05-HLA-DQB1*04:01	Using GWAS, HLA-DRB1*04:05-HLA-DQB1*04:01 associated with shrimp allergy	(46)

*Represents the allele of this gene.

Immunology (EAACI) guidelines for IgE-mediated food allergy (57). The important step of the diagnostic process involves reviewing the patient's history to identify any known reactions to shellfish. If a reaction has occurred recently, there is a higher risk of current allergy. When patients ingest TM, it may cause a Type II-mediated immunological reaction, manifesting in symptoms such as urticaria, flushing or urticarial rashes on the face and/or extremities, localized itching, and nausea. The patient may experience severe reactions, including vomiting, difficulty breathing, widespread urticarial rashes, swelling (angioedema) of the mouth and throat, or anaphylaxis (58).

The administration of a SPT entails puncturing the skin to deliver a food allergen. A reaction to the allergen is characterized by wheal and rash around the area of application. Skin prick testing offers fast results at a relatively low cost and is known to have high negative accuracy, in which a lack of response is generally attributed to a lack of allergy. However, the variable protein concentrations of the food allergens in extracts and fresh food may lead to inconsistent results for these foods (59).

ImmunoCAP^{TM}, a fluorescence enzyme immunoassay, is a useful tool in the diagnostics of shellfish allergy to measure the serum-specific IgE (sIgE) against whole food (f24, shrimp allergens), including shrimp tropomyosin (f351 rPen a 1, TM), including TM or other minor allergens. Shrimp specific IgE binding proteins, like other allergens, can be identified by Western blotting and mass spectrometry (60–63). Specific IgE diagnostic tools are very useful but cannot unilaterally determine shrimp food allergy reactivity. Patients with a clinical history of mild reactions to shellfish may exhibit high levels of tropomyosin sIgE, while others with a history of severe anaphylaxis may have low or even undetectable levels with conventional assays (64, 65). Dust mite and cockroach sensitization can cause positive testing due to homology and IgE cross-reactivity.

The gold standard for diagnosing food allergy remains the double-blind, placebo-controlled food challenge (DBPCFC) (66) using oral food allergens. This allows clinicians to confirm or deny a patient's stated history within a controlled environment and administration of known concentrations of whole allergen. Titration upward of the allergen administration beginning with protein levels far below what would be found in the actual food allows for significantly safer evaluations of patients even with severe shellfish allergy.

There are also some experimental diagnostic tests in development. Basophil activation tests (BAT) measure the degree of degranulation and activation of basophils caused by the cross-linking of IgE to the FcεRI. This test utilizes flow cytometry to analyze specific cell surface markers (including CD63) presenting on the activated basophils. It provides insight into the patient's expected degree of reactivity (67). This test has had mixed results, with basophils being short-lived and present in low concentrations or absent in 10%−15% of patients, it can be falsely negative, especially immediately post allergic reaction. Recently, a novel test has emerged, IgE-crosslinking-induced luciferase expression. A complete set of FcεRI subunits was transfected into a rat basophilic leukemia-derived mast cell line and sensitized with patient sera. This test was shown to have lower accuracy than shrimp extract-based BAT (64, 68) but holds the potential for testing specific epitopes and peptide segments of shrimp allergens, allowing for further elucidation of the specific mechanisms behind an individual's allergy. The mast cell activation test is also a sensitive test for peanut allergy (67). Component-resolved diagnosis by Western blot, Enzyme-Linked Immunosorbent Assays (ELISA), light-initiated chemiluminescent assay, mass spectroscopy, and bead-based epitope assays all suggest that TM has a higher diagnostic value than shrimp extract (64).

In summary, currently, diagnostic tools for food allergy including shrimp allergy remain unsatisfactory, with a shared decision-making process for use recommended by experts in the field (64). In the future, combined genetic, epigenetic, skin prick tests, and blood tests with the family history and presence of atopic co-morbidities of patients will further refine our ability to diagnose and predict the development of shrimp and other food allergies. Consideration of other samples such as feces, saliva, and urine for other novel tests and metabolic biomarkers may be utilized in the future. More accurate, earlier, and sensitive diagnosis tools are urgently needed.

3 Food allergy prevention

Education is critical for shrimp allergy prevention. For example, the knowledge of reading labels to limit accidental exposure to allergenic foods containing shrimp and other shellfish, as well as educating parents on the early introduction of a variety of foods gradually to their children is essential for prevention of allergic reactions (66). Proper vitamin D intake is helpful, as deficiency is associated with food IgE sensitization (69).

Smeekens et al., revealed that the vaccination with shellfish allergen DNA using a PowderJect XR DNA vaccine delivery system increased shrimp-specific IgG and C3H/HeJ is the best among three strains of mice (70). Kubo et al. reported that a single DNA plasmid vaccine constructed from Litopenaeus vannamei (Lit)-lysosomal-associated membrane protein (lit-LAMP-DNA-vaccine) promoted Th1 responses, thwarting anaphylaxis in shrimp-sensitized mice, suggested the lit-LAMP-DNA-vaccine can be developed to prevent or treat shrimp allergy (69–71). Wai et al., showed two hypoallergenic TM molecules could reduce IgE reactivity and allergenicity and induce blocking IgG antibodies in humans as a proof of concept for peptide vaccination (71). Overall, given the difficulty of developing clinical trials for vaccines to patients at risk for anaphylaxis, it is unclear how long and how safe and efficacy of these successful vaccines in mouse models will translate clinically to humans. Therefore, other interventions for effective prevention strategies with less or no advert event and stress for shrimp allergy urgently need to be developed.

4 Management of shrimp allergy

4.1 Conventional management

The management of shrimp allergy is based on the guidelines for diagnosing and managing food allergy in the United States

(72). In practice, the key current management for shrimp allergy is to avoid eating shrimp. A strict avoidance or an elimination diet is the best way to prevent any allergic reaction to food. Hence, it is imperative to educate parents and pediatric and adult patients with food allergies on how to avoid consuming allergenic foods.

In addressing shrimp allergy, researchers aim to decrease IgE expression, increase blocking IgG expression, and prevent pro-inflammatory responses. Shrimp oral immunotherapy (OIT) (73, 74) has been shown to be successful in case series with and without omalizumab co-treatment. Sublingual immunotherapy for shrimp also improved the clinical symptoms for shrimp allergic patients who have house dust mite allergy (75). Refaat et al. (2014) administered shrimp sublingually to shrimp-allergic patients and observed lower specific-IgE (76). Most recently Theodoropoulou and colleagues reported that sublingual immunotherapy exhibited safe and effective desensitization to shrimp (74). Oral food Challege (OFC) is the gold standard for diagnosing a food allergy, including a shrimp allergy, and practitioners should follow standardized protocols to achieve consistent outcomes.

On February 16, 2024, following the success of the OUtMATCH study, the FDA approved omalizumab, the first drug treatment for adults and children >1 year with food allergies, including shrimp-allergic patients. Omalizumab is an injectable monoclonal antibody (mAb) drug that binds to and neutralizes IgE, the human antibody that mediates allergic reactions. Initially approved for chronic spontaneous urticaria, omalizumab has proved efficacious in the management of multiple food allergies and functions best when paired with OIT and an avoidance diet (77). However, the primary adverse effects of OIT and omalizumab, separately, include life-threatening anaphylaxis in 1.65–10.9% and 0.2% of treated patients, respectively (78).

4.2 Experimental management

Many promising treatments are on the horizon for the treatment of food allergies, including other monoclonal antibodies. Tezspire (tezepelumab) is currently the only approved thymic stromal lymphopoietin (TSLP) inhibitor for asthma and is also under evaluation as a potential candidate for food allergies. TSLP is a protein that binds to many pro-inflammatory cells and is stimulated by a variety of inducers (79). Etokimab is a monoclonal antibody (mAb) that allosterically inhibits IL−33, a pleiotropic cytokine that regulates many immune responses, including those in inflammatory allergic reactions (80). Dupilimab, also a mAb, allosterically inhibits IL4 and IL13, two TH2 cytokines that are implicated in allergy and IgE-mediated immune responses (81). However, all these potential therapies remain in the experimental stage. This is the same for probiotics, herbal medicine, and other vaccination strategies which are all being explored as potential therapies (82–85). Recently shrimp allergy animal models are allowing for the development of better diagnostic and therapeutic tools (85–90).

In summary, the conventional management for shrimp allergy includes avoiding eating allergic foods, OIT, and omalizumab. Vaccination is an emerging treatment that may be developed in the future (Table 3). More effective and less risky management strategies are urgently needed for shrimp allergy.

TABLE 3 Shrimp allergy management.

|		Management Strategy	Description	Advantages	Limitations	References
1	Mainstream	Allergic food avoidance	Know the specific foods that trigger an allergic reaction and avoid consumption of these foods. Educate yourself, inform others, and understand how to read food labels.	The best way to prevent an allergic reaction	Can be hidden or unlabeled ingredients	(72)
2		Oral immunotherapy	Oral immunotherapy can be used to desensitize food allergy. One consumes increasingly small amounts to bolster resistance then maintains a daily dosage.	Potential for long-term protection or toleration of small doses and improved quality of life	Risk of adverse reaction and significant commitment required	(73, 74)
3		Omalizumab	Monoclonal antibodies can target IgE to elicit immune response. Omalizumab is a new injectable therapy that has shown potential in increasing reaction threshold for peanut and other food allergies.	Increased tolerance of food allergen and reduced anxiety for allergic reaction	Potential high costs and/or side effects	(77)
4		Herbal medicine	It is based on the traditional Chinese medicine formula WuMei Pill and is aimed to improve the body's immune system.	Natural and personalized approach, cost-effective	Not standardized and less accepted. It is hard to generalize as it is a personalized and precious medicine.	(82–84)
5		Vaccination strategies	Various potential vaccination strategies to protect from food allergy are being researched, including allergen-specific immunotherapy. This includes DNA vaccines that can build tolerance.	Potential for widespread availability and long-term management	May be me with more hesitancy and variance among individual responses	(69–71)
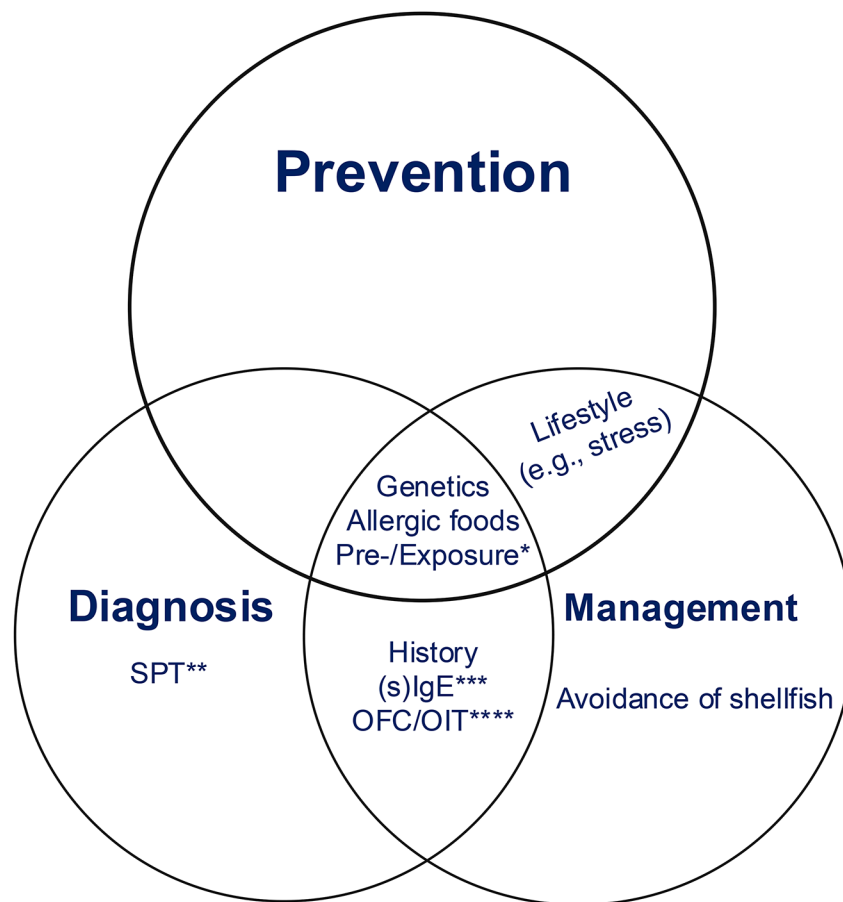
FIGURE 1
Diagnosis, prevention, and treatment of Shrimp allergy. Genetic predisposition, pre- or/and exposure, and dietary choice may be three important points to consider for diagnosing, preventing, and managing shrimp allergy. Prevention is the most important among these three. The lifestyle, such as stress or stable emotion, is for prevention and management, OFC and sIgE are for diagnosis and management. *Pre-exposure or and exposure to microbes, toxins, or other allergens. **Skin prick test. ***Specific IgE for diagnosis and monoclonal antibody against humanimmunoglobulin E (e.g., omalizumab) for management. ****Specific food allergens-challenge for Diagnosis and specific food allergens-oral immunotherapy for Management.

5 Conclusion

The intricate relationship between genetic predisposition and environmental exposures to cross-reactive allergens and food allergens highlights the personalized nature of food allergic responses. Genetic markers associated with the immune system and environmental and food exposures significantly contribute to an individual's susceptibility, severity, and onset of shrimp allergy and food allergy in general (Figure 1). This knowledge not only enhances our understanding of the underlying mechanisms but also has practical implications for diagnosis and personalized treatment strategies, ultimately improving the management of shrimp allergy for affected individuals. There is a critical need to develop more effective diagnostic tools, and effective treatments for the millions of patients who suffer from life-threatening shrimp allergy.

Author contributions

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Conflict of interest

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