



Shellfish and House Dust Mite Allergies: Is the Link Tropomyosin?

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Crustacean shellfish allergy is an important cause of food allergy and anaphylaxis in Asia. The major allergen in shellfish allergy is tropomyosin, a pan-allergen that is also found in house dust mites and cockroaches. Tropomyosins from house dust mites (HDMs) have a high sequence homology to shellfish tropomyosins, and cross-reactivity between HDM and shrimp tropomyosins has been demonstrated. Exposure to inhaled tropomyosins from house dust mites has been postulated to be the primary sensitizer for shellfish allergy, in a reaction analogous to the oral allergy (inhalant-food) syndrome. This notion is supported by indirect data from the effects of HDM immunotherapy on shellfish allergy, and strong correlations of shellfish and HDM sensitization. HDM immunotherapy has been reported to induce both shrimp allergy in non-allergic patients and shrimp tolerance in shrimp-allergic patients. Epidemiological surveys have also demonstrated a strong correlation between shellfish and HDM sensitization in both hospital-based and community-based studies. Unexposed populations have also been shown to develop sensitization—shellfish sensitization in orthodox Jews with no history of shellfish consumption was associated with HDM sensitization. Reciprocally, HDM sensitization in an Icelandic population living in a HDM-free environment was associated with shrimp sensitization. *In vitro* IgE inhibition studies on sera in shrimp-allergic Spanish patients indicate that mites are the primary sensitizer in shrimp-allergic patients living in humid and warm climates. Current data supports the hypothesis that tropomyosin is the link between HDM and shellfish allergies. The role of tropomyosin in HDM and shellfish allergies is a fertile field for investigation as it may provide novel immunotherapeutic strategies for shellfish allergy.

Key Words: House dust mite; shellfish allergy; tropomyosin; Asia

INTRODUCTION

In the last several decades, we have witnessed an allergy epidemic that documented a striking global rise in the prevalence of asthma, allergic rhinitis, and eczema. More recently, the prevalence of food allergy has been rising particularly in the Western world and has been considered the second wave of the allergy epidemic. Aside from egg and cow's milk allergies that are the most prevalent food allergies in infants and young Asian children, the pattern of food allergy shows significant differences from those of Western populations.

In the Asian region, fish and peanut allergies are not common^{1,2} Instead, crustacean shellfish allergy is an important cause of food allergy. A summary of epidemiological studies of shellfish allergy are presented in Table. Population surveys show that the prevalences in teenagers are 5.12% in the Philippines and 5.23% in Singapore.¹ Hospital-based studies on anaphylaxis show that crustacean shellfish is a leading cause of food-induced anaphylaxis in Singapore,^{3,4} Thailand,⁵ Hong Kong,⁶ and Taiwan.⁷ One unique feature in the clinical manifestation of shellfish allergy in

Asia is the predominance of a milder form of allergy with reactions localized to the oral mucosa, as reported by recent studies from Singapore⁸ and Thailand.⁹

The major allergen in shrimp and shellfish allergies is tropomyosin, a pan-allergen involved in muscle contraction in invertebrates. Tropomyosins from house dust mites (HDMs) and cockroaches share a high sequence homology to shellfish tropomyosins, with an 81% amino acid sequence similarity between prawns and HDMs, and 82% similarity between prawns and cockroach.^{10,11} Cross-reactivity between tropomyosins from HDMs and shellfish has been well demonstrated.¹² House dust mites thrive in the humid tropical Asian environment, and there is a high prevalence of HDM allergy and IgE sensitization in our

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Table. Population studies on shellfish allergy prevalence in Asia

Country	Shellfish (%)	Population (n)	Age (year)	Methodology	Year published	Reference
China	0.17-0.42	1604	0-2	Report, SPT, FE, DBPCFC	2012	45
Hong Kong, China	0.9	3677	2-7	Report / Doctor-diagnosed	2009	46
Hong Kong, China	37.8	7393	0-14	Report	2012	47
Philippines	5.12	11,158	14-16	Convincing history	2010	1
Singapore	1.19	4115	4-6	Convincing history	2010	1
	5.23	6342	14-16	Convincing history		
Taiwan	1.1	813	<3	Convincing history +/- SPT/IgE	2012	48
	7.71	15,169	4-18	Convincing history +/- SPT/IgE		
	7.05	14,036	>19	Convincing history +/- SPT/IgE		
Thailand	0.88	452	3-7	Report, SPT, OFC	2005	49

Report: self/parent-reported based on symptoms provided only; Convincing history: symptoms occurring in less than 2 hours. SPT, skin prick test; DBPCFC, double-blinded placebo-controlled food challenge; OFC, open food challenge; FE, food elimination.

Asian population.¹³⁻¹⁶ In a recent report from Singapore on 39 shrimp-allergic patients, all subjects with shrimp allergy were also sensitized to HDMs.⁸ This review explores the hypothesis that inhalant exposure to tropomyosins from HDMs is the primary sensitizer for shellfish allergies, and IgE cross-reactivity with shellfish tropomyosins accounting for mild oral allergies upon consumption of shellfish.¹⁷ This may be similar to the oral allergy (inhalant-food) syndrome seen commonly in Europe, where birch pollen-allergic individuals react to cross-reactive allergens in fruits and nuts. The predominant clinical features are of lip itch and swelling, and are confined to the oral mucosa.¹⁸ Heat-labile pathogenesis-related (PR) proteins elicit IgE reactions from local tissue bound serum IgE in the oral mucosa, which are then rapidly denatured during digestion, halting the progression to systemic symptoms.¹⁹ Heat and proteolysis-stable Profilin and lipid transfer proteins have also been found to be involved in cross-reactivity, which likely accounts for the small subgroup of patients who do experience anaphylaxis.²⁰ Tropomyosin is as a heat stable protein, and this may explain the spectrum of severity of reactions, although most reactions in tropical cohorts are confined to the oral mucosa. This hypothesis is supported by intriguing epidemiological, clinical, and immunochemical data that reinforces this HDM and shellfish allergy link and that tropomyosin plays a major role in these interactions.

MOLECULAR ASPECTS OF TROPOMYOSIN

The amino acid sequences of allergic tropomyosin are compared in Figure. Tropomyosins of shrimps, prawns, lobsters, and crabs share sequence identity between 91% and 100%. The snail tropomyosin Hel a 1 and the fish tropomyosin Ore m 4 have 63.7% and 57.4% sequence identity to the shrimp tropomyosin Pen a 1, respectively. Tropomyosins of mites and cockroaches have 78.5%-81.7% and 82.4% sequence identity to Pen a 1, re-

spectively. The sequence identity of Pen a 1 to tropomyosins of midge (chi k 10), parasite (Ani s 3), and silverfish (Lep s 1) are 78.5%, 72.9%, and 67.9%, respectively.

To investigate this homology, IgE-binding epitopes have been evaluated. The IgE epitopes of shrimp tropomyosin was first studied using the approach of peptide epitope mapping.^{21,22} Eight IgE-binding epitopes were identified in Pen a 1 from *Penaeus aztecus*.²¹ Further investigations showed that the 2 sequences 145-164 and 263-280 inhibited IgE-binding reactivity to tropomyosin of *Penaeus monodon* (Pen m 1) in all the shrimp-allergic sera tested, and these were proposed to be the major IgE epitopes.²³

The multiple sequence alignment of tropomyosin from shrimp (Pen a 1, Pen m 1), crab (Por p 1), lobster (Hom a 1), and HDM (Der p 10 and Blo t 10) revealed that the shrimp tropomyosin Pen m 1 and the lobster tropomyosin Pro p 1 and Hom a 1 have almost identical sequences at all the 8 identified Pen a 1 IgE epitopes. The sequence identity of the HDM tropomyosins Der p 10 and Blo t 10 to Pen a 1 at these 8 IgE epitopes was also high (>80%), with the exception of the first epitope 43-55 for which the sequence identity is 58% (Figure). Pen a 1 epitopes and their homologous sequences in Hom a 1 (lobster tropomyosin) have similar IgE-binding reactivity to sera from shrimp-allergic subjects. In contrast, these sera showed similar IgE-binding reactivity to only 4 homologous sequences in Der p 10 (187-197, 249-259, 266-273, and 273-281) and had less or no IgE reactivity to the other 4 homologous sequences.²⁴

An earlier study using *Blomia tropicalis*-allergic sera revealed that the IgE epitopes of Blo t 10 were mainly located at N- and C-terminal of the molecule.²⁵ Only one-third of subjects had IgE reactivity to the middle region 125-214, indicating that the middle region of Blo t 10 is less allergenic. This may explain the reduced IgE cross-reactivity of shrimp-allergic sera to 2 IgE epitopes of Pen a 1 homologous sequences (137-141, 144-151) in Der p 10.

This data indicates the presence of IgE cross-reactivity between

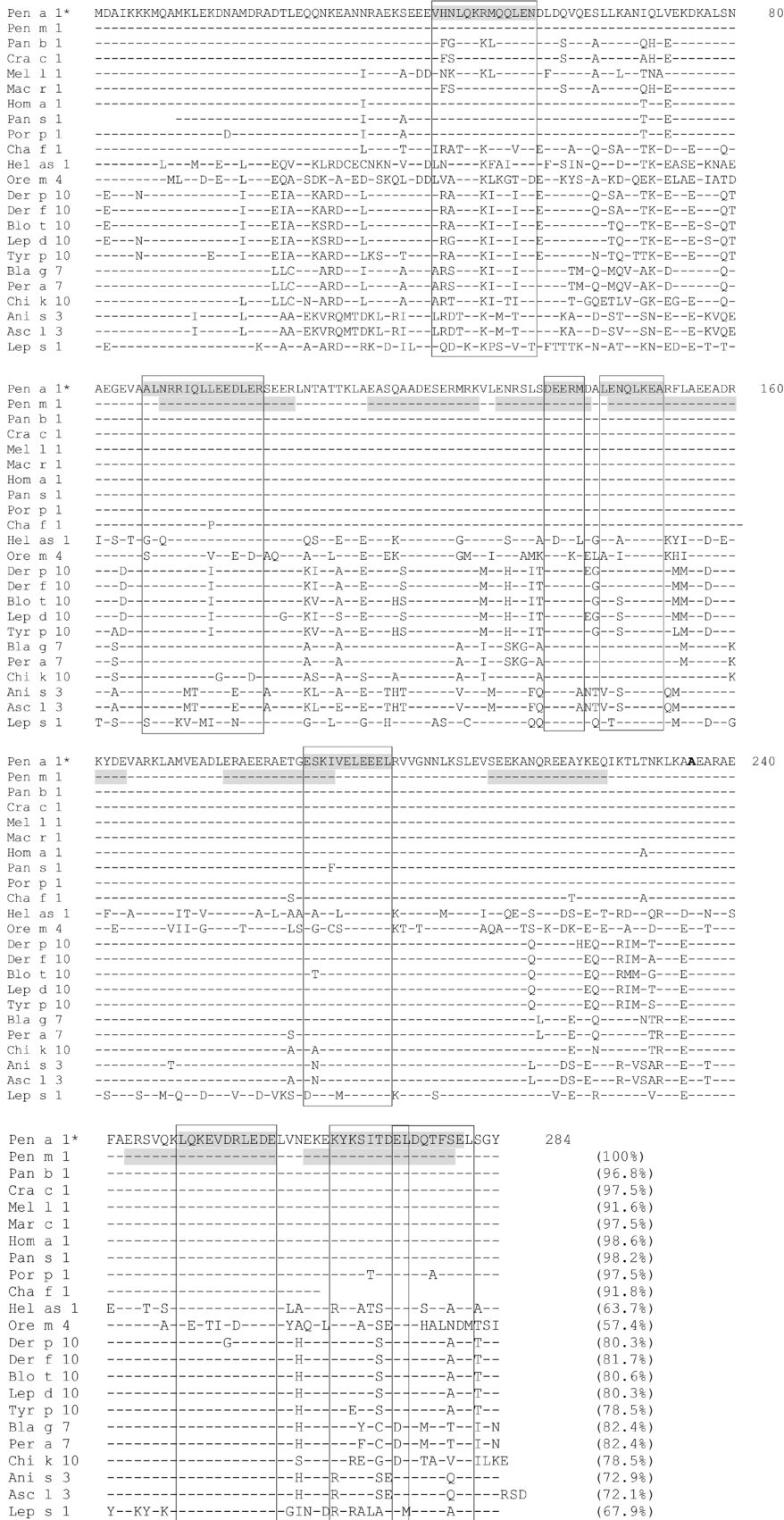


Figure. Comparison of identified Pen a 1 IgE-binding epitopes with homologous sequences in other allergenic tropomyosins. Pen a 1 (Genbank accession number AAZ76743) from shrimp *Penaeus aztecus*, Pen m 1 (BAF47262) from shrimp *Penaeus monodon*, Pan b 1 (CBY17558) from shrimp *Pandalus borealis*, Cra c 1 (ACR43473) from shrimp *Crangon crangon*, Mel l 1 (AGF86397) from prawn *Melicer-tus laticulatus*, Mar c 1 (ADC55380) from prawn *Macrobrachium rosenbergii*, Hom a 1 (AAC48288) from lobster *Homarus americanus*, Pan s 1 (AAC38996) from Lobster *Panulirus stimpsoni*, Por p 1 (AGE44125) from crab *Portunus pelagicus*, Cha f 1 (AAF35431) from crab *Charybdis feriatus*, Hel as 1 (CAB38044.1) from snail *Helix aspersa*, Ore m 4 (AFV53352) from fish *Oreochromis mossambicus*, Der p 10 (CAA75141) from mite *Dermatophagoides pteronyssinus*, Der f 10 (BAA04557) from mite *Dermatophagoides farinae*, Blo t 10 (ABU97466) from mite *Blomia tropicalis*, Lep d 10 (CAB71342) from mite *Lepidoglyphus destructor*, Tyr p 10 (AAT40866) from mite *Tyrophagus putrescentiae*, Bla g 7 (AAF72534) from cockroach *Blattella germanica*, Per a 7 (AAD19606) from cockroach, Chi k 10 (CAA09938) from Midge *Chironomus kiiensis*, Ani s 3 (CAB93501) form parasite *Anisakis simplex*, Asc l 3 (ACN32322) from parasite *Ascaris lumbricoides*, Lep s 1 (CAC84590) from silverfish *Lepisma saccharina*. IgE epitopes on the studies of Pen a 1 and Pen m 1 are shaded. Sequences that are aligned with the identified Pen a 1 IgE epitopes are boxed. The numbers in the parentheses indicated the percentages of identity as compared to the sequence of Pen a 1. *Let v1 and Pen a 1 have identical sequence.

tropomyosins of shellfish and HDMs; however, the cross reactivity is stronger within shellfish (shrimp and lobster) than between shellfish and HDMs.

HDM AND SHELLFISH LINK

HDM immunotherapy and crustacean allergy

The effect of HDM immunotherapy on shellfish allergy provides evidence for the link between HDM and shellfish tropomyosins. The induction of shrimp allergy with positive skin prick tests and food challenge in previously non-allergic patients receiving HDM immunotherapy has been reported.²⁶ Interestingly, clinical reactions were localized to the oral mucosa alone. On the other hand, sublingual HDM immunotherapy has also been reported to improve shrimp tolerance in a shrimp-allergic patient with previous anaphylaxis to shrimp—the same authors speculated that this effect may be related to the total dose of tropomyosin received, as this patient was treated with double the recommended dose of SLIT.²⁷ Subcutaneous immunotherapy has also been reported to be associated with a decrease in specific serum IgE and resolution of shrimp and squid allergy.²⁸ The effect of immunotherapy may be affected by the total dose of tropomyosin as well as the route of administration.

Some inference may also be drawn from the reported effects of HDM immunotherapy on snail allergy—although snails are molluscs and not crustaceans, inhibition experiments have confirmed the cross-reactivity between snail and HDM tropomyosins.^{29,30} HDM immunotherapy has been reported to worsen respiratory symptoms in snail-allergic patients,³⁰ with induction of anaphylactic episodes in patients with previously mild symptoms.³¹

Conversely, the lack of neosensitization to shrimp-specific tropomyosin has also been reported in prospective studies of patients receiving SLIT HDM immunotherapy.^{32,33} These diverse observations suggest that the effect of HDM immunotherapy on induction of allergy or tolerance may depend on the level of tropomyosin in the immunotherapy extracts.

IgE sensitization to shrimp correlates with HDM sensitization

Shellfish sensitization has been shown to correlate with HDM sensitization and allergy in several different populations. A hospital-based study of atopic Singaporean children showed that 72.4% of shellfish-sensitized patients are also sensitized to HDMs.³⁴ Asthmatic children from the US also demonstrated a strong positive correlation between shrimp and HDM IgE levels.³⁵

Studies of HDM and shellfish sensitization occurring in populations with little or no exposure to either HDMs or shellfish provide evidence to suggest primary sensitization with subsequent cross-reactivity. A study of unexposed Jews who observed strict Kosher dietary rules prohibiting consumption of shellfish showed that sensitization to shrimp was related to cross-reacting tropomyosin allergens in HDMs.³⁶ They also showed that

the IgE cross-reactivity translated into clinical allergy to shrimp in some of the subjects. Reciprocally, a population-based study of young adults from Iceland where exposure to HDMs is extremely rare showed that HDM sensitization is associated with sensitization to shrimp.³⁷

Indirect *in vivo* data from a cohort of Singaporean shrimp-allergic patients revealed a subgroup of patients with mite sensitization and no evidence of shrimp sensitization, (negative skin prick tests to shrimp).⁸ Similar findings were also reported in a subgroup of patients from a Spanish study of shrimp-allergic patients living in the warm humid climate.³⁸ Taken together, these findings suggest that HDMs are the likely primary sensitizer for shrimp allergy in these patients living in warm humid climates.

To further confirm this, sera of shrimp-allergic patients were investigated with IgE inhibition studies. A Spanish study investigating patients with both HDM and shrimp allergies found a strong correlation between sIgE to shrimp and HDM tropomyosins, with almost complete inhibition of shrimp extract by a mite (*Chortoglyphus arcuatus*) on immunoblot inhibition studies, suggesting that HDMs are the primary sensitizer.³⁹ A more recent study, also from Spain, demonstrated through reciprocal inhibition assays that *Dermatophagoides pteronyssinus* is the primary sensitizer in shrimp-allergic subjects living in a humid climate, while shrimp is the primary sensitizer in shrimp-allergic subjects living in a dry climate.³⁸ These findings further substantiate the mite-shellfish link in populations living in tropical climates.

IS TROPOMYOSIN THE MOST IMPORTANT ALLERGEN IN SHELLFISH ALLERGY?

Tropomyosin remains the most thoroughly investigated and most prevalent allergen in shellfish allergy, with considerable evidence of cross-reactivity with HDMs, snails, and other molluscs. Sensitization to shellfish tropomyosins has been investigated through specific serum IgE measurement and has higher sensitivity and specificity in prediction of shellfish allergy than skin prick tests for the whole shrimp extract.⁴⁰ Arginine kinase, a new class of invertebrate pan-allergens, has been shown to be cross-reactive in a Malaysian study of patients allergic to both red crab and blue crab.⁴¹ Myosin light chain kinase (Lit v 3)⁴² and sarcoplasmic calcium-binding protein (Lit v 4)⁴³ have recently been identified as allergens in the Pacific white shrimp. In addition, α -actinin, β -actin, fructose biphosphate aldolase, and ubiquitin have been identified as allergens in the *Solenocera melanthero* (red shrimp) species.³⁸ A recent review of 40 shrimp-allergic patients from Italy showed that 10%-15% were sensitized to arginine kinase and Lit v4, suggesting that tropomyosin remains the primary allergen.⁴⁴ However, only 1 case of co-sensitization with tropomyosin was recorded, suggesting that these minor allergens remained clinically relevant. Low rates of sensitization to other shrimp allergens, such as Lit v2, Lit v3, and Lit v4, have

also been documented in a cohort of 39 shrimp-allergic patients from Singapore,⁸ indicating that in some populations, these non-tropomyosin allergens may be of less clinical importance.

CONCLUSIONS

We have reviewed the evidence to support the hypothesis that inhaled tropomyosins from HDMS are the primary sensitizer for shellfish allergy in warm and humid tropical climates. These findings open the possibility of novel therapeutic approaches with allergen immunotherapy for shellfish allergy.

The unique epidemiology of shellfish allergy in Asia raises intriguing questions: Is the high prevalence of shellfish allergy merely related to repeated exposure to inhaled HDM tropomyosins? Further studies on the temporal relationship between shellfish and HDM sensitization and the effect of genetic background on the development of shellfish allergy would provide insights into the mite-shellfish link.

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