

Tropomyosin: A panallergen that causes a worldwide allergic problem

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ABSTRACT

Background: Panallergens are proteins that take part in key processes of organisms and, therefore, are ubiquitously distributed with highly conserved sequences and structures. One class of these panallergens is composed of the tropomyosins. The highly heat-stable tropomyosins comprise the major allergens in crustaceans and mollusks, which make them important food allergens in exposed populations. Tropomyosins are responsible for a widespread immunoglobulin E cross-reactivity among allergens from different sources. Allergic tropomyosins are expressed in many species, including parasites and insects.

Methods: This panallergen class is divided, according to its capacity of induced allergic symptoms, into allergenic or nonallergenic tropomyosin. Although vertebrate tropomyosins share ~55% of sequence homology with invertebrate tropomyosins, it has been thought that the invertebrate tropomyosins would not have allergic properties. Nevertheless, in recent years, this opinion has been changed. In particular, tropomyosin has been recognized as a major allergen in many insects.

Results: A high grade of homology has been shown among tropomyosins from different species, such as crustaceans and insects, which supports the hypothesis of cross-reactivity among tropomyosins from divergent species. Moreover, the emerging habit of consuming edible insects has drawn the attention of allergists to invertebrate tropomyosin protein due to its potential allergenic risk. Nevertheless, evidence about tropomyosin involvement in clinical allergic response is still scarce and deserves more investigation.

Conclusion: This review intended to report allergic reactions associated with different tropomyosins when considering house dust mites, parasites, seafood, and insects, and to summarize our current knowledge about its cross-reactivity because this could help physicians to accurately diagnose patients with food allergy.

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Nowadays, analysis of epidemiologic data suggests that immunoglobulin E (IgE) mediated food allergies affect up to 10% of the U.S. general population¹ and the prevalence has been increasing at least in the past 2 to 3 decades.² It is well known that food allergies affect people from industrialized and/or westernized countries; they are more common in children compared with adults; and the most frequent foods account for this serious disease are peanut, tree nuts, fish, shellfish, egg, milk, wheat, soy, and seeds. During the past 2 decades, considerable progress in biochemistry and molecular biology enabled the characterization, cloning, and recombinant production of several food allergen components that became available for quantification of specific IgE (sIgE) antibodies, *viz.*, molecular diagnosis.

To understand the mechanisms of allergic sensitization, it is crucial to constantly work in the identification and characterization of novel allergens to enhance diagnostics and to develop correct strategies for personalized treatment. It is well known that, sIgE antibodies against food proteins are the principal immunologic mechanism that cause immediate-type I reactions. Worldwide, fish and seafood are among the list of the most frequent triggers of IgE-mediated food allergic reactions in both children and adults, and constitute an important and increasing health issue.³ Parvalbumins have been identified as the major fish allergen, whereas tropomyosin has been recognized as the main allergen for seafood allergy.⁴

Tropomyosin belongs to a group of proteins called panallergens. Tropomyosin has the specific characteristic of being widely distributed and is responsible for a widespread IgE cross-reactivity among allergens from different sources.⁵ Tropomyosin from different species can be distinguished into allergenic or nonallergenic forms according to its ability to induce allergic symptoms. The allergenic form is a protein that belongs to muscle of invertebrates, and it is present not only in seafood species but also, with a high degree of similarity, in cockroaches and house-dust mites (HDM) (Fig. 1), whereas the nonallergenic form is found in vertebrate species.⁶ Tropomyosin has been well studied as a crustacean

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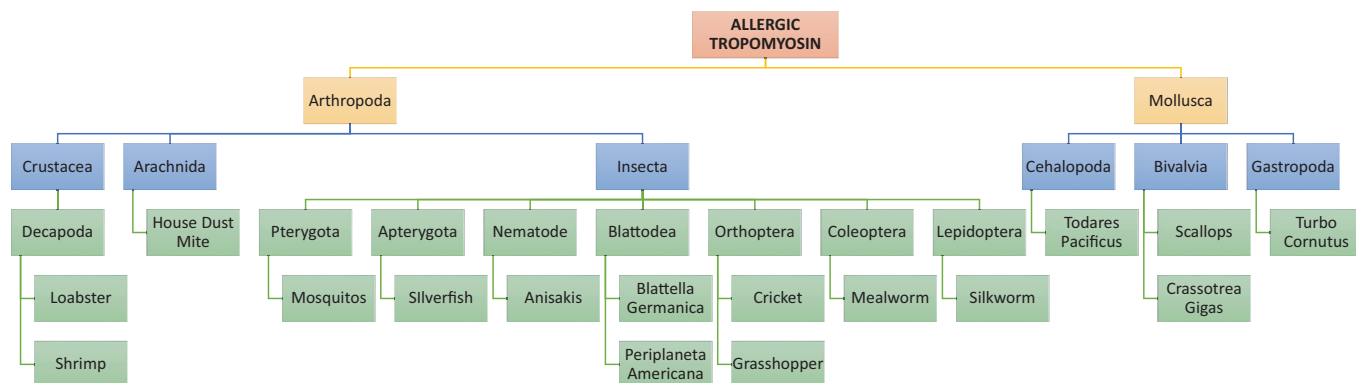


Figure 1. Taxonomy of allergic tropomyosin.

allergen, and it was first described in 1981 as a shrimp allergen.⁷ It is the principal crustacean allergen due to its abundant expression in muscle; however, in the last years, other crustacean allergens, such as arginine kinase, myosin light chain, sarcoplasmic calcium-binding protein, troponin, triose phosphate isomerase, and paramyosin, have been discovered.⁸

It is well known that allergen cross-reactivities occur when IgE antibodies, originally raised against a specific allergen, bind to identical or highly similar surface areas of another related allergen. These cross-reactivities are largely determined by secondary and tertiary structural similarities between allergens. It is a commonly held view that cross-reactivity requires a >70% sequence identity, whereas proteins that share a <50% sequence identity are rarely cross-reactive.⁹ This also implies that cross-reactive proteins have a similar 3-dimensional fold and belong to the same protein family.¹⁰ As part of an allergenicity assessment, linear sequence alignments are frequently used to compare amino acid sequences of the query proteins with sequences of known allergens to predict potential cross-reactivities. One of the main criteria to predict cross-reactivity is a search for a >35% sequence identity over a window of 80 amino acid residues between a query protein and all known allergens.¹¹

Of special interest is the high amino acid homology of 81% among tropomyosins from crustacean, HDM and cockroach, which possibly explains aero-sensitization by tropomyosins from HDM and/or cockroach as a cause of shellfish allergy in Asia, where HDM sensitization is prevalent.¹² Moreover, this panallergen is highly conserved among arthropods and mollusks, with an average homology of 61% shared between the two large groups of cross-reactive tropomyosins.¹³ Interesting, the link between tropomyosin and parasites, particularly *Anisakis simplex*, was described and tropomyosin was identified as the allergen Ani s 3.¹⁴ Nowadays, many tropomyosins have also been identified in several invertebrates such as snails, mussels, squid, termite, mealworms and others (Table 1). This review intended to emphasize the importance of understanding the cross-reactivities among different allergen

sources to establish sensitization profiles of patients, predict outcomes for persistent allergies, avoid unnecessary allergen challenges, and personalize allergy treatment.

TROPOMYOSIN IN HDM AND SEAFOOD

The first studies on tropomyosin were conducted in HDM.¹⁵ Indeed, Thomas *et al.*¹⁶ analyzed different species of HDM specifically, the Acaridae, Glycophagidae, and Pyroglyphidae families, and identified 19 groups, each of them corresponded to a specific protein. Tropomyosin was identified in the groups of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, *Lepidoglyphus destructor*, and *Blomia tropicalis*. In 1999, Reese *et al.*¹⁷ demonstrated that tropomyosin was not only a major allergen in HDM but also in cockroach, lobster, squid, and other mollusks. One of the most well-studied shellfish allergens is shrimp tropomyosin, which has been cloned as a recombinant allergen, *viz.*, Pen a 1 from *Penaeus aztecus*.¹⁸ Sensitization to shrimp tropomyosin ranged from 23 to 83% of the subjects, depending on the geographic populations, whereas IgE against whole shrimp extract was present in 94% of the subjects¹²; suggesting that there are other minor shellfish allergens.⁸

López-Matas *et al.*¹⁹ evaluated the relevance of tropomyosin in patients with mite and shellfish sensitivity by using skin-prick testing, which showed that the prevalence of tropomyosin sensitization was low in patients who were mite sensitized (2.7%), higher in patients with shellfish allergy (28.6%), and with the highest prevalence in patients who were sensitized to both mite and shellfish allergens (38.5%). In a recent Italian multicenter study,²⁰ shrimp allergy seemed to occur uniquely in association with hypersensitivity to HDM allergens, and tropomyosin is the main shrimp allergen but not the only one, at least in that geographical area. In addition, monosensitization to HDM seemed to represent a risk factor for the development of shrimp allergy among Italian patients with HDM allergy.²⁰ Leung *et al.*²¹ identified a protein of 38 kD, similar to shrimp tropomyosin, in a number of

Table 1 Summary of the main tropomyosin allergens from the WHO-IUIS Database

Species	Allergen	Biochemical Name	Molecular Weight, kDa*	Route of Allergen Exposure
<i>Aedes aegypti</i> (Yellow fever mosquito)	Aed a 10	Tropomyosin	32	Airway
<i>Anisakis simplex</i> (herring worm)	Ani s 3	Tropomyosin	41	Food
<i>Ascaris lumbricoides</i> (common roundworm)	Asc 1 3	Tropomyosin	40	Food
<i>Blattella germanica</i> (German cockroach)	Bla g 7	Tropomyosin	33	Airway
<i>Blomia tropicalis</i> (storage mite)	Blo t 10	Tropomyosin	33	Airway
<i>Charybdis feriatus</i> (crab)	Cha f 1	Tropomyosin	34	Food
<i>Chironomus kiiensis</i> (midge)	Chi k 10	Tropomyosin	32.5	Injection
<i>Chortoglyphus arcuatus</i> (storage mite)	Cho a 10	Tropomyosin	42	Airway
<i>Coptotermes formosanus</i> (Formosan subterranean termite)	Copt f 7	Tropomyosin	35.4	Airway
<i>Crangon crangon</i> (North Sea shrimp)	Cra c 1	Tropomyosin	~38	Food
<i>Crassostrea gigas</i> (Pacific oyster)	Cra g 1	Tropomyosin	38	Food
<i>Dermatophagoides farinae</i> (American house-dust mite)	Der f 10	Tropomyosin	37	Airway
<i>Dermatophagoides pteronyssinus</i> (European house dust mite)	Der p 10	Tropomyosin	36	Airway
<i>Exopalaemon modestus</i> (white legged freshwater shrimp)	Exo m 1	Tropomyosin	38	Food
<i>Haliotis laevis</i> × <i>Haliotis rubra</i> (jade tiger abalone)	Hal l 1	Tropomyosin	33.4	Food
<i>Helix aspersa</i> (brown garden snail)	Hel as 1	Tropomyosin	36	Food
<i>Homarus americanus</i> (American lobster)	Hom a 1	Tropomyosin	34	Food
<i>Lepidoglyphus destructor</i> (storage mite)	Lep d 10	Tropomyosin	40	Airway
<i>Lepisma saccharina</i> (silverfish)	Lep s 1	Tropomyosin	36	Airway
<i>Litopenaeus vannamei</i> (white shrimp)	Lit v 1	Tropomyosin	36	Food
<i>Macrobrachium rosenbergii</i> (giant freshwater prawn)	Mac r 1	Tropomyosin	37	Food
<i>Melicertus latisulcatus</i> (king prawn)	Mel l 1	Tropomyosin	38	Food
<i>Metapenaeus ensis</i> (shrimp)	Met e 1	Tropomyosin	34	Food
<i>Oreochromis mossambicus</i> (Mozambique tilapia)	Ore m 4	Tropomyosin	33	Food
<i>Pandalus borealis</i> (northern shrimp)	Pan b 1	Tropomyosin	37	Food
<i>Pangasianodon hypophthalmus</i> (striped catfish)	Pan h 4	Tropomyosin	35	Food
<i>Panulirus stimpsoni</i> (spiny lobster)	Pan s 1	Tropomyosin	34	Food
<i>Penaeus aztecus</i> (brown shrimp)	Pen a 1	Tropomyosin	36	Food
<i>Penaeus indicus</i> (shrimp)	Pen i 1	Tropomyosin	34	Food
<i>Penaeus monodon</i> (black tiger shrimp)	Pen m 1	Tropomyosin	38	Food
<i>Periplaneta americana</i> (American cockroach)	Per a 7	Tropomyosin	33	Airway
<i>Portunus pelagicus</i> (blue swimmer crab)	Por p 1	Tropomyosin	39	Food
<i>Procambarus clarkii</i> (red swamp crayfish)	Pro c 1	Tropomyosin	36	Food
<i>Saccostrea glomerata</i> (Sydney rock oyster)	Sac g 1	Tropomyosin	38	Food
<i>Salmo salar</i> (Atlantic salmon)	Sal s 4	Tropomyosin	37	Food
<i>Scylla paramamosain</i> (mud crab)	Scy p 1	Tropomyosin	38	Food
<i>Todarodes pacificus</i> (Japanese flying squid)	Tod p 1	Tropomyosin	38	Food
<i>Tyrophagus putrescentiae</i> (storage mite)	Tyr p 10	Tropomyosin	33	Airway

*SDS-PAGE (sodium dodecyl sulphate–polyacrylamide gel electrophoresis).

mollusks and Cephalopoda, which suggests that this muscle protein is the major cross-reactive allergen in these species.

Moreover, an interesting study found similar characteristics in the function and structure of tropomyosin in shrimp, lobster, crab, mollusk, *Anisakis*, mite, and insects, and provided the molecular basis for the cross-reactivity among these species.²² It is well known that tropomyosin can cause allergic reactions by inhalation or ingestion

(Table 1), which, in some cases, becomes an occupational disease. An example of this is the report of occupational asthma in a seafood restaurant worker who developed urticaria and asthma after being in contact with shrimp and scallops.²³ Another case is of a cook's mate working³ in an Austrian restaurant who reported acutely occurring urticarial skin lesions after processing and cooking squid. Both patients^{23,3} were diagnosed with a clinically and occupationally type I allergy to tropomyosin with

cross-reaction with other invertebrates. In a cohort of 77 pediatric patients with fish allergy²⁴ the allergen repertoire of two highly farmed fish species, salmon and catfish, was described. Interestingly, IgE binding to fish tropomyosins and triosephosphate isomerase was demonstrated for the first time. Thus, tropomyosins, in addition to parvalbumins, should be considered for improved fish allergy diagnostics.²⁴

TROPOMYOSIN AND PARASITES

The relationship of parasite infections and the promotion or protection from allergy and asthma is controversial. Currently, >1.5 billion people are infected with parasites worldwide, and *Ascaris lumbricoides* is the most frequent soil-transmitted helminth.²⁵ Tropomyosin is known as a clinically relevant allergen in *A. lumbricoides*, and it has been identified as the Asc 1 3 allergen.²⁶ A study done with a Brazilian patient with asthma and/or rhinitis suggests that IgE responses to tropomyosin from *A. lumbricoides* may enhance reactivity to homologous allergens (HDM, cockroach) on exposure by inhalation or ingestion, which promote allergic reactions and asthma, or increase the severity of these clinical conditions.²⁷ Another parasite that can induce allergic reactions is the raw seafood *Anisakis*. Several allergens have been described, including tropomyosin. Nieuwenhuizen and Lopata²⁸ described 12 allergens from the *Anisakis* parasite and identified tropomyosin as Ani s 3, an allergen of 39 kDa with controversial clinical relevance. Ani s 3 sensitization has been detected in many countries, with a prevalence of ~4% in the Mediterranean area.²⁹

Nevertheless, the role of tropomyosin in allergy to *Anisakis* is still debated because some investigators³⁰ have described a different pattern of sensitization in patients who did or did not present with symptoms. It seems that patients who were sensitized to *Anisakis* tropomyosin were often asymptomatic, whereas those who presented with symptoms were not. However, *Anisakis* tropomyosin may mime heat-stable shrimp tropomyosin, recognized as an important seafood allergen, which elicits symptoms of food allergy after the ingestion of cooked seafood.³⁰ In a recent study, *Anisakis pegreffii* tropomyosin was compared with that of *A. simplex* and crustaceans, and it was demonstrated that *A. pegreffii* tropomyosin shares one or more epitopes with crustacean tropomyosin, which lacked a specific antigenic determinant defined by the antitropomyosin monoclonal antibody in crustaceans.³¹ It should be noted that *A. pegreffii* sensitization showed a higher prevalence than did the *A. simplex*, especially in the Mediterranean area.³² A Spanish study conducted in patients with urticaria associated with ascarid infections revealed *Anisakis* tropomyosin as a very potent discriminative urticaria marker in this geographical region.³³

TROPOMYOSIN AND INSECTS

With an increasing world population and demand for sustainable food sources, insects are a promising alternative source of protein. Although insects have never been considered as a food source in Western countries, for today's consumers who are looking for nutrient-rich and ecologically sustainable sources for food, edible insects can be a perfect candidate.³⁴ Because insects will be consumed more frequently in the future, it is expected that the prevalence of insect food allergy will increase due to its rich protein content and potential allergenic risk. de Gier and Verhoeckx³⁵ reported that insect tropomyosin, but also other insect proteins, may be involved in allergic reactions and in cross-reactivity with other allergenic species. This cross-reactivity could be explained by the strong homology between the tropomyosin of different allergens. In fact, tropomyosin of mealworm has a high percent homology with tropomyosin of midge (91.17%), American cockroach (>90%), and shrimp (>85%).

Interesting, tropomyosin has been detected in the extract of insects, such as mealworm, cricket, grasshopper, wax moth, and black soldier fly, and cross-reacted with sIgE of patients with shrimp allergy.³⁶ Also, patients with HDM and crustacean allergy may react to foods that contain yellow mealworm proteins.³⁷ Ribeiro *et al.*³⁸ showed that yellow mealworm tropomyosin as well as other common food protein allergens, *e.g.*, crustacean tropomyosin, also maintains its allergenic characteristics after thermal processing and *in vitro* denaturation. It should be noted that most of the allergic reactions to insects occurred in Asian countries, where silkworm pupae are widely consumed. Based on this observation, a study showed that silkworm pupa tropomyosin had a large homology with previous known allergenic tropomyosin (~70–90%), particularly Chi k 10, Per a 7, Bla g 7, Pen a 1, and Hom a 1. Furthermore, a significant proportion of the sera from patients with allergy to silkworm pupa reacted with recombinant tropomyosin and, specifically, with shrimp and crab tropomyosin.³⁹

Other edible mealworm species, such as *Tenebrio molitor*, *Zophobas atratus*, and *Alphitobius diaperinus*, were analyzed and studied for their cross-reactivity with other species.⁴⁰ The sIgE from patients with crustaceans or HDM allergy showed cross-reactivity to mealworm tropomyosin or α -amylase, hexamerin-1 β precursor and muscle myosin. In particular, the tropomyosins identified in mealworm species showed 60–90% sequence identity to tropomyosin from other insect species and crustaceans. Results obtained with mealworm tropomyosin indicated that 100% of protein segments of ≥ 80 amino acids showed $\geq 35\%$ identity to known allergenic forms of tropomyosin. Recently, a Japanese study⁴¹ assessed the risk of allergic reactions associated with cricket (*Gryllus bimaculatus*) consumption in individuals with crustacean allergy. They found a strong correlation

between shrimp- and *Gryllus*-sIgE response and determined that a protein of ~40 kDa reacted with shrimp sIgE positive sera when using ImmunoCAP (Thermo-fisher, Japan) test. Further analysis identified tropomyosin as the major allergen in shrimp and *Gryllus*.⁴¹

As an intriguing hypothesis, it has been proposed that there is a potential cross-reaction between Formosan termite (*Coptotermes formosanus*) proteins and cockroach allergens. A study showed that peptides from whole termite extract were matched to those of the tropomyosin cockroach (Bla g 7) and other proteins. Several termite proteins, including tropomyosin orthologs of Bla g 3 and Bla g 7, were shown to cross-react with cockroach allergens.⁴² The investigators described that the *C. formosanus* tropomyosin was identical to tropomyosin from American (99% identify with Per a 7) and German (98% identify with Bla g 7) cockroaches. In addition, they demonstrated that a recombinant termite tropomyosin cross-reacted with IgE from patients with cockroach and shrimp allergy.⁴³ Two cases of anaphylaxis due to grasshopper allergy⁴⁴ in polysensitized patients to HDM, cockroach, and crustaceans were described. Both patients had a clinical history of urticaria and angioedema after the ingestion of crustaceans and onset of an anaphylactic reaction after the ingestion of chapulines and grasshopper.⁴⁴ Immunoblot analysis detected a 30-kDa protein in chapulines and grasshopper species, also recognized as tropomyosin.⁴⁴

TROPOMYOSIN AND MOSQUITOES

Mosquitoes are distributed worldwide and have many IgE-binding proteins, some of which cross-react with allergens from other arthropods. Some years ago, Cantillo *et al.*⁴⁵ wanted to evaluate the presence of tropomyosin in *Aedes aegypti* and found that natural mosquito tropomyosin, specifically variants Aed a 10.0101 and Aed a 10.0201, reacted with 33% of sera from patients with asthma or allergy rhinitis and with polyclonal antishrimp tropomyosin antibodies, which suggests that tropomyosin may be involved in the cross-reactivity between these two allergens. Interestingly, they described the existence of a different grade of cross-reactivity between tropomyosin from different arthropods, with the higher cross-reactivity between natural mosquito tropomyosin and Blo t 10, Der p 10 and Lit v 1, which suggests that cross-reactivity may have a variable impact when different arthropods are considered.

The complete allergenoma of the *A. aegypti* mosquito has been characterized by immunoblot by using sera from 15 patients sensitized to mosquito.⁴⁶ Tropomyosin reacted with patients' IgE, and this reaction was inhibited when serum was preincubated with rAed a 10.0101. Moreover, tropomyosin, together with Heat Shock Protein 70 Kd, were considered major allergens, which react with > 50% of sera. Compelling experimental

evidence demonstrated the cross-reactivity between Der p 10 and Aed a 10.01 allergens at both humoral and cellular levels.⁴⁷ These findings highlight the presence of significant cross-reactivity between mosquitoes and other arthropods, and this may be explained by tropomyosin.

Few studies have been conducted on *Aedes communis* (Ac) specie, and no Ac molecule has been registered to date in the World Health Organization /International Union Of Immunological Societies Allergen Nomenclature Sub-committee (WHO/IUIS) data base.⁴⁸ A multicenter Italian study⁴⁹ enrolled 205 patients and studied for cutaneous or IgE reactivity to Ac, *Blattella germanica*, *Penaeus monodon*, and *D. pteronyssinus*. Extract and molecular IgE reactivity to bees, wasps, hornets, and yellow jacket venoms were also studied. A strict relationship⁴⁹ between Ac and *D. pteronyssinus*, *B. germanica*, *P. monodon*, or *Apis mellifera* reactivity on skin-prick tests was observed; however, no cross-reactive allergenic protein could be identified. Nevertheless, evidence about mosquito tropomyosin involvement in a clinical allergic response is still scarce and deserves more investigation.

CONCLUSION

The importance of tropomyosin as a panallergen has been known for many years. Several studies investigated tropomyosin in different species, such as HDM, shrimp, or mollusk, and explained the allergic cross-reactions that occurred in patients who were sensitized. The molecular analysis of tropomyosin, achieved only in recent years, has facilitated the isolation of allergens and their recognition. It should be noted that tropomyosin shares a high homology (up to 98%) among crustacean species, whereas the amino acid sequence identity between crustacean and mollusk tropomyosins is lower (~65%). Recently, the recombinant tropomyosin from *P. aztecus* (rPen a 1) has become commercially available for molecular diagnostics, which provides a useful diagnostic tool in comparison with the whole-shrimp extract.

Nevertheless, in recent years, the opinion that tropomyosin of invertebrates does not have allergic properties has been revised. Recent studies^{15,16,18,19,20} showed that insect tropomyosin has similar characteristics and a high homology structure to that of HDM and shrimps. Due to globalization, the ingestion of insects, such as silkworm and cricket, has increased in Western European countries and, as a consequence, so have allergic reactions. Furthermore, the exposure to insects such as termites, worm, cricket, and grasshopper may act as a primary sensitizing agent in infested areas. Sokol⁴⁴ reported an increased trend in the ingestion of insects, such as grasshopper and chapulines not only in the United States and Mexico but also in west Europe. Based on the reported data, the increase in the

ingestion of these novel foods could be associated with an increase in allergic reactions.

Future Perspectives

To date, interesting discoveries of the presence of tropomyosin have emerged in recent years, particularly on mosquito species. These findings highlight the need of considering new sources of tropomyosin allergens as a possible cause of sensitization or cross-reactivity reactions in patients who are sensitive to HDM, crustaceans, or parasites. Knowledge gained on identifying and defining the immunomolecular and cross-reactivity features of tropomyosin panallergen have gradually translated into the design of new diagnostic and treatment options for allergy. A molecular-based allergy diagnosis should be implemented into practice routine to improve patient management and establish the risk assessment of novel foods for personalized patient treatment. The key message is that the information about potential cross-reactivity is important for allergy diagnostics, the safety, and efficacy of allergy vaccines and to determine the risk assessment of novel foods.

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