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Food allergen families common to different arthropods (mites, insects, crustaceans), mollusks and nematods: Cross-reactivity and potential cross-allergenicity

Les grandes familles d'allergènes communes aux arthropodes (acariens, insectes, crustacés), mollusques et nématodes : réactions croisées et allergies croisées

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Abstract

Allergies to animal foods essentially result from the consumption of shellfish, including crustaceans and mollusks, and even edible insects traditionally eaten in different countries around the world. In all of these countries, the statistical data collected during the last decade point out the consumption of shellfish products as a likely cause of the most severe allergic reactions associated to animal-based foods. The allergens responsible for the shellfish allergies mainly consist of pan-allergens belonging to a limited number of protein families, widely distributed in mites, crustaceans, insects, mollusks and nematods. Major allergens are represented by muscle proteins (tropomyosin, troponin C, myosin, sarcoplasmic calcium-binding protein) and enzymes (α -amylase, arginine kinase, glutathione S-transferase, serine protease, triosephosphate isomerase), associated to other functional (hemocyanin, hexamerin) and structural (tubulin) proteins. Most of these pan-allergens exhibit quite well conserved amino acid sequences and readily superposable three-dimensional structures. Although they remain closely phylogenetically-related, they fall into distinct groups more or less distantly related within the phylogenetic trees, depending of the proteins. In this respect, insect tropomyosins fall into two separate groups closely related to mite and crustacean tropomyosin groups, respectively, whereas the mollusk tropomyosin group deviates from all other tropomyosin groups. Alpha-amylase and arginine kinase groups of insects and crustaceans remain closely related but are much more distant from the corresponding groups of mite, mollusk and nematod enzymes. Overall, allergens from insects and crustaceans feel closer whereas mollusks allergens clearly differ from all the other allergen groups. According to these phylogenetic relationships, the IgE-binding cross-reactivities frequently reported between these allergens of different origin could trigger some unexpected crossed allergic reactions in susceptible individuals. In this respect, the consumption of edible insects by shellfish allergic patients should be avoided.

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Keywords: Pan-allergen; Arthropods; Mites; Insects; Crustaceans; Mollusks; Nematods; IgE-binding cross-reactivity; Crossed allergies; Phylogenetic relationships

Résumé

Les allergies alimentaires causées par les aliments d'origine animale proviennent essentiellement de la consommation de crustacés et de mollusques, voire d'insectes comestibles qui commencent à s'introduire sur le marché européen des produits alimentaires. Depuis plusieurs années, les statistiques établies par le CICBAA (centre d'investigations cliniques et biologiques en allergologie alimentaire) soulignent l'importance des crustacés et des mollusques dans la survenue de réactions systémiques sévères liées à l'alimentation. L'allergénicité de ces aliments dépend de quelques familles d'allergènes communes aux arthropodes, aux mollusques et aux nématodes, qu'il est nécessaire de bien identifier pour diagnostiquer les allergies dont elles sont responsables. Ces allergènes correspondent à des protéines musculaires (tropomyosine, troponine C, myosine, actine, protéine sarcoplasmique fixant le calcium ou SCBP), des enzymes variées (α -amylase, arginine-kinase AK, glutathion S-transférase GST, trypsine, protéase à sérine, triosephosphate isomérase TPI) et des protéines circulantes (hemocyanine, hexamérine) ou structurales (tubulines).

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La plupart de ces protéines sont ubiquitaires et possèdent des séquences et surtout des structures très conservées et parfaitement superposables. Elles se répartissent dans les arbres phylogénétiques en groupes distincts dont les affinités restent élevées mais peuvent varier considérablement selon les allergènes. Ainsi, les tropomyosines des mollusques s'écartent nettement de celles des autres groupes et les tropomyosines d'insectes se répartissent en deux groupes dont un est proche des tropomyosines des acariens, l'autre des tropomyosines des crustacés. Les α -amylases et les arginine kinases des insectes et des crustacés sont très proches et toujours plus éloignées de celles des acariens, des mollusques et des nématodes. Globalement, les allergènes des insectes et des crustacés paraissent les plus proches tandis que les allergènes des mollusques s'écartent le plus des allergènes des autres groupes. L'existence, souvent rapportée, de réactions croisées entre ces différents groupes d'allergènes laisse présager des possibilités d'allergies croisées entre les acariens, les crustacés, les insectes, les mollusques et les nématodes. En particulier, le risque de réaction allergique associé à la consommation d'insectes comestibles (entomophagie) par des patients allergiques aux crustacés doit être envisagé.

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Mots clés : Pan-allergènes ; Arthropodes ; Acariens ; Insectes ; Crustacés ; Mollusques ; Nématodes ; Réactions croisées ; Allergies croisées ; Affinités phylogénétiques

1. Introduction

Among the food allergic manifestations due to allergens of animal origin, allergens from invertebrates and, especially from edible shellfishes (crustaceans and mollusks), occupy a prominent place, followed by mites (pancake oral anaphylaxis), insects (edible insects) and nematods (anisakis and parasitic worms). Anaphylaxis to edible crustaceans like shrimps, crabs of lobsters, consist of the most widespread allergic reactions to seafoods, followed by oysters, squids, poulp and mussels, other currently consumed seafood products. For a long time, some IgE-binding cross-reactivity has been reported between seafoods of different origin, and some IgE-binding allergens belonging to a few protein families have been recognized as pan-allergens, responsible for this cross-reactivity. Early on, proteins involved in the muscle contraction process (tropomyosin, troponin C, sarcoplasmic calcium-binding protein or SCBP) and various enzymes (arginine kinase, α -amylase, triosephosphate isomerase or TPI) have been identified as being the main pan-allergens in invertebrates, including crustaceans, mollusks, mites, insects and nematods. Other proteins with different functions, like hemocyanin, hexamerin and tubulins, have been also recognized as pan-allergens in invertebrates. Usually, all of these pan-allergen proteins possess extremely conserved three-dimensional structures and exhibit rather closely-related amino acid sequences. Here, we review the pan-allergens proteins of invertebrates with respect to their distribution, phylogenetic relationships and IgE-binding cross-reactivity.

2. Pan-allergens in invertebrates

To date, a huge number of IgE-binding allergens have been characterized in the main groups of invertebrates including mites, crustaceans, arachnids, insects, mollusks and nematods. Most of them consist of pan-allergens widespread in all the invertebrate groups (Table 1). Pan-allergens from different shellfish (shrimps, prawns, crabs, lobsters), mollusk (squids, oysters, octopus, mussels) and insect (mites, cockroaches) organisms, have been particularly investigated due to their capacity to trigger food or contact allergic reactions in susceptible individuals. The invertebrate pan-allergen proteins belong to a limited number of protein families involved in various functional (muscle

contraction proteins, enzymes, storage proteins) and structural (actin, tubulins) activities [1].

2.1. Tropomyosin

Tropomyosin, a double-stranded α -helicoidal actin-binding protein which regulates the interaction actin-myosin necessary to the muscle contraction, is by far one of the most prominent invertebrate allergen. Tropomyosin has been identified as being the major pan-allergen occurring in edible crustaceans [2–4] and mollusks [5–7]. It also occurs in mites [8] and other insects [9,10] as a very conserved cross-reactive pan-allergen. However, tropomyosins Bla g 7 and Per a 7 of the cockroaches apparently represents minor allergens in the cockroach extracts [11]. In addition, tropomyosin was identified as a major allergens in nematods, e.g., Ani s 3 of the fish parasitic worm *Anisakis simplex* [12], and as a cross-reacting pan-allergen common to ascaris worms and mites [13].

Troponin C, another protein associated to muscle contraction, has been reported as a relevant cross-reacting pan-allergen in mites (Tyr p 24 of *Tyrophagus putrescentiae*), crustaceans (Cra c 6 of *Crangon crangon*, Hom a 6 of *Homarus americanus*, Pen m 6 of *Penaeus monodon*) [14,15], insects (*Bombyx*, *Drosophila*) [16], and nematods (*Anisakis*) [17]. The sarcoplasmic calcium-binding protein (SCBP) also occurs as a pan-allergen, essentially in crustaceans (Cra c 4 of *Crangon crangon*, Lit v 4 of *Litopenaeus vannamei*, Hom a 4 of *Homarus americanus*, Scy p 4 of *Scylla paramamosain*) [18–20] and insects (Aed a 5 of *Aedes aegypti*, Aed al 5 of *A. albopictus*, Cul q 5 of *Culex quinquefasciatus*) [21] but its occurrence in mollusks (oyster, octopus) has been also reported [22].

2.2. Pan-allergens with enzymatic activities

Arginine kinase (AK), α -amylase and glutathione S-transferase (GST), have been identified as being among the most relevant enzymatic pan-allergens occurring in shellfishes [23–27], insects [28,29], and nematods [AK acces. KX_965683.1, Gonzalez-Fernandez et al., unpublished]. Owing to their specific enzymatic activities, all of these enzymes exhibit extremely conserved three-dimensional structures and are readily superimposed irrespective of their origin (Fig. 1).

Table 1

List of some allergens common to arthropods (dust mites, crustaceans, insects), mollusks and nematods (according to the IUIS nomenclature and Allergome.org).

Type of proteins	Proteins	Allergens	Occurrence
Muscle protein	Tropomyosin	Ale o 10, Blo t 10, Cho a 10, Der f 10, Der p 10, Lep d 10, Tyr p 10,	Mites
		Cha f 1, Cra c 1, Hom a 1, Lit v 1, Met e 1, Pan b 1, Pan s 1, Pen a 1, Pen i 1, Pen m 1, Por p 1, Pro c 1, Aed a 10, Ano g 7, Bla g 7, Bomb m 7, Per a 7, Chi k 10, Copt f 7, Lep s 1,	Crustaceans Insects
		Ana br 1, Cra g 1, Hal l 1, Hel as 1, Mac r 1, Mel l 1, Sac g 1, Tod p 1, Ani s 3, Asc l 3,	Mollusks Nematods
		Tyr p 34,	Mites
		Cra c 6, Hom a 6, Pen m 6, Pon l 7,	Crustaceans
	Troponin C	Bla g 6, Per a 6,	Insects
		Der f 26,	Mites
		Art fr 5, Cra c 5, Hom a 3, Lit v 3, Pen m 3, Pro c 5,	Crustaceans
		Bla g 8,	Insects
		Der f 17,	Mites
	Myosin	Cra c 4, Lit v 4, Pen m 4, Pon l 4, Scy p 4,	Crustaceans
	SCBP		
Enzymes	alpha-amylase	Blo t 4, Der f 4, Der p 4, Eur m 4, Tyr p 4	Mites
		Bla g 11, Per a 11, Sim vi 4	Insects
	Arginine kinase	Der f 20, Der p 20,	Mites
		Cra c 2, Lit v 2, Pen m 2, Pro c 2, Scy p 2,	Crustaceans
	Chitinase	Bla g 9, Bomb m 1, Per a 9, Plo i 1,	Insects
		Blo t 15, Blo t 18, Der f 15, Der f 18, Der p 15, Der p 18	Mites
	GST	Per a 12,	Insects
		Blo t 8, Der f 8, Der p 8,	Mites
	Cysteine protease	Bla g 5, Per a 5,	Insects
		Asc l 13, Asc s 13,	Nematods
	Serine protease	Blo t 1, Der f 1, Der m 1, Der p 1, Eur m 1,	Mites
		Ani s 4	Nematods
	TPI	Ale o 9, Blo t 9, Der f 9, Der f 25, Der p 9	Mites
		Api m 7, Per a 10, Pol d 4, Sim vi 2	Insects
	Trypsin	Ani s 1	Nematods
		Blo t 13, Der f 25, Der p 3, Eur m 3, Tyr p 3,	Mites
		Arc s 8, Cra c 8, pen m 8, Pro c 8, Scy p 8,	Crustaceans
		Bla g TPI,	Insects
		Aca s 3, Blo t 3, Der f 3, Der p 3, Eur m 3, Tyr p 3,	Mites
		Bla g 10	Insects
Other proteins	FABP (Lipocalin)	Aca s 13, Arg r 1, Blo t 13, Der f 13, Der p 13, Lep d 13, Tyr p 13	Mites
		Bla g 4, Per a 4, Tria t 1	Insects
	Hemocyanin	Lit v hemo, Mac r hemo, Pan b hemo	Crustaceans
		Bla g 3, Per a3	Insects
	Tubulin	Der f 28, Tyr p 28	Mites
		Aed a 8, Vesp a HSP70	Insects
		Der f 33, Lep d 33, Tyr p 33	Mites
		Aed ae tub, Aed alb tub, Ano g tub, Bomb m tub, Cul quin tub	Insects

FABP: Fatty acid-binding protein; GST: Glutathione S-transferase; HSP70: Heat-shock protein 70; SCBP: Sarcoplasmic calcium-binding protein; TPI: Triose-phosphate isomerase.

Recently, these three enzymes have been shown to occur in yellow mealworm (*Tenebrio molitor*) and other insect species, as major pan-allergens in the allergen repertoire of edible insects [30–34].

Other conserved proteins with enzymatic functions like triosephosphate isomerase (TPI), enolase, trypsin and serine protease, have been identified as pan-allergens widely distributed in mites, shellfishes, insects and nematods (Table 1).

2.3. Pan-allergens with a structural function

Actin and tubulins fall within the category of pan-allergens with a structural function as components of the cytoskeleton of invertebrate cells. However, in spite of their widespread distribution in all groups of invertebrates, they only consist of mite pan-allergens like Der f 33 (tubulin) and Der f 30 (actin) pan-allergens of *Dermatophagoides farinae* [35].

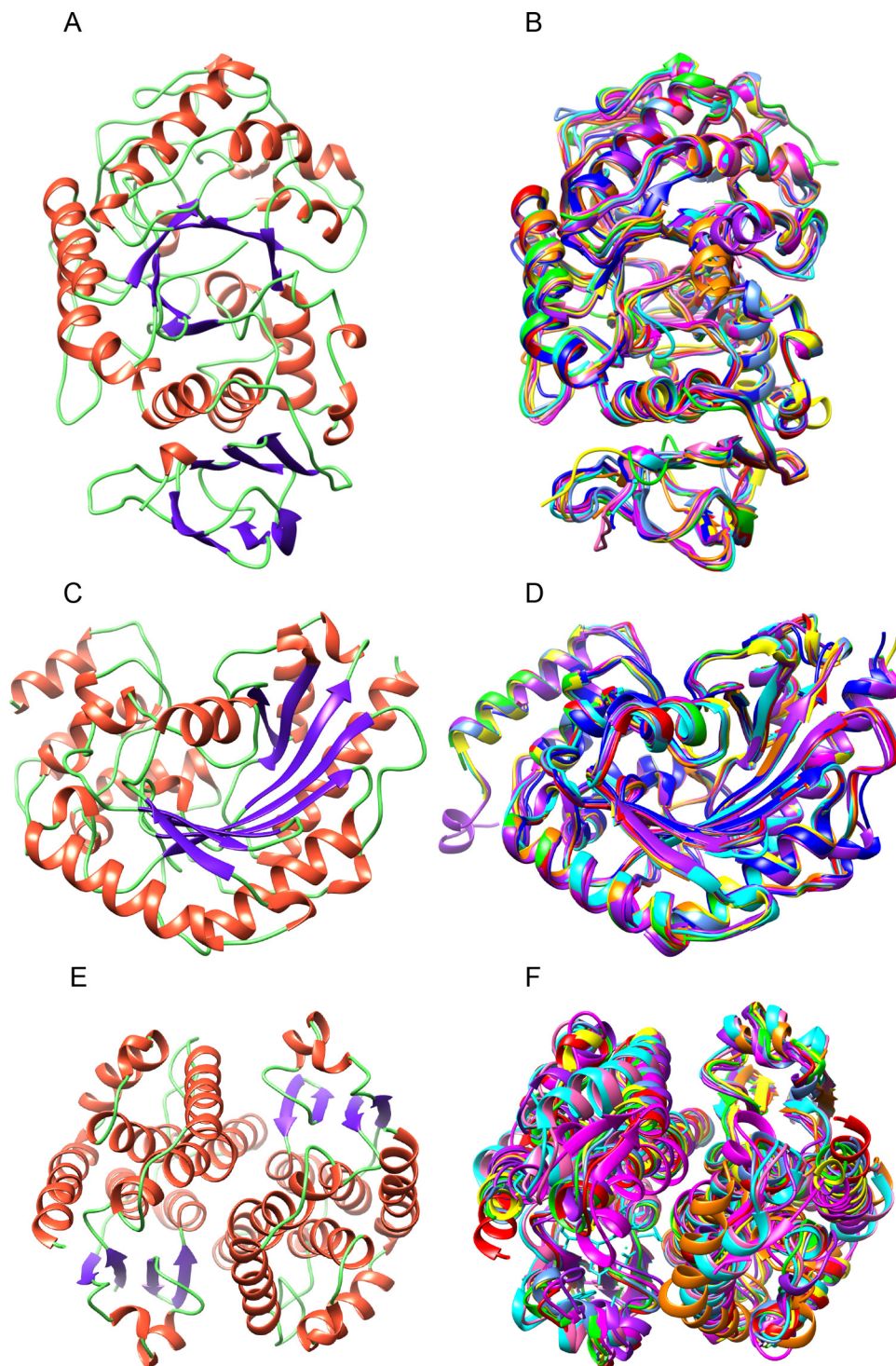


Fig. 1. A. Three-dimensional model built up for the yellow mealworm (*Tenebrio molitor*) α-amylase, showing the α8β8 TIM-barrel made of a central crown of eight β-strands linked by short loops to a peripheral crown of eight α-helices. B. Superposition of the α-amylase three-dimensional models of *Tenebrio molitor* (colored red), *Blomia tropicalis* Blo t 4 (colored pale blue), *Dermatophagoides pteronyssinus* Der p 4 (colored yellow), *Bombyx mori* (colored green), *Hermetia illucens* (colored purple), *Musca domestica* (colored orange), *Apis mellifera* (colored deep blue), *Lithopenaeus vannamei* (colored magenta), *Marsupenaeus japonicus* (colored cyan), *Crassostrea gigas* (colored pink). C. Three-dimensional model built up for the arginine-kinase (AK) of the shrimp *Penaeus monodon*, made of a curved antiparallel β-sheet, surrounded by α-helices. D. Superposition of the arginine kinase three-dimensional models of *Penaeus monodon* (colored red), *Scylla paramamosain* (colored yellow), *Crangon crangon* (colored magenta), *Aleuroglyphus ovatus* (colored pale blue), *Glycyphagus domesticus* (colored green), *Bombyx mori* (colored purple), *Locusta migratoria* (colored cyan), *Tenebrio molitor* (colored orange), *Crassostrea gigas* (colored pink), *Octopus vulgaris* (colored deep blue). E. Three-dimensional model built for the glutathione S-transferase (GST) of *Blattella germanica* Bla g 5, made of two symmetrically associated domains, each consisting of a central β-sheet surrounded by α-helices. F. Superposition of the GST three-dimensional models of *Blattella germanica* (colored red), *Tenebrio molitor* (colored pale blue), *Galleria mellonella* (colored green), *Apis mellifera* (colored yellow), *Locusta migratoria* (colored purple), *Musca domestica* (colored magenta), *Bombyx mori* [PDB code 3VUR] (colored orange), *Ascaris lumbricoides* [PDB code 4Q5F] (colored cyan), *Ascaris suum* (colored pink).

Other functional protein components of invertebrate like the circulating copper-containing hemocyanins [36,37] and the closely-related hexamerins [38], have been also identified as potential pan-allergens. The storage protein vitellogenin was also characterized as a conserved pan-allergens of mites (Ale o 14 of *Aleuroglyphus ovatus*, Blo t 14 of *Blomia tropicalis*, Der f 14 of *Dermatophagoides farinae*, Der p 15 of *D. pteronyssinus*), crustaceans [39], and insects (honeybee, cockroach, wasp). Recently, TPI and filamin C, an actin-binding protein, from the freshwater crayfish *Procambarus clarkii*, were shown to share common epitopes that apparently accounts for their IgE-binding cross-reactivity [40]. Filamin, which also occurs in mites (*Ixodes scapularis*, *Euroglyphus maynei*), insects (*Bombyx mori*, *Aedes aegypti*, *Anopheles gambiae*, *Musca domestica*), mollusks (*Crassostrea gigas*, *Octopus bimaculoides*) and nematods (*Ancylostoma duodenale*, *Trichinella spiralis*), apparently consists of another cross-reacting pan-allergen widely distributed in invertebrates, except for crustaceans.

3. Phylogenetic relationships of invertebrate pan-allergens

Phylogenetic trees built from the multiple alignment of amino acid sequences of the invertebrate pan-allergens reflect the high degree of conservation of these proteins across the different groups of mites, crustaceans, insects, mollusks and nematods (Figs. 2–4). However, depending on the pan-allergens, phylogenetic relationships are more or less pronounced inside a group or between the groups. As an example, tropomyosins of different origin are clustered in two discrete groups, a first group closely-related to the tropomyosins from crustaceans, and a second group closer to the tropomyosins of mites (Fig. 4). In contrast, tropomyosins from mollusks form an homogeneous group, apart from the other tropomyosin groups. Looking at the phylogenetic grouping of α -amylase (Fig. 2) and arginine kinase (Fig. 3), similar phylogenetic relationships occur with a clustering of enzymes from insects closer to crustacean cluster compared to the mollusk and nematod clusters, with the difference, however, that insect enzymes are always clustered into a single homogeneous group. Usually, allergens from mollusks appear as being more distantly related to other groups compared to other allergen groups.

4. Cross-reactivity and cross-allergenicity

According to their high degree of sequential and structural conservation, IgE-binding cross-reactivity has been often reported to occur between the pan-allergens of invertebrates. This is especially true for tropomyosin and various enzymes like the widely distributed α -amylase, arginine kinase and GST [3,10,13,41–44]. Using the AllergenOnline program, the search for global (>35% identity over a sliding window of 80 amino acid residues) identities, using tropomyosin Pen m 1 from *Penaeus monodon* as a probe, resulted in the identification of five groups of potentially cross-reactive tropomyosin allergens from mites, crustaceans, insects, mollusks and nematods (Table 2). Both the tropomyosin groups of crustaceans and

mollusks are the most abundantly represented. Similarly, using the AK Bomb m 1 from *Bombyx mori* (Table 3) and the GST Tyr p 8 from *Tyrophagus putrescentiae* (Table 4), resulted in the identification of pan-allergen groups common to mites, crustaceans, insects and mollusks for AK, and restricted to mites, insects and nematods for GST, respectively. In addition to these global identities, local identities (100% identity over a sliding window of 8 amino acid residues), were identified but their number decline faster, compared to the previously calculated global identities, suggesting that lower global identities do not necessarily rely on corresponding IgE-binding epitopic sequences.

The increasing consumption of edible insects in European countries could be accompanied by a concomitant increase of crossed allergies, especially in shellfish allergic patients [45–48]. In this respect, a majority of people suffering from shrimp allergy were identified as being allergic to the yellow mealworm *Tenebrio molitor* [49,50]. In addition to tropomyosin, many other pan-allergens have been characterized in the protein repertoire of *T. molitor* [30,31] and other edible insects [33,34]. Very recently, the first French case of anaphylaxis due to the consumption of a single yellow mealworm, was reported by the Réseau d'Allergo-Vigilance (reseau@allergyvigilance.org).

Another source of food allergens has been identified, essentially in Spain and other South America countries, the so-called pancake anaphylaxis syndrome, due to the consumption of mite-contaminated foods [51,52]. However, the heat-resistant (pan?)-allergens responsible for the pancake anaphylaxis syndrome are still waiting to be unambiguously identified.

5. Discussion and conclusion

The frequently observed anaphylaxis reactions to seafoods, essentially consist of shellfish allergies associated to the consumption of shrimp, prawn, crab and lobster products. Tropomyosin, an actin-binding protein involved in the muscle contraction process, is often responsible for these allergic manifestations but other allergens including many other proteins with either an enzymatic function like arginine-kinase AK, α -amylase, glutathione S-transferase GST, or a structural role like troponin C and tubulin, could be implicated. In fact, all of these proteins allergens correspond to ubiquitous proteins that are widely distributed among different groups of invertebrate including mites, insects, mollusks and nematods. Accordingly, they offer as pan-allergens, a molecular basis for the IgE-binding cross reactivity currently observed between invertebrates of different origin.

Although most of the invertebrate pan-allergens exhibit rather conserved amino acid sequences and three-dimensional structures, their degree of phylogenetic relationships can vary highly according to the pan-allergen. In this respect, most of the crustacean, mite and insect tropomyosins are more closely-related, compared to mollusk and nematod tropomyosins which usually stand more distantly from other invertebrate groups, in the phylogenetic trees. Similarly, arginine kinase and GST allergens of crustaceans, mites and insects, appear as more closely-related, compared to other mollusk and nematod enzymes. Dues to these

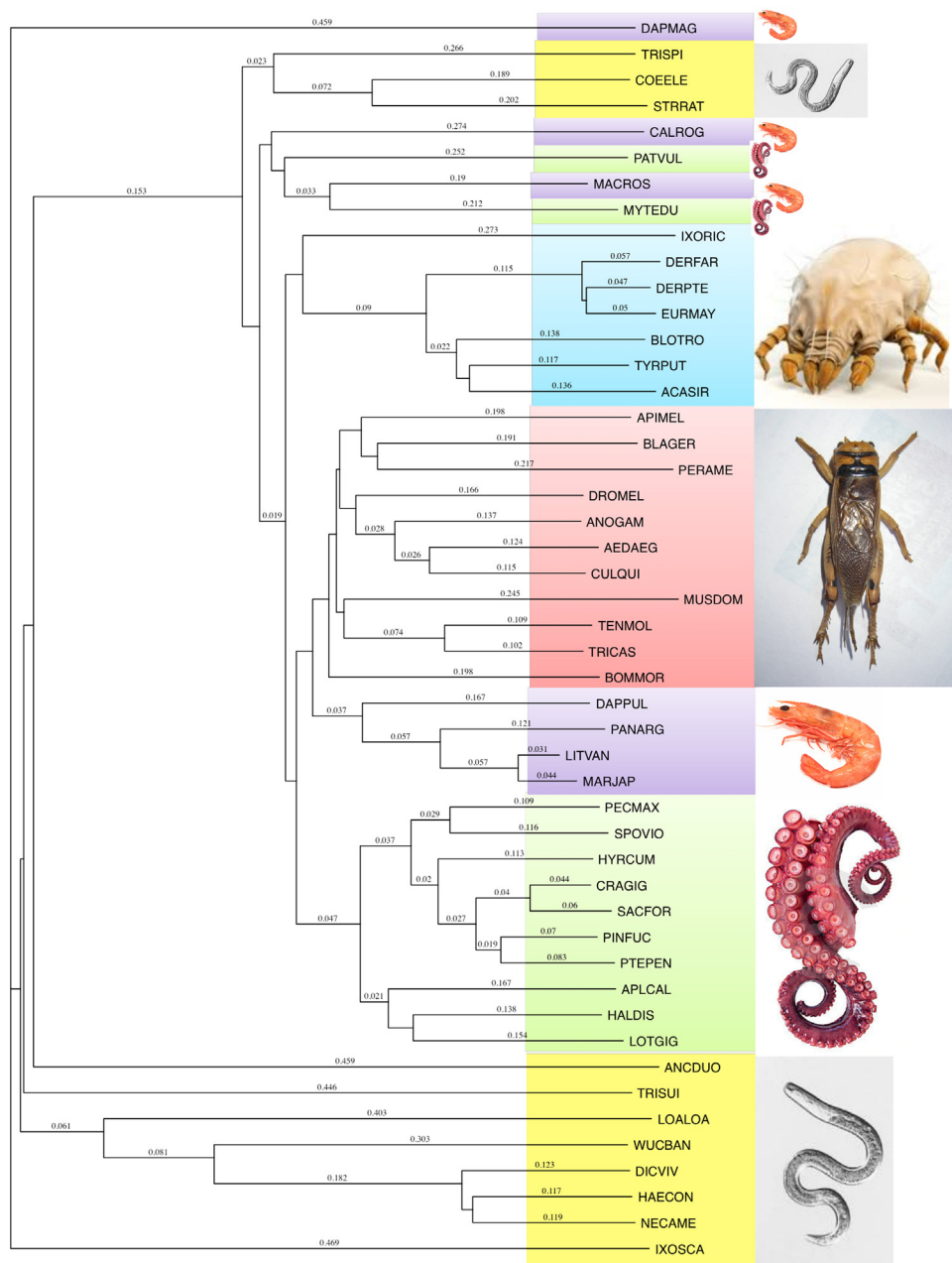


Fig. 2. Unrooted phylogenetic tree built up from the multiple alignment of α -amylase allergens of mites (colored cyan), crustaceans (colored violet), insects (colored red), mollusks (colored green) and nematods (colored yellow), using the neighbour-joining method. Abbreviations used for the species names are defined in Section 6.

discrepancies, the IgE-binding cross-reactivity more frequently occurs between shellfish and insects or mites.

Even though IgE-binding cross-reactivity does not necessarily means cross-allergy, the potential risk of crossed allergy is all the more important that a high degree of cross-reactivity occurs between allergens of distinct origin. Accordingly, the risk for shrimp allergic people to trigger some allergic manifestation upon eating the newly introduced edible insect snacks in European countries. In this respect, it seems prudent 1) to recommend shellfish allergic people to avoid edible insect consumption and 2) to ask the edible insect producers to properly label the edible insect packages with an appropriate mention alerting the shrimp allergic consumers.

6. Bioinformatics

The amino acid sequences of the α -amylase allergens of mites [*Acarus siro* Aca s 4 (ACASIR, acces. DQ979807.1), *Blomia tropicalis* Blo t 4 (BLOTRO, acces. AY291324.1), *Dermatophagoides farinae* Der f 4 (DERFAR, acces. AHX03180.1), *D. pteronyssinus* Der p 4 (DERPTE, acces. AF144060.1), *Euroglyphus maynei* Eur m 4 (EURMAY, acces. AFA44061.1), *Ixodes ricinus* (IXORIC, acces. JAB71331.1), *Tyrophagus putrescentiae* Tyr p 4 (TYRPUT, acces. DQ983318.1)], crustaceans [*Calygus rogerresseyi* (CALROG, acces. ACO10437.1), *Daphnia magna* (DAPMAG,

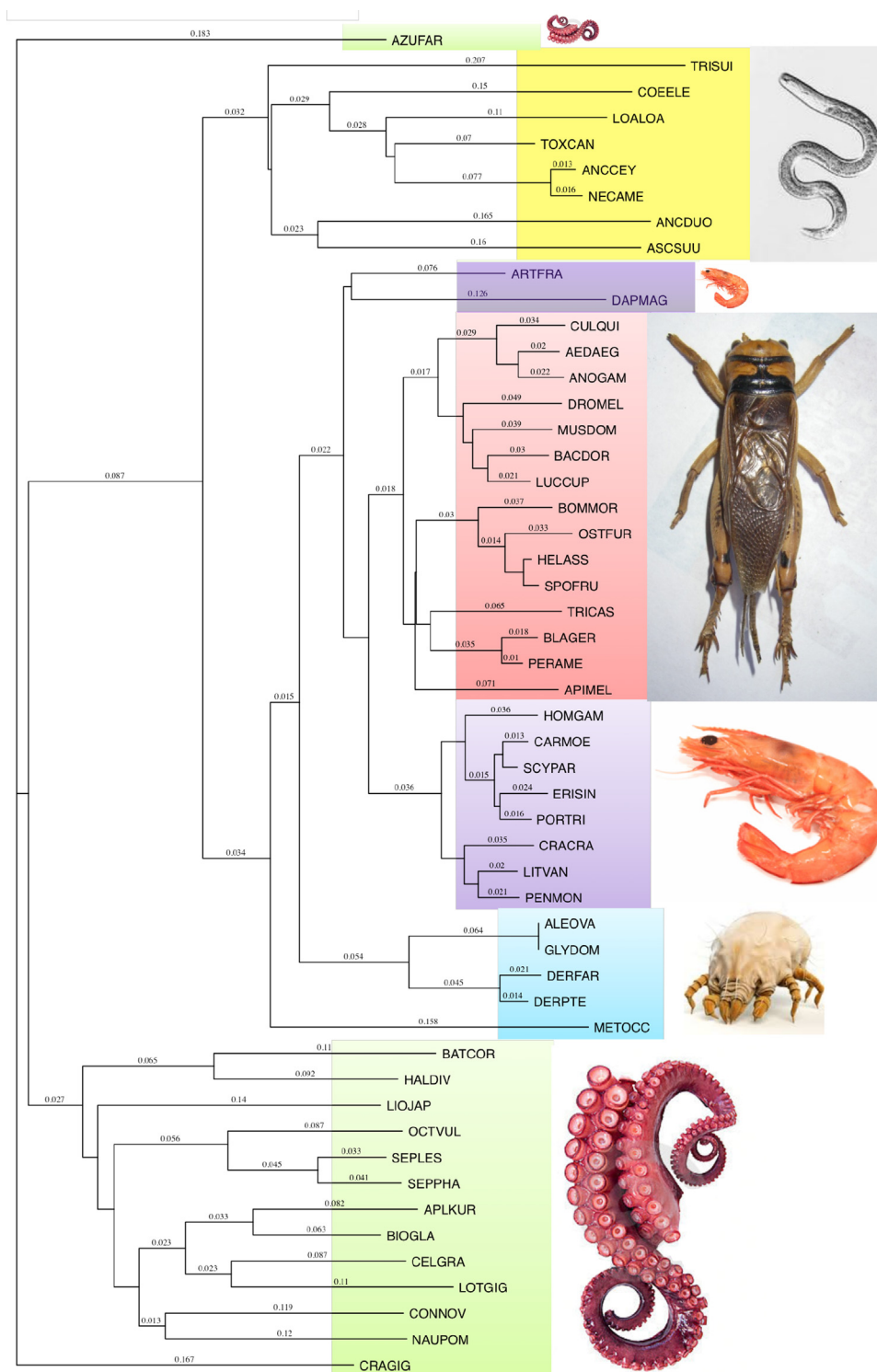


Fig. 3. Unrooted phylogenetic tree built up from the multiple alignment of arginine kinase allergens of mites (colored cyan), crustaceans (colored violet), insects (colored red), mollusks (colored green) and nematods (colored yellow), using the neighbour-joining method. Abbreviations used for the species names are defined in Section 6.

accès. KZS13652.1), *D. pulex* (DAPPUL, accès. EFX75681.1), (*Lito*)*Penaeus vannamei* (LITVAN, accès. AJ133526.1), *Macrobrachium rosenbergii* (MACROS, accès. AKL71614.1), (*Marsu*)*Penaeus japonicus* (MARJAP, accès. AHN91843.1), *Panulirus argus* (PANARG, accès. CDU84835.1)], insects

[*Aedes aegypti* (AEDAEG, accès. AF000568.1), *Anopheles gambia* (ANOGAM, accès. L04753.1), *Apis mellifera* (APIMEL, accès. AF259649.1), *Blattella germanica* Bla g 11 (BLAGER, accès. DQ355516.1), *Bombyx mori* (BOMMOR, accès. GQ274006.1), *Culex quinquefasciatus* (CULQUI,

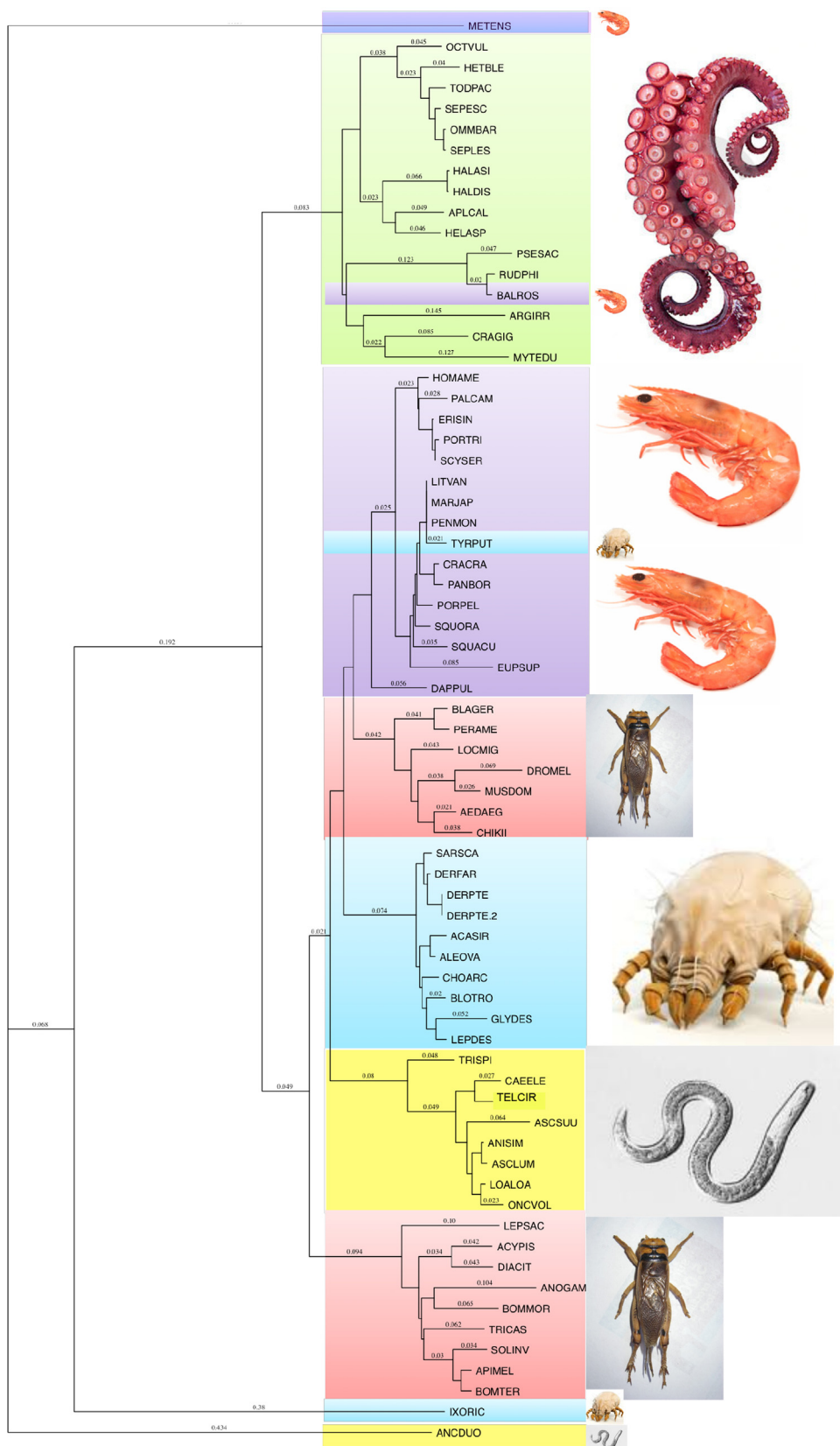


Fig. 4. Unrooted phylogenetic tree built up from the multiple alignment of tropomyosin allergens of mites (colored cyan), crustaceans (colored violet), insects (colored red), mollusks (colored green) and nematods (colored yellow), using the neighbour-joining method. Abbreviations used for the species names are defined in Section 6.

Table 2

Number of hits resulting from probing the Allergen Online bank, using Pen m 1 as a template, for the search of Global (>35% identity over a sliding window of 80 residues) and Local (100% identity over a sliding window of 8 residues) identities Pen m 1 shares with other cross-reacting allergens.

Mites	G (%)	L (n°)	Crustaceans	G (%)	L (n°)	Insects	G (%)	L (n°)	Mollusks	G (%)	L (n°)	Nematods	G (%)	L (n°)
Der f 10	81.7	93	Pen m 1	100.0	277	Lep s 1	68.0	102	Oct v 1	63.7	22	Ani s 3	72.9	61
Der p 10	81.0	93	Lit v 1	97.5	277	Chi k	79.7	93	Hel as 1	63.7	17	Asc l trop.	72.9	66
Tyr p 10	97.9	240	Por p 1	92.6	230	10	82.7	116	Cra g 1	63.0	10	Onc v trop	70.8	
Lep d 10	80.3	85	Por s 1	100	200	Bla g 7	81.5	98	Tod p 1	63.0	22			
Blo t 10	80.3		Pro c 1	96.8	220	Aed a	82.7	108	Sep e 1	63.4	22			
			Pan s 1	98.2	235	10	83.0	108	Hal di 1	63.4	8			
			Cra c 1	97.5	247	Per a 7			Sep l 1	62.7	21			
			Par c 1	96.8	235	Per f 7			Omm b 1	62.7	21			
			Por tr 1	92.3	192				Sca b trop	59.5	6			
			Eri i 1	90.1	192				Bat c trop	59.5	–			
			Mac r 1	97.5	256				Nep po 1	60.2	18			
			Hom a 1	98.6	250				Cra v 1	67.5	6			
			Pan b 1	96.8	242				Ful mu 1	58.3	6			
			Chi o 1	89.1	176				Sin c 1	57.2	15			
			Far a 1	100.0	277				Sol st 1	68.0	14			
			Met e 1	99.6	259				Bal r 1	58.7	17			
			Eri s 1	93.0	205				Pse s trop	56.2	16			
			Cha f 1	91.7	172				Mim n 1	57.7	–			
			Mar j 1	100.0	277				Ven ph 1	58.7	17			
			Scy s 1	92.6	200				Tre ke 1	57.2	11			
			Mel l 1		232				Per v 1	56.0	7			
			Ora o 1	95.1	237									
			Eup s 1	91.5	143									

Mites: Der f 10 (*Dermatophagoides farinae*), Der p 10 (*D. pteronyssinus*), Tyr p 10 (*Tyrophagus putrescentiae*), Lep d 10 (*Lepidoglyphus destructor*), Bot t 10 (*Blomia tropicalis*). Crustaceans: Pen m 1 (*Penaeus monodon*), Lit v 1 (*Litopenaeus vannamei*), Por p 1 (*Portunus pelagicus*), Por s 1 (*P. sanguinolentus*), Pro c 1 (*Procambarus clarkii*), Pan s 1 (*Panulirus stimpsoni*), Cra c 1 (*Crangon crangon*), Par c 1 (*Paralithodes camtschaticus*), Por tr 1 (*Portunus trituberculatus*), Eri i 1 (*Erimacrus isenbeckii*), Mac r 1 (*Macrobrachium rosenbergii*), Hom a 1 (*Homarus americanus*), Pan b 1 (*Pandalus borealis*), Chi o 1 (*Chionoecetes opilio*), Far a 1 (*Farfantepenaeus aztecus*), Met e 1 (*Metapenaeus ensis*), Eri s 1 (*Eriocheir sinensis*), Cha f 1 (*Charybdis feries*), Mar j 1 (*Marsupenaeus japonicus*), Scy s 1 (*Scylla serrata*), Mel l 1 (*Meliceratus laticulatus*), Ora o 1 (*Oratosquilla oratoria*), Eup s 1 (*Euphosia pacifica*). Insects: Lep s 1 (*Lepisma saccharina*), Chi k 10 (*Chironomus kiiensis*), Bla g 7 (*Blattella germanica*), Aed a 10 (*Aedes aegypti*), Per a 7 (*Periplaneta americana*), Per f 7 (*P. fuliginosa*). Mollusks: Oct v 1 (*Octopus vulgaris*), Hel as 1 (*Helix aspersa*), Cra g 1 (*Crassostrea gigas*), Tod p 1 (*Todarodes pacificus*), Sep e 1 (*Sepia esculenta*), Hal di 1 (*Haliothis discus discus*), Sep L 1 (*Sepioteuthis lessoniana*), Omm b 1 (*Ommastrephes bartramii*), Sca b trop (*Scapharca broughtonii*), Bat c trop (*Batillus cornutus*), Nep po 1 (*Neptunea polycostata*), Cra v 1 (*Crassostrea virginica*), Ful mu 1 (*Fulvia mutica*), Sin c 1 (*Sinonovacula constricta*), Sol st 1 (*Solen strictus*), Bal r 1 (*Balanus rostratus*), Pse s trop (*Pseudocardium sachalinensis*), Mim n 1 (*Mimachlamys nobilis*), Ven ph 1 (*Venerupis philippinarum*), Tre ke 1 (*Tresus keenae*), Per v 1 (*Perna viridis*). Nematods: Ani s 3 (*Anisakis simplex*), Asc l trop (*Ascaris lumbricoides*), Onc v trop (*Onchocerca volvulus*).

Table 3

Number of hits resulting from probing the Allergen Online bank, using Bomb m 1 as a template, for the search of Global (>35% identity over a sliding window of 80 residues) and Local (100% identity over a sliding window of 8 residues) identities Bomb m 1 shares with other cross-reacting arginine kinase allergens.

Mites	G (%)	L (n°)	Crustaceans	G (%)	L (n°)	Insects	G (%)	L (n°)	Mollusks	G (%)	L (n°)
Der p 20	77.8	64	Scy p	82.6	109	Bomb m 1	100.0	348	Amp f ak	57.1	11
Der f 20	77.8	60	Lit v 2	83.1	108	Plo i 1	92.4	191			
			Pro c 2	81.7	108	Per a 9	87.6	126			
			Pen m 2	82.0	92	Bla g 9	87.6	126			
			Cra c 2	81.5	103						
			Fen c 2	81.1	15						

Mites: Der p 20 (*Dermatophagoides pteronyssinus*); Der f 20 (*D. farinae*); Scy p 2 (*Scylla paramamosain*); Lt v 2 (*Litopenaeus vannamei*); Pro c 2 (*Procambarus clarkii*); Pen m 2 (*Penaeus monodon*); Cra c 2 (*Crangon crangon*); Fen c 2 (*Fenneropenaeus chinensis*); Bomb m 1 (*Bombyx mori*); Plo i 1 (*Plodia interpunctella*); Per a 9 (*Periplaneta americana*); Bla g 9 (*Blattella germanica*); Amp f ak (*Amphioctopus fangsiao*).

acces. DS231920.1), *Drosophila melanogaster* (DROMEL, acces. L22716.1), *Musca domestica* (MUSDOM, acces. ZF494036.1), *Periplaneta americana* Per a 11 (PERAME, acces. KR019685.1), *Tenebrio molitor* (TENMOR, acces. PBD code 1VIW), *Tribolium castaneum* (TRICAS, acces. U04271.1)], mollusks [*Aplysia californica* (APLCAL, acces.

XP-005103373.1), *Crassostrea gigas* (CRAGIG, acces. L EKC28393.1), *Haliothis discus* (HALDIS, acces. AB026611.1), *Hyriopsis cumingii* (HYRCUM, acces. AGW45296.1), *Lottia gigantea* (LOTGIG, acces. KB202163.1), *Mytilus edulis* (MYT-EDU, acces. ACA34372.1), *Patella vulgata* (PATVUL, acces. ACA34388.1), *Pecten maximus* (PECMAX, acces. X99729.1),

Table 4

Number of hits resulting from probing the Allergen Online bank, using Tyr p 8 as a template, for the search of Global (>35% identity over a sliding window of 80 residues) and Local (100% identity over a sliding window of 8 residues) identities Tyr p 8 shares with other cross-reacting GST allergens.

Mites	G(%)	L (n°)	Insects	G (%)	L (n°)	Nematods	G (%)	L (n°)
Tyr p 8	100.0	211	Bla g 5	37.0	–	Asc s	38.3	–
Der p 8	76.8	14				GST		
Sar sc	74.4	13						
GST	72.0	6						
Der f 8	48.7	–						
Blo t 8								

Mites: Tyr p 8 (*Tyrophagus putrescentiae*); Der p 8 (*Dermatophagoides pteronyssinus*); Sar sc GST (*Sarcoptes scabiei* type *hominis*); Der f 8 (*Dermatophagoides farinae*); Blo t 8 (*Blomia tropicalis*); Insects : Bla g 5 (*Blattellagermanica*); Nematods: Asc su GST (*Ascaris suum*).

Pinctadafucata (PINFUC, acces. AGN55419.1), *Pteria penguin* (PTEPEN, acces. AEI58894.1), *Saccostrea forskali* (SACFOR, acces. AHA11414.1), *Spondylus violaceus* (SPOVIO, acces. AFE48186.1)] and nematods [*Ancylostoma duodenale* (ANCDUO, acces. KIH63276.1), *Caenorhabditis elegans* (CAEELE, acces. NP503064.1), *Dictyocaulus viviparus* (DICVIV, acces. KJH49023.1), *Haemonchus contortus* (HAECON, acces. CDJ98092.1), *Ixodes scapularis* (IXOSCA, acces. L P002401557.1), *Loa loa* (LOALOA, acces. XP020307273.1), *Necator americanus* (NECAME, P013302750.1), *Strongyloides ratti* (STRRAT, acces. XP_024508147.1), *Trichinella spiralis* (TRISPI, acces. KRY42836.1), *T. suis* (TRISUI, acces. KDF61817.1), *Wuchereria bancrofti* (WUCBAN, acces. EJJW83340.1)], were taken from the NCBI protein database (<http://www.ncbi.nlm.nih.gov/pubmed>).

The amino acid sequences of the arginine kinase allergens of mites [*Aleuroglyphus ovatus* (ALEOVA, acces. EU106612.1), *Glycyphagus domesticus* (GLYDOM, acces. EU106620.1), *Dermatophagoides farinae* (DERFAR, acces. AY211951.1), *D. Pteronyssinus* (DERPTE, acces. EU684970.1), *Metaseiulus occidentalis* (METOCC, acces. XM_003738186.2)], crustaceans [*Artemia franciscana* (ARTFRA, acces. Q95V58), *Carcinus maenas* (CARMAE, acces. Q9U9J4), *Crangon crangon* (CRACRA, acces. ACR43474.1), *Daphnia magna* (DAPMAG, acces. KJ944636.1), *Eriocheir sinensis* (ERISIN, acces. Q9NH48), *Homarus gammarus* (HOMGAM, acces. P14208), (*Lito*)*Penaeus vannamei* (LITVAN, acces. ABY57915.1), *Penaeus monodon* (PENMON, acces. AAO15713.1), *Portunus trituberculatus* (PORTRI, acces. ADO22721.1), *Scylla paramamosain* (SCYPAR, acces. AFA45340.1)], insects [*Aedes aegypti* (AEDAEG, acces. XP_021697335.1), *Anopheles gambiae* (ANOGAM, acces. XP_315641.1), *Apis mellifera* (APIMEL, acces.), *Bactrocera dorsalis* (BACDOR, acces. XM_011214400.2), *Blattella germanica* (BLAGER, acces. DQ358231.1), *Bombyx mori* (BOMMOR, acces. DQ272299.1), *Culex quinquefasciatus* (CULQUI, acces. XP_001849654.1), *Drosophila melanogaster* (DROMEL, acces. NP_729448.1), *Helicoverpa assulta/armigera* (HELASS, acces. XP_021185573.1), *Lucilia cuprina* (LUCCUP, acces. KNC27254.1), *Ostrinia furnacalis* (OSTFUR, acces. AIY31784.1), *Periplaneta americana* (PERAME, acces. AY563004.1), *Spodoptera frugiperda* (SPOFRU, acces. AGH14259.1), *Tribolium*

castaneum (TRICAS, acces. XP_971800.2)], mollusks [*Aplysia kuroda* (APLKUR, acces. BAB41095.1), *Azumapecten farreri* (AZUFAR, acces. AEX08673.1), *Batillus cornutus* (BATCOR, acces. O15989.1), *Biomphalaria glabrata* (BIOGLA, acces. ADH59421.1), *Cellana grata* (CELGRA, acces. BAB41096.1), *Conus novahollandiae* (CONNOV, acces. ADK73590.1), *Crassostrea gigas* (CRAGIG, acces. EKC24881.1), *Haliotis diversicolor* (HALDIV, acces. AJW60778.1), *Loliophura japonica* (LIOJAP, acces. O15990.1), *Nautilus pompilius* (NAUPOM, acces. BAA95594.1), *Lottia gigantea* (LOTGIG, acces. XP_009060266.1), *Octopus vulgaris* (OCTVUL, acces. BAA95609.1), *Sepioteuthis lessoniana* (SEPLES, acces. BAA95610.1), *Sepia pharaonis* (SEPPHA, acces. AKS26488.1)] and nematods [*Ancylostoma ceylanicum* (ANCEY, acces. EYC23758.1), *A. duodenale* (ANCDUO, acces. KIH65495.1), *Ascaris suum* (ASCSUU, acces. ACO56119.1), *Caenorhabditis elegans* (CAEELE, acces. NP_509217.2), *Necator americanus* (NECAME, acces. XP_013303820.1), *Toxocara canis* (TOXCAN, acces. KHN76773.1), *Trichuris suis* (TRISUI, acces. KHJ42364.1)], were taken from the NCBI protein database.

The amino acid sequences of the tropomyosin allergens of mites [*Acarus siro* (ACASIR, acces. ABL09305.1), *Aleuroglyphus ovatus* (ALEOVA, acces. AAX37287.1), *Blomia tropicalis* (BLOTRO, acces. ABU97466.12), *Chortoglyphus arcuatus* (CHOARC, acces. AEX31649.1), *Dermatophagoides farinae* (DERFAR, acces. AIO08865.1), *D. pteronyssinus* (DERPTE, acces. AAB69424.1), *Glycyphagus domesticus* (GLYDOM, acces. AAQ54614.1), *Ixodes ricinus* (IXORIC, acces.), *Lepidoglyphus destructor* (LEPDES, acces. Q9NF), *Sarcoptes scabiei* (SARSCA, acces. SHD75396.1), *Tyrophagus putrescentiae* (TYRPUT, acces. AAT40866.1)], crustaceans [*Balanus rostratus* (BALROS, acces. BAF46896.1), *Crangon crangon* (CRACRA, acces. ACR43473.1), *Daphnia pulex* (DAPPUL, acces. EFX89938.1), *Eriocheir sinensis* (ERISIN, acces. ABO71783.1), *Euphosia superba* (EUPSUP, acces. BAF76430.1), *Homarus americanus* (HOMAME, acces. O44119.1), (*Lito*)*Penaeus vannamei* (LITVAN, acces. EU410072.1), *Marsupenaeus japonicus* (MARJAP, acces. AB270630.1), *Metapenaeus ensis* (METENS, acces. Q25456.1), *Paralithodes camtschaticus* (PARCAM, acces. BAF47265.1), *Pandalus borealis* (PANBOR, acces. P86704.1), *Penaeus monodon* (PENMON, acces. AIKYZ2.1),

Portunus pelagicus (PORPEL, acces. AGE44125.1), *P. trituberculatus* (PORTRI, acces. ABS12234.1), *Squilla aculeata* (SQUACU, acces. AAR87379.1), *S. oratoria* (SQUORA, acces. ABQ57495.1)], insects [*Acyrtosiphon pisum* (ACYPIS, acces. XP_001947820.1), *Aedes aegypti* (AEDAEG, acces. XP_001655951.1), *Anopheles gambiae* (ANOGAM, acces. XP_003435947.1), *Apis mellifera* (APIMEL, acces. XP_006560146.1), *Blattella germanica* (BLAGER, acces. PSN29794.1), *Bombus terrestris* (BOMTER, acces. XP_003400287.1), *Bombyx mori* (BOMMOR, acces. NP_001040445.1), *Chironomus kiiensis* (CHIKII, acces. 096764), *Diaphorina citri* (DIACIT, acces. XP_0084770475.1), *Drosophila melanogaster* (DROMEL, acces. ABK30920.1), *Lepisma saccharina* (LEPSAC, acces. Q8T380.1), *Locusta migratoria* (LOCMIG, accers. P31816), *Musca domestica* (MUSDOM, acces. XP_005181068.1), *Periplaneta americana* (PERAME, acces. AVA17392.1), *Solenopsis invicta* (SOLINV, acces. XP_011162964.1), *Tribolium castaneum* (TRICAS, acces. XP_967128.1)], mollusks [*Aplysia californica* (APLCAL, acces. XP_005089094.1), *Argopecten irradians* (ARGIRR, acces. AAX37290.1), *Crassostrea gigas* (CRAGIG, acces. XP_011437706.1), *Haliotis asinina* (HALASI, acces. AAP85231.1), *H. discus* (HALDIS, acces. BAH10148.1), *Helix aspersa* (HELASP, acces. CAB38044), *Heterololigo bleekeri* (HETBLE, acces. ADD64463.1), *Mytilus edulis* (MYTEDU, acces. AAA82259.1), *Octopus vulgaris* (OCTOVUL, acces. AB218917.1), *Ommastrephes bartramii* (OMMBAR, acces. BAE54432.1), *Pseudocardium sacdhalinense* (PSESAC, acces. BAH10154.1), *Ruditapes philippinarum* (RUDPHI, acces. BAH10157.1), *Sepia esculenta* (SEPESC, acces. BAE54429.1), *Sepioteuthis lessoniana* (SEPLES, acces. BAE54430.1), *Todarodes pacificus* (TODPAC, acces. BAE54431.1)] and nematods [*Ancylostoma duodenale* (ANCDUO, acces. KN769411.1), *Anisakis simplex* (ANISIM, acces. Q9NAS5.1), *Ascaris lumbricoides* (ASCLUM, acces. ACN32322.1), *A. suum* (ASCSUU, acces. ADY44806), *Caenorhabditis elegans* (CAEELE, acces. NP_001021695.1), *Loa loa* (LOALOA, acces. XP_020306016.1), *Onchocerca volvulus* (ONCVOL, acces. Q25632), *Teladorsagia circumcincta* (TELCIR, acces. GU290222.1), *Trichinella spiralis* (TRISPI, acces. XP_003372651.1)], were similarly taken from the NCBI protein database.

The multiple amino acid sequence alignments was performed with MacVector, using the CLUSTAL-W program [53]. Unrooted phylogenetic trees were built up from the multiple alignments of α -amylases, AK and GST using the uncorrected neighbour joining method integrated in MacVector.

Homology modeling of the different α -amylase allergens of *Tenebrio molitor*, *Blomia tropicalis* (Blot4), *Dermatophagoides pteronyssinus* (Derp4), *Apis mellifera*, *Bombyx mori*, *Hermetia illucens*, *Musca domestica*, *Litopenaeus vannamei*, *Marsupenaeus japonicus*, *Crassostrea gigas* were modeled with the YASARA Structure program [54], using different X-ray solved α -amylase structures as templates. Arginine kinases of *Penaeus monodon* (Penm2), *Scylla paramamosain* (Scyp2), *Crangon crangon* (Cra c2), *Aleuroglyphys ovatus*, *Glycyphagus domesticus*, *Bombyx mori* (Bombm1), *Locusta migratoria*, *Tenebrio*

molitor, *Crassostrea gigas* and *Octopus vulgaris*, were similarly modeled with YASARA. Glutathione S-transferases of *Ascaris lumbricoides* Asc13 (PDB code 4Q5F), *Bombyx mori* (PDB code 3VUR), and *Onchocerca volvulus* (PDB code 1TU7), were taken from the Protein Data Bank [55]. Other GST from *Ascaris suum* Asc s13, *Apis mellifera*, *Blattella germanica* Bla g5, *Galleria mellonella*, *Locusta migratoria* and *Musca domestica*, were modeled with YASARA.

All the molecular cartoons were drawn with Chimera [56].

According to the pioneering works performed on the bioinformatic methods for the allergenicity assessment of potentially cross-reactive proteins [57–62], a search for global (>35% identity over a sliding window of 80 amino acid residues) and local (100% identity over a sliding window of 8 amino acid residues) with genuine food allergens, was performed with the web server of AllergeOnline (version # 188 of March 23 2018) program of the FARRP allergen protein database (University of Nebraska-Lincoln, USA) (<http://www.allergenonline.org>).

Disclosure of interest

The authors declare that they have no competing interest.

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