



# Why is there a greater incidence of allergy to the tropomyosin of certain animals than to that of others? ☆

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**Summary** Tropomyosin is a major allergen in various foods, implicated in a spectrum of mild to life threatening systemic reactions. The incidence of allergy to tropomyosin varies greatly by species, with sensitivity to crab, shrimp, cockroach, and dust mite tropomyosins, among others, being the highest, while tropomyosins in vertebrate species are considered non-allergenic. We have analyzed the possible fragments which may result from Pepsin A digestion of tropomyosins from various species and find that larger fragments of the tropomyosins from crab, shrimp, cockroach, and especially, dust mites will probably survive gastric digestion, compared to those from, for example, chicken, cattle, rabbit, or fish. These larger peptide fragments may enter the bloodstream and assume a three-dimensional structure whose stability approaches that of the intact molecule. Antibodies, including IgE, would be expected to be produced specifically against stable regions of the tertiary structure. We propose that this is a plausible explanation for the greater ability of the larger molecules derived from invertebrate tropomyosins to trigger an immediate hypersensitivity response.

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Allergic diseases are some of the most common chronic illnesses in industrialized nations and individuals can develop allergic responses to a myriad of foods, drugs, pollens, animals, and arthropods. Allergic rhinitis affects up to 10–30% adults and up to 40% of children in the United States [1]. Approximately 2% of the United States adult population is

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affected by food allergies, and shellfish allergy has an estimated frequency of 0.5% [2]. Most allergens are proteins, some with enzymatic activities. Allergens can enter the human body through the respiratory, gastrointestinal, cutaneous, on injection routes and may cause localized or systemic reactions depending on the route of entry.

Tropomyosin is a protein found in the striated muscle of many mammals and in non-muscle cells of species of vertebrates and invertebrates. Tropomyosins are the major allergens in invertebrates such as crustaceans (shrimp, crab, lobster), arachnids (dust mites), insects (cockroaches, midges), and mollusks (squid, snail, and oyster). While the

**NP\_001013608** Bos Taurus (cattle)  
mdaikkkmqmkldkenaldraegaeadkkaaedrsqgledelvslqkklkatedeldkY  
**sealkdageklelaekkatdaeadvaslnrriqlveeeldraerlatalqkleaaekaa**  
**desergmkviesraqkdeekmeiqeqlkeakhiaeadrky** eevarklviiesdler  
aeraelsegkcaeleelktvtnnlksleagaekY sqkedkY eeeikvlsdklike  
aetraeF aersvtkleksiddledelY aqklkY kaiseeldhalndmtsi

**P58772** Oryctolagus cuniculus (rabbit)  
mdaikkkmqmkldkenaldraegaeadkkaaedrsqgledelvslqkklkgtedeldkY  
**sealkdageklelaekkatdaeadvaslnrriqlveeeldraerlatalqkleaaekaa**  
**desergmkviesraqkdeekmeiqeqlkeakhiaeadrky** eevarklviiesdler  
aeraelsegkcaeleelktvtnnlksleagaekY sqkedkY eeeikvlsdklike  
aetraeF aersvtkleksiddledelY aqklkY kaiseeldhalndmtsi

**P04268** Gallus gallus (chicken)  
mdaikkkmqmkldkenaldraegaeadkkaeersqgledelvalqkklkgtedeldkY  
**seslkdagekleladkatdaeevaslnrriqlveeeldraerlatalqkleaaekaa**  
**desergmkvienraqkdeekmeiqeqlkeakhiaeadrky** eevarklviiesdler  
aeraelsegkcaeleelktvtnnlksleagaekY sqkedkY eeeikvlttdklike  
aetraeF aersvtkleksiddledelY aqklkY kaiseeldhalndmtsi

**AAB36559** Salmo salar (salmon)  
mdaikkkmqmkldkenaldraegaegdkkaaedksqgledelvalqkklkgtedeldkY  
**seslkdageklelaektatdaeadvaslnrriqlveeeldraerlatalqkleaaekaa**  
**desergmkvienraskdeekmelqdiqlkeakhiaeadrky** eevarklviiesdler  
teeraelsegkcaeleelktvtnnlksleagaekY sqkedkY eeeikvlttdklike  
aetraeF aersvaklektiddledelY aqklkY kaiseeldhalndmtsi

**AAZ76743** Farfantepenaeus aztecus (shrimp)  
mdaikkkmqamklekdnamdradtlegqnkeannraekseeevhnlgkrmqqlendldqv  
qesllkaniqlvekdkaalsnaegevaalnrrriqlleedlerseerlntattklaeasqaa  
desermrkvlenrslsdeermaldenqlkearF laeeadrkY devarklamveadl  
eraeraetgeskiveleelrvvgnnlkslevseekanqreeaY keqiktlttnklka  
aearaeF aersvqlqkevdrledelvnkeekY ksitdeldqtF selsgY

**AAF35431** Charybdis feriatus (crab)  
mdaikkkmqamklekdnamdradtlegqnkeanlraekteeeiratqkkmqgveneldqa  
**qeqlsaantkldekekalqnaegevaalnrrriqlpeedlerseerlntattklaeasqaa**  
**desermrkvlenrslsdeermaldenqlkearF** laeeadrkY devarklamveadl  
eraeraesgeskiveleelrvvgnnlkslevseekanqreetY keqiktlttnklka  
aearaeF aersvqlqkevdrledelvnke

**AAD19606** Periplaneta americana (cockroach)  
mdaikkkmqamklekdnamdrallceqgkardnlaekaeaaarslqkkgqiendldqt  
**meqlmqvnacldekdkaalqnaegevaalnrrriqlleedlerseerlatataklaeasqaa**  
**desermrkileskgladeermaldenqlkearF** maeaadkY devarklamveadl  
eraeraesgeskiveleelrvvgnnlkslevseekanlreeeY kqgiktlttnklka  
aearaeF aersvqlqkevdrledelvnkeekY kF icddldmtF telign

**Q23939** Dermatophagoides farinae (dust mite)  
**meaikkkmqamklekdnaidraeiaeqkardnlaekseeevralqkkgqiendldqv**  
**qeqlsaantkleekalqtaegdvaalnrrriqlleedlerseerlkiataklaeasqaa**  
**desermrkmlhrsitdeermaldenqlkearmmaeadrky** devarklamveadler  
aeraetgeskiveleelrvvgnnlkslevseekaqgreeaY eqqirimtaklkeae  
araeF aersvqlqkevdrledelvnkeekY ksisdeldqtF aeltgY

**Figure 1** Comparison of the probable pepsin A fragments of the longer (284 amino acids) isoform of tropomyosins from various organisms. The sequences were obtained from the database at <http://www.ncbi.nlm.nih.gov> and are identified by their access codes. The fragments are separated by spaces and the longest fragment in each sequence is shown in bold letters and underlined.

tropomyosins of vertebrates including cattle, chicken, and other animals are considered non-allergenic, the incidence of allergy to the invertebrate tropomyosins of dust mites, shrimp, and certain other invertebrates is high [3,4]. The allergic responses to these invertebrate tropomyosins range from mild cutaneous symptoms to severe, life threatening anaphylactic reactions. Tropomyosin has been implicated as an important cross-sensitizing allergen between crustaceans, cockroaches, and dust mites and is more likely if the sequence homology between proteins exceeds 80%.

Food allergens are traditionally water-soluble, heat, acid, and protease resistant glycoproteins with molecular weights ranging from 10 to 70 kD [5]. In shellfish allergy, tropomyosins are the major Group 1 allergens identified. At least 80% of shrimp-allergic individuals react to tropomyosin [6]. In contrast, the major allergens identified in ingested mammalian meats are not tropomyosins, but mainly other proteins like serum albumins, immunoglobulins, and transferrins.

House dust mites including *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* are the most common mite species involved in allergic responses. Dust mite hypersensitivity has been associated with chronic rhinitis, asthma, and atopic dermatitis. It has also been implicated in allergic conjunctivitis, urticaria, and anaphylaxis. Recent case reports have described systemic anaphylaxis after ingestion of dust mite infested baked goods in dust mite sensitive individuals [7]. One of the major allergens of dust mites, Der p 10, is a tropomyosin with 81% reactivity in allergic individuals – the highest known. Per a 7 is one of the major allergens identified in the American cockroach, *Periplaneta americana*, with 50% frequency of reactivity in sensitized individuals, while >50% reactivity is observed for the tropomyosins of shrimp, crab, and squid [2].

While any accessible region of an antigen can elicit an antibody response [8,9], the stability of its structure determines the specificity of this immune response. Unstructured, or loosely structured, regions would be expected to elicit a larger number of varied antibody combining sites. Tropomyosins are alpha-helical, coiled-coil dimers and as such are strong and stable structures; antibodies, including IgE, would be expected to be produced specifically against stable regions [10].

We have compared the sequences of tropomyosins from a variety of organisms and analyzed them in terms of their susceptibility to gastric digestion. The major gastric protease is pepsin A and this enzyme shows preference for peptide bonds following phenylalanine or tyrosine. The major products of

pepsin A action are large fragments and some free amino acids (see, for example, [11]). The longer (284 amino acids) isoform of the tropomyosins from various animals are compared in Fig. 1 where the probable pepsin A fragments are highlighted.

It is seen in Fig. 1 that significantly larger pepsin A fragments are present in the tropomyosins from dust mites, shrimp, crab, and cockroaches compared to those from chicken, cattle, rabbits, and salmon. In chicken, cattle, rabbits, and salmon, 102 residues out of the 284 total (36%) are in the longest pepsin A fragment. In crabs, shrimp and cockroaches, 153 residues (54%), and in dust mites, 162 residues (57%) are in the longest fragment (Fig. 1).

We propose that the primary cause of the higher incidence and severity of the allergic response to the tropomyosins of shrimp, crabs, cockroaches, and, especially, dust mites, is the possibility that larger fragments of those molecules enter the blood stream where they can assume a three-dimensional structure whose stability approaches that of the intact molecule, so that they elicit a more specific antibody response.

If our hypothesis is correct, the larger pepsin A fragments would be antigenic in most individuals, even if they are not allergenic. Our hypothesis could therefore be validated by testing non-atopic individuals, who are not allergic to dust mite tropomyosin, for example, for the presence of non-IgE antibodies in their sera that bind to the large dust mite pepsin A fragment in Fig. 1.

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