

# Cockroach, tick, storage mite and other arthropod allergies: Where do we stand with molecular allergy diagnostics?

## Part 15 of the Series Molecular Allergology

CHRISTIANE HILGER<sup>1</sup>, ANNETTE KUEHN<sup>1</sup>, MONIKA RAULF<sup>2</sup>, THILO JAKOB<sup>3</sup>

<sup>1</sup>Laboratory of Immunogenetics and Allergology, Centre for Public Health Research, Luxembourg, Luxembourg; <sup>2</sup>Institute for Prevention and Occupational Medicine of the German Statutory Accident Insurance, Institute of the Ruhr University Bochum (IPA); <sup>3</sup>Allergy Research Group, Department of Dermatology, Medical Center – University of Freiburg, Germany

### Key words

Allergy –  
diagnostics –  
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– storage mite –  
arthropod

### Abstract

Arthropods form a broad phylum within the animal kingdom, comprising widely varying members such as insects, arachnids, crabs and centipedes. In addition to common allergies to house dust mites or hymenoptera venom, there are also rarer allergies that can be attributed to three major sources of allergens: cockroaches, ticks and storage mites. Other less known allergen sources include spiders, mosquitos, horseflies, red chironomid larvae, silverfish and ladybugs, as well as a variety of storage pests. At present, only extract-based test systems are available for the majority of allergens in IgE-based diagnostics. Molecular characterisation of numerous individual allergens has already been carried out. However, these individual allergens are only available for a small num-

ber of allergen sources (e. g. cockroaches and storage mites) in routine diagnostics. Particularly in the case of allergen sources with known high cross-reactivity, the use of marker allergens is believed to improve diagnostics. The currently known individual allergens of the above-mentioned allergy triggers from the arthropod realm are summarized and their potential use in allergy diagnostics discussed.

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### Introduction

Arthropods form an extensive phylum of the animal kingdom, comprising widely varying members such as insects, arachnids, crabs and centipedes (Fig. 1). The molecular diagnostics of the frequent house dust mite allergy and the hymenoptera venom allergy has already been discussed in separate articles [1, 2]. The present article deals with rarer allergies to specific members of the arthropod realm, describes the extracts available for diagnostic purposes as well as the currently known individual allergens and discusses their potential application in allergy diagnostics.

### Cockroach allergy

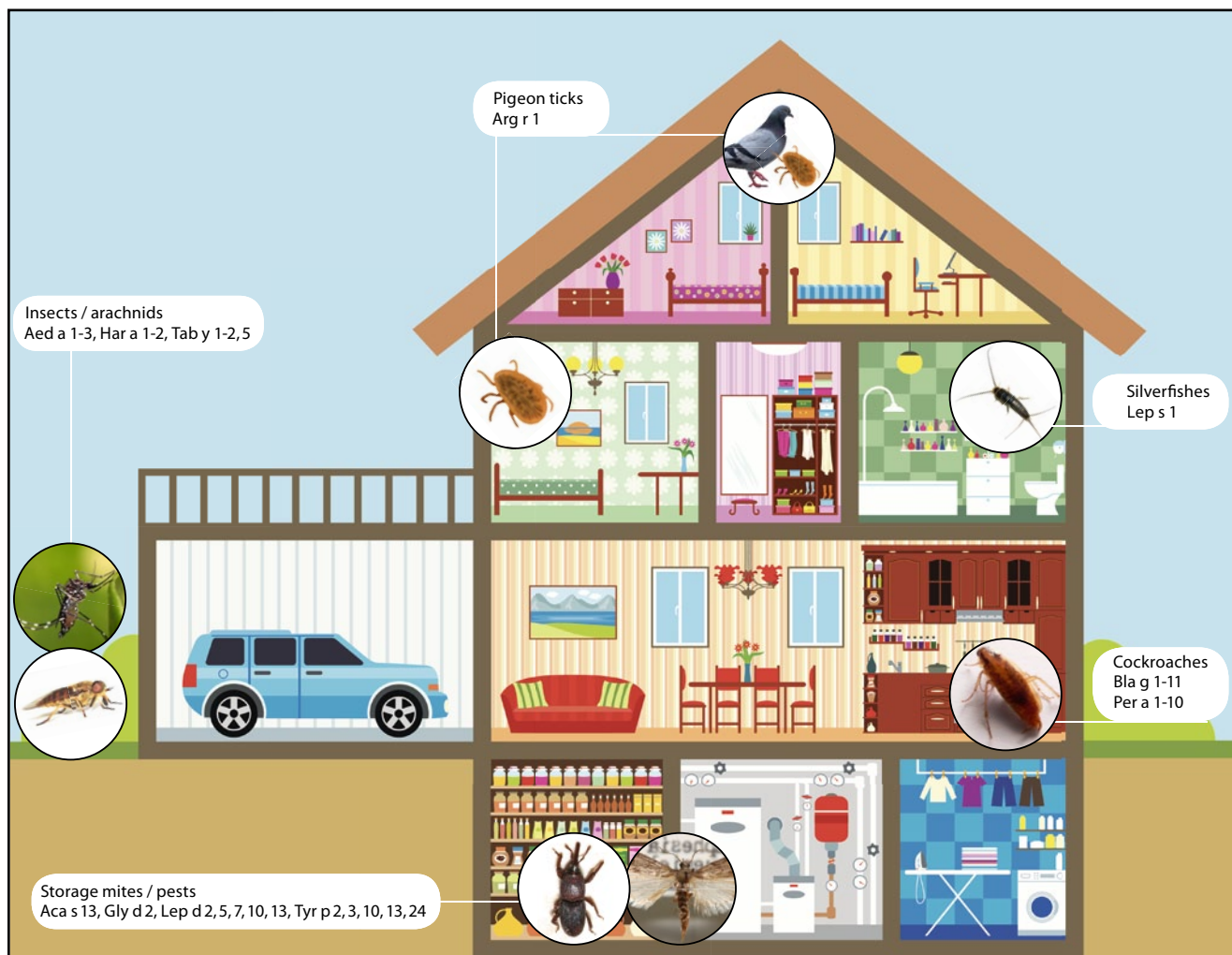
#### Exposure and distribution

The cockroach order (Blattodea) is made up of more than 4,600 species and its members are found worldwide. Cockroaches are nocturnal and are found primarily in the Tropics and Subtropics. The domestic cockroaches best investigated as allergen sources include the German cockroach (*Blattella germanica*), which dominates in the US in terms of numbers, as well as the American cockroach (*Periplaneta americana*) and the oriental cockroach (*Blatta orientalis*). The *Periplaneta fuliginosa* cockroach, which was originally indige-

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**Fig. 1:** Favored habitations of various allergenic arthropods around the house and the garden. Characterized allergens are indicated.

nous only to Japan, Southeast Asia and the Southern United States, has spread worldwide by infesting containers transported either by ship or air. The frequency of cockroach allergies depends to a great extent on the level of exposure to cockroach allergens [3]. Allergen exposure in urban areas is on the whole significantly higher than in suburban areas, where, nevertheless, allergen concentrations are measured in as much as 30 % of US households [4, 5, 6].

#### Allergen identification

The official allergen database ([www.allergen.org](http://www.allergen.org)) includes important allergens from the German and US cockroaches: Bla g 1–11 and Per a 1–10. These cockroach allergens can be subdivided into more than 10 protein groups on the basis of highly varying physiological functions [3] (**Tab. 1**). They have been identified in cockroach faeces, eggs or exoskeletons. Homologous, possibly cross-reactive aller-


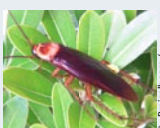
gens have been described in other cockroach species ([www.allergome.org](http://www.allergome.org)).

#### Relevance

Whilst cockroach allergen sensitization is one of the greatest risk factors for increased asthma-related morbidity among the low-income population in the US (referred to as the inner-city asthma problem in the US), sensitization rates in Germany and Europe are generally far lower [6]. A study by Hirsch et al. [7] found that only 4.2 % of approximately 3,000 children in Dresden, Germany, had specific immunoglobulin E (IgE) (> 0.7 kU/l) to the German cockroach (*Blattella germanica*), whereby the prevalence of sensitization among asthmatic children was 6.1 %. Most cockroach-sensitized children in this study were also sensitized to other allergens. Also in a patient-based study carried out by several European centres, where skin tests were performed using different indoor and outdoor

Table 1

### Individual allergens of the German and US cockroach identified according to the IUIS Allergen Nomenclature Sub-Committee

Allergen	Name	Molecular weight (kDa)
<i>Blattella germanica</i> <sup>a, c, d, e, f</sup> (German cockroach) 		
Bla g 1 <sup>b</sup>		46
Bla g 2 <sup>b</sup>	Aspartate protease	36
Bla g 3	Hemocyanin	78,9 (Mass spectrometry)
Bla g 4	Calycine	21
Bla g 5 <sup>b</sup>	Glutathione S-transferase	23
Bla g 6	Troponin C	21
Bla g 7 <sup>b</sup>	Tropomyosin	31
Bla g 8	Myosin, light chain	
Bla g 11	α-Amylase	57
<i>Periplaneta americana</i> <sup>a, c, d</sup> (American cockroach) 		
Per a 1		45
Per a 3	Arylphorin/hemocyanin	72
Per a 6	Troponin C	17
Per a 7	Tropomyosin	33
Per a 9	Arginine kinase	43
Per a 10	Serine protease	28

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allergens in over 3,000 patients, an overall prevalence of sensitization to cockroach (in this case *Blattella germanica*) of 8.9% was found, and of 12% in German patients [8]. The prevalence of specific IgE-antibodies to individual cockroach allergens varies considerably; this appears to depend on regional exposure to cockroach allergens [9, 10]. The major allergens are found in the protein groups 1–5 (Bla g 1–5). Since group-1 and -2 cockroach allergens (Bla g 1 and Bla g 2) are released into the environment, they serve well as detection molecules in the assessment of allergen exposure [3].

#### Cross-reactive allergens

Homologous allergens from different cockroach species, e.g. Bla g 1 and Per a 1, exhibit high – albeit variable – cross-reactivity. The tropomyosins Bla g 7 and Per a 7, as well as arginine kinase (Per a 9), are highly similar to the homologous allergens of other arthropods (> 80% identity). The clinical significance of IgE cross-reactivity between tropomyosins

and arginine kinases of cockroaches, shellfish and house dust mites has not been fully elucidated as yet [11, 12].

#### Tick allergy

##### Exposure and distribution

Cases of anaphylactic reactions to pigeon ticks have been consistently reported in recent years, most notably in France, Poland and Italy, but also in Germany [13, 14]. The pigeon tick (*Argas reflexus*), which belongs to the soft-tick family, is a temporary ectoparasite of wild pigeons in southern and central Europe. It feeds primarily on blood from its host at night and seeks refuge in wall crevices and wood cracks during the day. If the pigeon is unable to return to its nest due to, e.g. building work, the tick will seek new hosts by invading homes, where it will infest humans. Adult ticks can survive for several years without food and are extremely challenging to combat. In addition to the severe anaphylactic reactions described in the literature, there are also many instances of mild local reactions. A study carried out in Leipzig, Germany found an 8% rate of severe systemic reactions and a 99% rate of local reactions [14].

In addition to pigeon ticks, occasional cases of classic immediate-type reactions are described following bites from the common wood tick (*Ixodes ricinus*), the Australian paralysis tick (*Ixodes holocyclus*) and the brown dog tick (*Rhipicephalus sanguineus*), which is found primarily in southern Europe. Such cases involve an IgE-mediated reaction to protein in tick saliva.

One particular form of allergy, the delayed red-meat allergy, is also associated with tick bites. This allergy involves IgE sensitization to a sugar epitope, galactose-α-1.3-galactose, which is believed to be triggered by tick bites [15]. Whilst in the US the American lone star tick (*Amblyomma americanum*) and in Australia the Australian paralysis tick (*Ixodes holocyclus*) are discussed as allergy triggers, the common wood tick (*Ixodes ricinus*) and the marsh tick (*Dermacentor*) are associated with sensitization to galactose-α-1.3-galactose in Europe.

##### Allergen identification

The major allergen of the pigeon tick, Arg r 1, is a lipocalin. A number of major mammalian allergens also belong to the lipocalin family, such as Can f 1, Can f 2, Equ c 1 and Mus m 1, among others. However, since their amino acid sequences are highly distinct, any cross-reactivity appears to be ruled out.

No allergens from other tick species have been isolated or characterized to date.

Galactose-α-1.3-galactose, the allergen relevant in delayed red-meat allergy, is found on bovine thyroglobulin. Galactose-α-1.3-galactose bovine thyro-

globulin is available for the diagnosis of galactose- $\alpha$ -1.3-galactose sensitization in the ImmunoCAP® system (Phadia/Thermo Scientific).

### Storage mite allergy

#### Exposure and distribution

Storage mites, microscopic arachnids that feed on plant and animal matter, are typical storage pests. Depending on the species, they are found in grain and animal feed, as well as in hay and straw. The mites most commonly found in Europe include the storage mite (*Lepidoglyphus destructor*), the flour mite (*Acarus siro*), the house mite (*Glycyphagus domesticus*) and the mould mite (*Tyrophagus putrescentiae*). The last of these has a predilection for foods containing protein and fat, such as ham or cheese. All species thrive optimally at temperatures of 20–30°C and at a relative air humidity of > 65 % [16, 17, 18].

#### Allergen identification

For both the storage mite and the mould mite, five different molecules are stored in the allergen database (Tab. 2), including the panallergen tropomyosin (Lep d 10, Try p 10). However, with around 13 % IgE recognition, tropomyosin is a minor allergen. Allergens have been identified in carcasses as well as in faeces. The major allergen belongs to group 2 (Lep d 2, Tyr p 2, Gly d 2) and has been found in mite intestine; its function, however, is unknown.

#### Relevance


Storage mite allergies frequently affect farmers and individuals working in the animal-feed industry. Symptoms often include bronchial asthma and allergic rhinitis. Occasional cases of oral dust mite allergy have been described. Severe allergic symptoms occurred following the ingestion of flour-based foods baked using contaminated ingredients [19]. These reports related to contamination with storage mites as well as with house dust mites.

#### Cross-reactive allergens

Although there is strong cross-reactivity between extracts from storage, house dust and flour mites, there is little IgE cross-reactivity between house dust and storage mites. However, co-sensitizations appear to be common. Group-2 allergens in particular (Lep d 2 and Gly d 2) exhibit high sequence identity. The tropomyosin from storage mites (Lep d 10) has a high degree of identity with Der f 10 and Der p 10 in the house dust mite, such that cross-reactivity is highly likely.

#### Allergies to other arthropods

A variety of other arachnids and insects can also cause allergies in rare cases (Tab. 3). Individuals who work in barns or stables, where spiders are







Allergen	Name	Molecular weight (kDa)
<i>Acarus siro</i> <sup>a, c, d, e, f</sup> (Flour mite)		
Aca s 13	Fatty-acid binding protein	15
<i>Glycyphagus domesticus</i> <sup>a, c, d, e, f</sup> (House mite)		
		
Gly d 2		15
<i>Lepidoglyphus destructor</i> <sup>a, c, d, e, f</sup> (Storage mite)		
Lep d 2 <sup>b</sup>	NPC2 family	16
Lep d 5		
Lep d 7		
Lep d 10	Tropomyosin	
Lep d 13	Fatty-acid binding protein	
<i>Tyrophagus putrescentiae</i> <sup>a, c, d, e, f</sup> (Mould mite)		
Tyr p 2	NPC2 family	16
Tyr p 3	Trypsin	26
Tyr p 10	Tropomyosin	
Tyr p 13	Fatty-acid binding protein	15
Tyr p 24	Troponin C	18

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found in abundance, can experience allergic reactions to the spiders themselves as well as to their cobwebs. Salivary proteins from mosquitos and horseflies can cause strong local allergic reactions and, more rarely, systemic reactions [20, 21]. To date, three mosquito allergens from *Aedes aegypti* have been included in the International Union of Immunological Societies (IUIS) database: Aed a 1, an apyrase (68 kDa), Aed a 2 (37 kDa) and Aed a 3 (30 kD), of as yet unknown function [20]. Other allergens, such as tropomyosin Aed a 7, have been described in the Allergome database. Three major allergens have been identified so far for the horsefly (*Tabanus spp.*): Tab y 1, an apyrase, Tab y 2, a hyaluronidase and Tab y 5, an antigen-5 protein [21]. The last two show cross-reactivity with hyaluronidase and antigen 5 of the Vespidae family [22] and offer an explanation for presumed cross-reactions between wasp venom and horsefly saliva.

The red chironomid larvae (*Chironomus thummi thummi*) are popular as fishing bait and are known to trigger allergic respiratory symptoms in individuals working in fish-food manufacture and in hobby aquarists [23]. Their various haemoglobin components are recorded in the IUIS database as allergens Chi t 1–4 and Chi t 9.

Table 3

Individual allergens of other arthropods identified according to the IUIS Allergen Nomenclature Sub-Committee			
Allergen	Name	Molecular weight (kDa)	
<i>Aedes aegypti</i> (Yellow fever mosquito), <i>Aedes spp.</i> , <i>Culex pipiens</i> <sup>a, c, d, e, f</sup> (Common house mosquito)			
	Aed a 1	Apyrase	68
	Aed a 2		37
	Aed a 3		30
<i>Argas reflexus</i> <sup>e</sup> (Pigeon tick)			
	Arg r 1	Lipokalin	17
<i>Chironomus thummi thummi</i> <sup>a, c, d, e, f</sup> (Red chironomid larvae)			
	Chi t 1	Hämoglobinkomponente III/IV	16
	Chi t 1	Hämoglobinkomponente I/IA	16
	Chi t 3	Hämoglobinkomponenten II-β, VI, VIII, IX	16
	Chi t 4	Hämoglobinkomponente IIIA	16
	Chi t 9	Hämoglobinkomponente X	16
<i>Harmonia axyridis</i> (Asian ladybug)			
	Har a 1		10
	Har a 2	Aldehyddehydrogenase	55
<i>Lepisma saccharina</i> (Silverfish)			
	Lep s 1	Tropomyosin	36
<i>Tabanus yao</i> , <i>Tabanus spp.</i> <sup>a, c, d, e, f</sup> (Horsefly)			
	Tab y 1	Apyrase	70
	Tab y 2	Hyaluronidase	35
	Tab y 5	Antigen-5-verwandtes Protein	26

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The silverfish (*Lepisma saccharina*) is found primarily in the kitchen, bathroom and cellar. In the

case of high levels of infestation, allergens may be present in house dust. The tropomyosin Lep s 1 is the only known allergen to date. It exhibits cross-reactivity with tropomyosin of other arthropods, such as the house dust mite, the cockroach and the shrimp [24].

The multicoloured Asian ladybug (*Harmonia axyridis*) was introduced in the US between 1960 and 1990 as a means of pest control. Since then, it has assumed plague proportions, as the animals swarm out and invade houses and other buildings in their hundreds in order to hibernate. They have become a new and significant source of seasonal indoor allergens in the US [25]. Extract-based diagnostics of ladybug allergy exhibits high cross-reactivity with cockroach extract (*Blattella germanica*). Two major allergens have been identified to date: Har a 1 (10 kDa), a protein believed to be specific for ladybug sensitisation and Har a 2 (55 kDa), a protein related to the aldehyde dehydrogenase of the red flour beetle [25].

Storage pests, such as the wheat weevil (*Sitophilus granarius*), the mealworm beetle (*Tenebrio molitor*), the confused flour beetle (*Tribolium confusum*), the Berlin beetle (*Trogoderma angustum*) or the Mediterranean flour moth (*Ephestia kuehniella*) have also been described as allergen sources (Tab. 4). Since these storage pests are found primarily in stored grain, occupational groups such as farmers, bakers, millers and grain storage workers are particularly affected and, depending on the duration of exposure, can develop symptoms like allergic rhinitis and bronchial asthma [6]. It has not been possible as yet to include any IgE-binding proteins – characterized in the context of case descriptions using immunoblot or inhibition experiments – in the IUIS allergen database.

### Diagnostics and treatment

Routine diagnosis of the rarer allergies to arthropods is carried out by means of skin testing or specific IgE antibody detection using extracts. At present, extracts from three cockroach species (*Periplaneta americana*, *Blattella germanica* and *Blatta orientalis*), four storage mite species (*Lepidoglyphus destructor*, *Acarus siro*, *Glycyphagus domesticus* and *Tyrophagus putrescentiae*) and a number of storage pests (e.g. *Sitophilus granarius*, *Tribolium confusum*, *Trogoderma angustum* and *Ephestia kuehniella*) are available from a variety of manufacturers for the purposes of in vitro diagnostics; *Argas reflexus* extract is available from only one manufacturer (Omega Diagnostics, Reinbeck). However, clinical history can provide a strong indication of pigeon tick allergy: night-time tick bite, typically during the warm season and direct proximity to wild pigeons. Allergen components (Lep d 2, Bla g 1, Bla g 2,

Bla g 5 and Bla g 7) are only available as yet in the ISAC test system (Thermo Scientific), not however in the ImmunoCAP® system (Thermo Scientific).

Preparations for specific immunotherapy are offered at present in Germany only for storage mite allergy. Studies on subcutaneous and sublingual immunotherapy of cockroach allergy are currently underway in the US [26] and the results are promising.

### Perspectives

Given that a variety of allergens (e. g. cockroach, tick and storage mite) are already well characterized and for the most part available as recombinant molecules, the way has been paved for the development of IgE-based diagnostic tests using individual allergen components.

### Conclusion

Although not well standardized, the available extracts permit IgE-based diagnosis of allergies to cockroaches, storage mites and storage pests. A broadening of IgE-based diagnostics in the future with various individual allergens would be beneficial. However, the aim of further developments in molecular testing systems should be to use marker allergens for the unequivocal detection of sensitization and differentiation from cross-reactions. Marker allergens for tick sensitization, such as Arg r 1 from the pigeon tick, could be used to exclude pigeon tick allergy in cases of unexplained anaphylaxis.

#### Christiane Hilger, PhD

Laboratory of Immunogenetics and Allergology  
Centre for Public Health Research  
84 Val Fleuri  
1526 Luxembourg  
E-Mail: christiane.hilger@crp-sante.lu

#### Conflict of interest

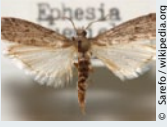



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Available storage pest extracts		Table 4
Latin name		Name
<i>Ephesia kuehniella</i> <sup>a, c, e</sup>		Mediterranean flour moth
<i>Sitophilus granarius</i> <sup>a, e</sup>		Wheat weevil
<i>Tenebrio molitor</i> <sup>a</sup>		Mealworm beetle
<i>Tribolium confosum</i> <sup>a, d, e, f</sup>		Confused flour beetle
<i>Trogoderma angustum</i> <sup>a, e, f</sup>		Berlin beetle

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