New insights into the composition of bee, wasp and ant venoms and how it can contribute to a better therapy of patients suffering sting allergy

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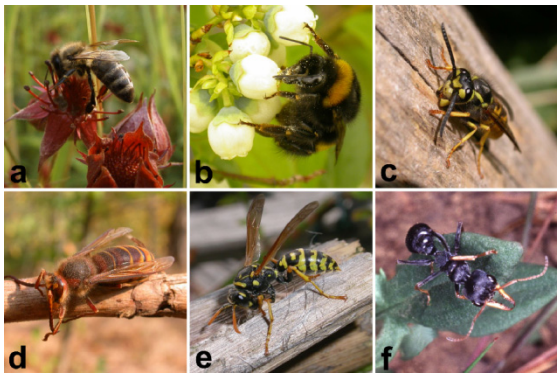
STING ALLERGY: Worldwide Hymenoptera venom allergy is generally caused by the stings of vespids of the genera Vespula (e.g., *Vespula vulgaris*, *V. germanica* and *V. maculifrons*), Vespa (*Vespa crabro*), Dolichovespula (*Dolichovespula maculate*, *D. media*) and Polistes (*Polistes gallicus*, *P. dominulus*, *P. annularis*, *P. exclamans*) and of apids of the genera Apis (*Apis mellifera*, *A. cerana*, *A. dorsata*) and Bombus (*Bombus terrestris*, *B. pennsylvanicus*). Two ant genera are also of importance: Solenopsis (*Solenopsis invicta*, *S. geminate*) and Myrmecia (*Myrmecia pilosula*) (Fig. 1). Hymenoptera venom allergy is an IgE-mediated allergic hypersensitivity of non-atopic origin [3] and the most frequent clinical patterns are: (i) large local reactions exceeding 10 cm in diameter and 24 h in duration and (ii) rapid-onset (usually within 10 min after sting) generalized immediate-type hypersensitivity reactions such as pruritus, urticaria, angioedema, nausea, vomiting, diarrhea, rhinoconjunctivitis, bronchiospasm, hypotension, cardiovascular collapse and unconsciousness [4]. Systemic reactions have been reported to occur in 0.8-5% of the general population [5, 6]; they may be severe and even life-threatening with 0.09-0.45 deaths per million within the general population [7].



1: Some stinging Hymenopteran species: *Apis mellifera* (a), *Bombus terrestris* (b), *Vespula germanica* (c), *Vespa cabrio* (d), *Polistes dominulus* (e) and *Myrmecia pilosula* (f) [pictures provided courtesy and remain copyright of respectively Informatiecentrum voor Bijenteelt, Ghent University (a); Biobest N.V. (b); Devalez Jelle (c-e); and Prof Simon GA Brown, University of Western Australia (f)].

2: *The normal reaction to a bee sting is characterized by pain, redness and swelling. Some parts of the body are more sensitive than others and swelling is most noticeable on the face.*

DIAGNOSIS: Generally, physicians rely upon quantification of specific IgE antibodies and skin tests to diagnose venom allergy. Unfortunately, these tests lack absolute sensitivity and specificity, making the diagnosis of Hymenoptera venom allergy not always straightforward [8]. Indeed, up to 50% of the diagnostic test output is double positive to both bee and vespid venoms. This can be explained by truly double sensitization if the patient was stung by both bees and wasps, or by cross-reactivity between allergens of the two venoms, particularly between the carbohydrate epitopes they share [9]. As the patient cannot always provide the entomologic identification of the culprit, it sometimes remains obscure which life-saving venom-specific immunotherapy should be started. Promising in vitro test methods based on the venom-specific stimulation of basophils are increasingly introduced, and pushed the sensitivity and specificity of the diagnostic tools further upwards [10, 11]. However, serologic as well as effector-cell based diagnosis of venom allergy is currently performed with whole venom preparations, containing in addition to allergens, other non-allergenic components. At the best, current diagnosis of bee or wasp venom allergy only permits the identification of a given allergen source, but not of the molecular entities involved in the adverse immunological reactions.

VENOMICS: Venomic approaches discovered several new proteins and peptides from honey bees, bumble bees, ants and different wasp species, and some of these constituents were proven to be of immunological significance (Table 1).

ALLERGEN CHIPS: Protein microarrays have recently been introduced as promising tools for the simultaneous assessment of specific IgE antibodies against multiple recombinant or purified natural allergens involved in food or pollen allergy [12-15]. The concept of using separate allergens to determine the patients sensitization profile was termed "component-resolved diagnosis" (CRD). Originally aimed at providing the basis for patient-tailored forms of immunotherapy [16], this approach was found to have several other advantages related to the diagnostic test requirements (little amounts of serum), performances (sensitivity, specificity), standardization (concentration, structural integrity, batch-to-batch variation) and interpretation (risk assessment on the likelihood and severity of allergic reactions) [17].

REFERENCES: see de Graaf *et al.* (2009) J. Proteomics 72: 145-154

Table 1 – Hymenoptera venom proteins/peptides recently found by venomic studies and their contribution to allergy

Species[a]	Common name	Protein/peptide	Allergen[b]	References
Agelaia pallipes	Wasp	Antigen 5	sIgE	[62]
		Serine protease	sIgE	[62]
Apis mellifera	Honey bee	Acid phosphatase	Api m 3	[28]
		Dipeptidylpeptidase IV	Api m 5	[28]
		Carboxylesterase	Api m 8	[28]
		Icarapin	sIgE	[26,28]
		PVF-1		[26]
		MRJP9		[26]
		Hexamerin-2		[28]
		MRJP8		[27]
Bombus lapidaries	Bumble bee	Bombolitin 6		[21]
		Bombolitin 7		[21]
		Bombolitin 8		[21]
Myrmecia pilosula	Australian jumper ant	Pilosulin 3.1	var. Myr p 2	[54]
		Pilosulin 4.1	Myr p 3	[54]
		Pilosulin 5		[54]
Polistes dominulus	Mediterranean paper wasp	Dominulin A		[53]
		Dominulin B		[53]
Polistes gallicus	Wasp	Phospholipase	Pol g 1	[57]
		Antigen 5	Pol g 5	[57]
		Hyaluronidase	sIgE	[57]
		Protease		[57]
Polistes major major	Wasp	PMM1		[80]
		PMM2		[80]
		PMM3		[80]
Polistes rothneyi	Wasp	Polistes-mastoparan-R1		[51]
		Polistes-mastoparan-R2		[51]
		Polistes-mastoparan-R3		[51]
		Polistes-protonectin		[51]
Polybia paulista	Wasp	Polybia-MPI		[49]
		Polybia-CP		[49]
Protopolybia exigua	Wasp	Protopolybia-MP I		[50]
		Protopolybia-MP II		[50]
		Protopolybia-MP III		[50]

[a] Underlined species names are not yet included in the IUIS allergen list.
[b] IUIS nomenclature of allergens was provided; sIgE, specific IgE response in patients with allergy detected; var., variant of a known allergen.