Published in final edited form as:
J Allergy Clin Immunol. 2012 May 1; 129(5): 1406–1408. doi:10.1016/j.jaci.2011.12.975.

High sensitivity of CAP-FEIA rVes v 5 and rVes v 1 for diagnosis of *Vespula* venom allergy

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To the Editor

Ves v 5 (antigen 5) is a 23-kDa protein from *Vespula* venom, and it is recognized as the most potent allergen in venoms of the *Vespidae* family.[1] There is a high sequence similarity of Ves v 5 within species of the same genus, such as yellow jacket, that is, *Vespula* (>95%); however, when it is compared with other genera such as *Dolichovespula* or *Polistes*, the sequence identity is much lower (about 60%).[2] Another potential *Vespula* allergen is a 37-kDa phospholipase A1, known as Ves v 1.[1] Neither Ves v 5 nor Ves v 1 is found in honeybee venom. Ves v 5 and Ves v 1 recombinant allergen components, both expressed in insect cells, became available in 2010 and 2011, respectively, for analyses on the ImmunoCAP solid-phase IgE assay (CAP-FEIA; Phadia, Uppsala, Sweden).

Very recently we demonstrated that the current CAP-FEIA recombinant major honeybee venom allergen rApi m 1 (i208) has a limited clinical usefulness for the detection of honeybee venom allergy because of its low diagnostic sensitivity, which was about 60%.[3] Similarly, low sensitivity for CAP-FEIA rApi m 1 was recently also demonstrated by another group.[4] For that reason we wanted to evaluate the diagnostic sensitivity of novel recombinant Ves v 5 (rVes v 5) and rVes v 1 in a routine clinical laboratory setting by analyzing a group of *Vespula* venom allergic patients.

In total, 200 subjects (mean age, 42 years; range, 16-81 years; 99 women) with established *Vespula* venom allergy (19 with large local reactions and 17, 42, 68, and 54 with Mueller grade I, II, III, and IV reactions, respectively) were recruited during a 4-year period. We included only those subjects in which the culprit insect was the yellow jacket. In all subjects, honeybee and yellow jacket (*Vespula* species) venom-specific IgE levels were measured with CAP-FEIA. Tests for CAP-FEIA rVes v 5 (i209) and rVes v 1 (i211) were performed in 2011 from serum samples stored at −40°C. We first tested the samples for rVes v 5, and if they were negative (<0.35 kUA/L), we tested them with rVes v 1. In addition, samples that

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Disclosure of potential conflict of interest: R.Valenta has received research support from the Austrian Science Fund, CDG, Biomas, and Phadia. The rest of the authors declare that they have no relevant conflicts of interest.

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were negative for rVes v 5 and rVes v 1 in the CAP were also tested for IgE reactivity to rVes v 2b (*Vespula hyaluronidase*), rVes v 5, and glycosylated nPhl p 4 by IgE dot-blotting as described previously.[5] rVes v 2b was produced by baculovirus-infected insect cells.[6]

In all study subjects, we demonstrated a positive specific IgE response (2.24 kUA/L [range, 0.41 to >100]) to yellow jacket venom and a negative specific IgE response (<0.35 kUA/L) to honeybee venom (Fig 1). The median concentration of specific IgE antibodies to yellow jacket venom was 1.34 (range, 0.44-87.4) in large local reactions and 1.17 (range, 0.57-71.2), 3.5 (range, 0.42 to >100), 2.16 (range, 0.41 to >100), and 2.51 kUA/L (range, 0.43-90.3) in Mueller grade I, II, III, or IV subgroup, respectively. Next, we examined the subjects for the presence of specific IgE antibodies to rVes v 5 or rVes v 1. We found that 84.5% of the subjects (169 of 200) had positive specific IgE for rVes v 5. Of 31 negative subjects, 15 subjects were positive for rVes v 1 (additional 7.5%). Thus, altogether 184 of 200 subjects (92%) were positive for either rVes v 5 or rVes v 1. The median concentration of rVes v 5 or rVes v 1 in all positive subjects was 2.78 kUA/L (range, 0.36 to >100) and 1.63 (range, 0.36-49.4), 2.08 (range, 0.39-44.7), 5.7 (range, 0.59 to >100), 2.58 (range, 0.39-39.6), and 2.24 kUA/L (range, 0.36 to >100) with sensitivities of 79% (15 of 19), 100% (all 17), 95% (40 of 42), 94% (64 of 68), and 89% (48 of 54) in large local reactions and Mueller grade I, II, III, or IV subgroup, respectively. Consequently, the diagnostic sensitivity of Ves recombinants was comparably high in all subjects who had experienced systemic reactions following a yellow jacket sting and also in those who experienced very severe reactions of Mueller grades III and IV. It was slightly lower (79%) only in those patients who experienced local reactions. Of the 16 sera that were negative to rVes v 5 and rVes v 1 in the CAP, 2 sera were positive to dot-blotted rVes v 2b (additional 1%). Both subjects experienced severe reactions of Mueller grade III or IV. In the dot blot, an additional 2 sera were positive to rVes v 5 and an additional 4 sera contained IgE antibodies specific for carbohydrates on Phl p 4.

These results are comparable with the previous rVes v 5 diagnostic evaluations by commercially available liquid phase detection system (ADVIA Centaur; Siemens Medical Solution Diagnostics, Deerfield, Ill).[7] In this report, specific IgE to rVes v 5 were demonstrated in 87% of 100 *Vespula* allergic subjects. An even higher ratio of identification (100%) was observed in our previous report by using in-house IgE immunoblotting and/or ELISA rVes v 5, but on limited number on *Vespula* allergic 20 patients.[5]

In this study, we demonstrated that additional use of Ves v 1 significantly enhances the diagnostic sensitivity (for almost 8%) of diagnostic tests based on recombinant yellow jacket venom allergens. Nevertheless, rVes v 5 and rVes v 1 had missed 8% of subjects with established allergy. Testing for rVes v 2b added only a minor contribution to diagnostic sensitivity. Primarily, 3 allergens were recognized as responsible for *Vespula* venom allergy, beyond Ves v 5 and Ves v 1, also Ves v 2, which occurs in isoforms.[1] Recently, a novel 100-kDa glycosylated protein with homology to dipeptidyl peptidases with allergenic potential, namely, Ves v 3, was reported as a yellow jacket allergen.[7] rVes v 3 showed IgE reactivity in approximately 50% of Vespula allergic subjects (in overall 54 tested)[8] and might be useful to diagnose the few patients who are not identified with rVes v 5, 1, and 2.

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Clinically, we cannot afford to miss a patient who is sensitive to insect venom; thus, the whole venom (that contains all the venom allergens as a single test) needs to be the first line of laboratory evaluation. However, the identification of the disease-causing insect venom in venom allergy is often difficult. In such cases, commercially available CAP-FEIA tests based on recombinant rVes v 5 and rVes v 1 allergens should be helpful for the serological dissection of *Vespula* venom allergy.

Acknowledgments

We thank Lucas Mach, Daniel Kolarich, and Friedrich Altmann, Department of Applied Genetics and Cell Biology, University of Natural Resources and Life Science, Vienna, Austria, for recombinant Ves v 2b.

This study was supported in part by the Slovenian research agency (ARRS), Christian Doppler Research Association, and the Austrian Science Fund (FWF).

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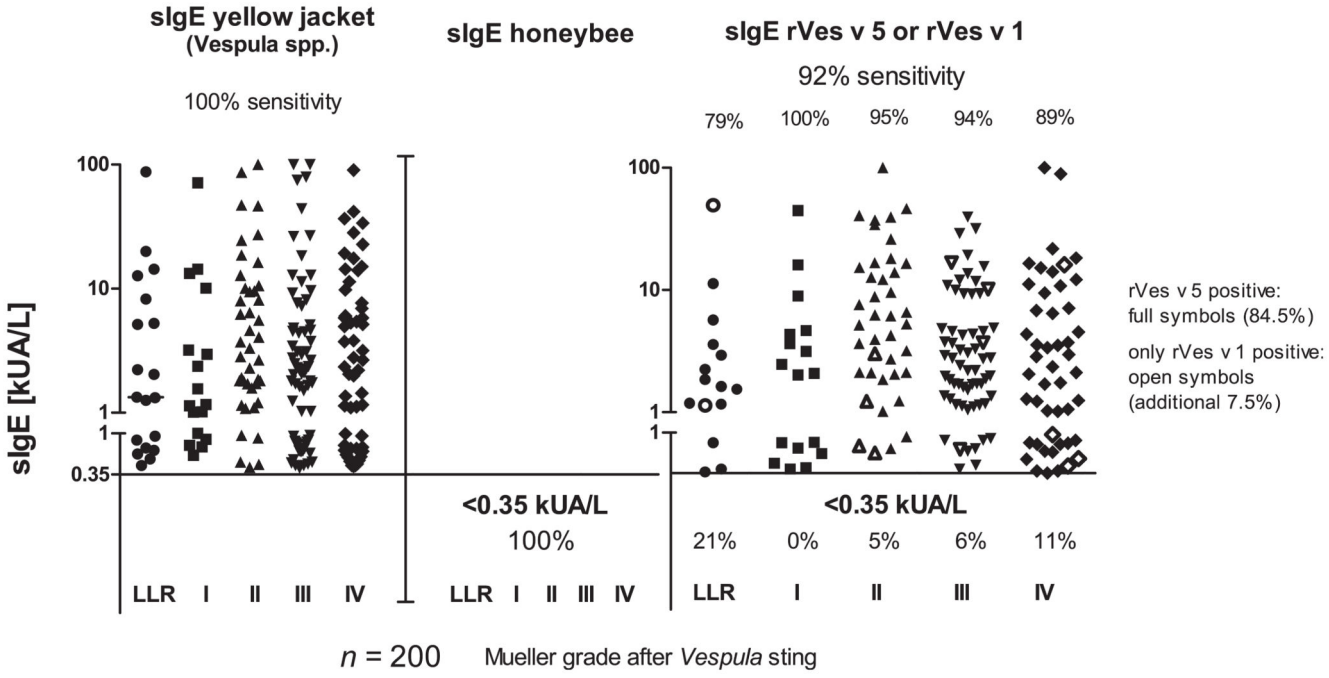

Fig. 1.

Wasp and honeybee venom, recombinant vesp v 5 and vesp v 1 CAP-FEIA specific IgE measurement in wasp venom–allergic subjects.

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