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## Molecular allergens in the diagnosis of latex allergy

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### KEY WORDS

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### SUMMARY

**Background:** Molecular allergens enable the definition of sensitization profiles in allergic patients. **Aim:** to validate the most helpful allergens for the diagnosis of latex allergy in different clinical situations. **Methods:** 130 patients suspected to be allergic to latex with positive IgE against natural rubber latex (NRL) have been studied: 97 were confirmed as latex allergic (among which 55 professionally exposed to latex and 35 with a peranaesthetic anaphylactic shock) and 33 were only sensitized to latex without clinical allergy. Each serum was tested for IgE against 9 recombinant latex allergens and bromelain using Phadia ImmunoCAP®250. **Results:** rHev b 6.01, 6.02, 2 and 5 were the major allergens in the allergic population. An excellent correlation (94%) was observed between IgE against rHev b 6.01 and latex prick test positivities. IgE against rHev b 1, 3 and 5 were more frequent and their levels significantly higher in patients with peranaesthetic anaphylactic shock. Among the asymptomatic patients (29/33 allergic to pollen), NRL IgE positivity is explained by the presence of anti-rHev b 8 and/or anti-carbohydrate IgE. **Conclusions:** rHev b 6.01 and rHev b 5 specific IgE are of major interest to confirm latex allergy diagnosis. rHev b 5 is particularly useful in case of monosensitization where clinical symptoms and latex skin prick tests may be discordant. rHev b1 and rHev b 3 are interesting to document multi-operated and peranaesthetic latex allergy. Finally, rHev b 8 is a helpful marker to highlight latex/pollen cross-reactivity which improves the specificity of the serological tests.

### Abbreviations

CCD: Cross-reactive Carbohydrate Determinants  
CRD: Component-resolved diagnosis  
HCW: Health Care Workers  
Hev b: *Hevea brasiliensis*  
NRL: Natural Rubber Latex  
RLA: Recombinant Latex Allergens  
sIgE: specific immunoglobulin E  
SPT: Skin Prick Test

### Introduction

Since the 1980s, allergy to natural rubber latex (NRL) has been a major clinical problem, particularly in risk group patients such as health care workers (HCW) or patients with multiple surgeries (1, 2). The diagnosis of latex allergy is based on polymorphous clinical signs, the positivity of cutaneous tests using latex extracts and the detection of specific IgE (3). The definitive diagnosis of latex allergy cannot be made on the single positivity of latex specific IgE since this positivity only reflects a sensitization and can be observed in

patients without overt latex allergy (false positivity). Therefore, additional reliable tests could be interesting.

13 proteins have been recognized as latex allergens by the International Union of Immunological Societies (4). They have been purified from crude NRL extract from *Hevea brasiliensis* and are referred to as Hev b allergens. They all have been cloned and sequenced (5, 6). Detecting IgE against these allergens allows a better understanding of sensitization profiles of latex allergic patients and of cross-reactions between latex and food or pollens. Previous studies have shown that Hev b 6.01 and Hev b 5 are major allergens in latex allergic patients (7-10) and that Hev b 2 and Hev b 13-specific IgE are often found in latex allergic HCW (8, 9). It is also demonstrated that Hev b 1 and Hev b 3 are major allergens for children undergoing multiple surgeries such as spina bifida patients (7, 9, 11). The aim of this study is to validate, using a component-resolved diagnosis approach (CRD), the most helpful molecular allergens for the diagnosis of genuine latex allergy in 130 patients who had positive IgE against NRL.

## Materials and methods

### Patients

We studied 130 patients (97 females/33 males, mean age: 34 years [range: 8 - 77 years]) suspected to be allergic to latex due to the positivity of specific IgE (sIgE) against NRL. These patients were divided into 2 groups following clinical findings and results of latex skin prick tests (SPT) (Table 1). The first group (97 patients, 73 females) included symptomatic patients with latex allergy. These patients developed typical allergic symptoms after latex exposure such as cutaneous (pruritus, urticaria, oedema...) and respiratory (sinusi-

tis, asthma) reactions or anaphylactic shock. In this group, 55 patients were professionally exposed to latex and 35 experienced a peranaesthetic anaphylactic shock. In addition, 54 patients of this group were allergic to pollen and 41 suffered from food allergy (avocado, banana, kiwi, chestnut, tomato or exotic fruits). Latex SPT were performed for 84 patients. The second group included patients without clinically documented latex allergy but presenting positive NRL sIgE (33 patients, 24 females). In this population, 29 patients were allergic to pollen and 20 presented with a food allergy (as described for the first group). 29 SPT were performed.

### Skin prick tests

SPT were carried out using two commercial NRL extracts: Allerbio (Paris, France) and Stallergènes (Anthony, France). Histamine and codeine sulphate were used as positive controls and normal saline as negative control. The immediate reaction was read at 15 min and a wheal of at least 3 mm greater than the negative control was considered as positive.

### IgE antibody analysis

Serological testing was performed using ImmunoCAP®250 system (Fluorescence Enzyme Immunoassay, FEIA) in accordance to the manufacturer's instructions (Phadia, Uppsala, Sweden). All sera were analyzed for specific IgE against a NRL extract supplemented with rHev b 5 (Phadia Latex Recombi+ k82 ImmunoCAP® [range: 0.1 - >100 kU/L]), 9 *Escherichia coli* recombinant latex allergens (rHev b 1, rHev b 2, rHev b 3, rHev b 5, rHev b 6.01, rHev b 6.02, rHev b 8, rHev b 9, rHev b 11 ImmunoCAP®) and bromelain (k202, ImmunoCAP®). Bromelain was used to detect IgE against cross-reactive carbohydrate determinants (CCD).

**Table 1** - Demographics and clinical data of the study population

Patients	Sex ratio (Male/Female)	Age (years) median (range)	Allergy to pollen only	Food allergy only	Allergy to pollen and food	NRL specific IgE (kU/L) median (range)	Positive prick test
• Symptomatic allergic patients (n=97)	24/73	37 (9 - 77)	26/97	13/97	28/97	18.4 (0.10 - >100)	76/84
HCW (n=55)	14/41	39 (23 - 41)	22/55	6/55	10/55	8.7 (0.2 - 47.1)	40/44
Peranesthetic shock due to latex (n=35)	7/28	39 (19 - 51)	4/35	5/35	13/35	31.4 (0.1 - >100)	30/33
Others (n=7)	3/4	32 (9 - 51)	0/7	2/7	5/7	29.4 (3.2 - 55.2)	6/7
• Asymptomatic sensitized patients (n=33)	9/24	27 (8 - 58)	10/33	1/33	19/33	6.2 (0.6 - 36.1)	0/29

sIgE values equal to or greater than 0.10 kU/L were considered positive.

#### Statistical analysis

The Mann-Whitney U-test was applied for sIgE means comparison. P-values of less than 0.05 were considered significant.

## Results

### *Recombinant latex allergens (RLA) recognition pattern among the allergic population (n=97)*

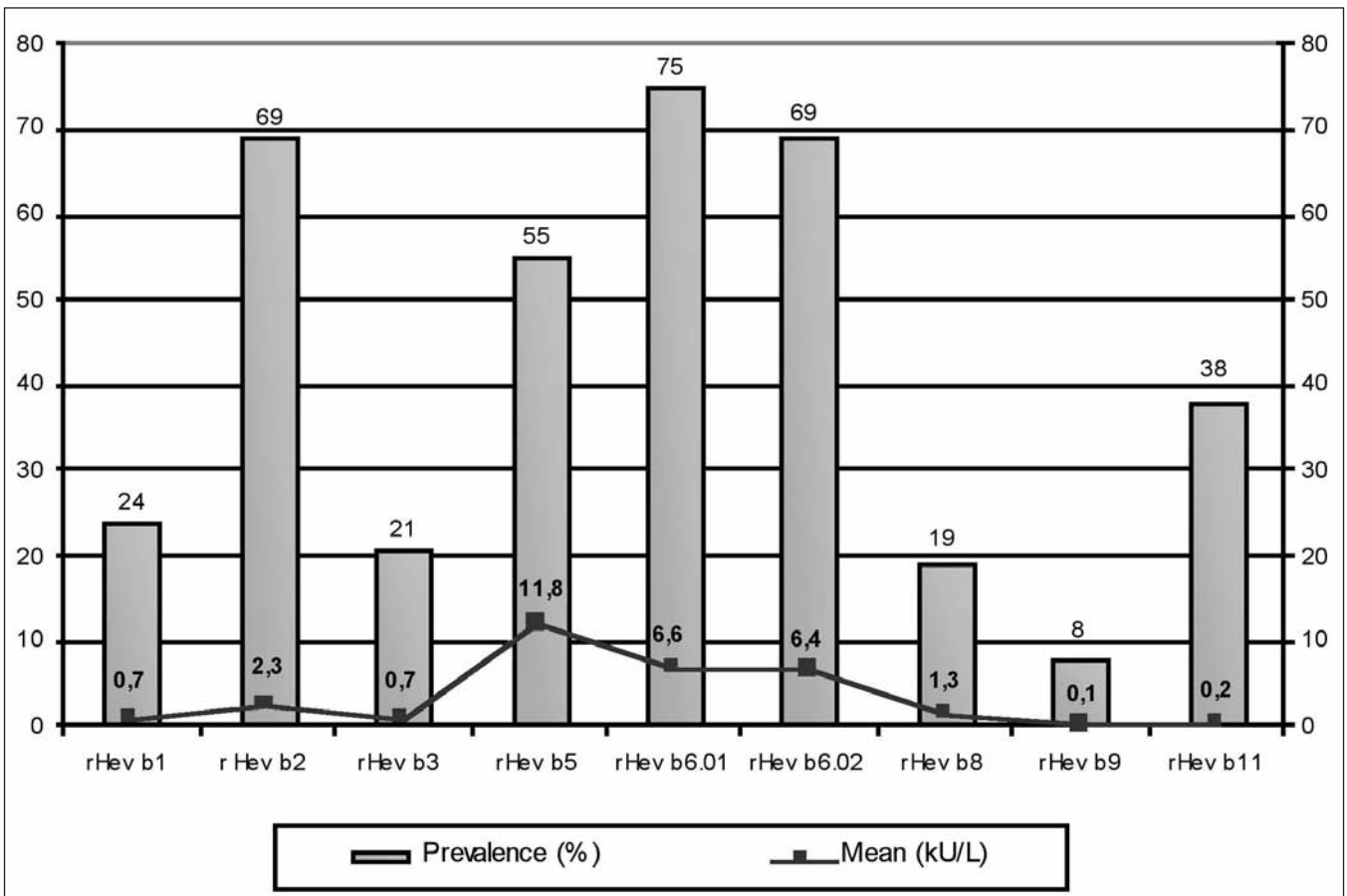
The highest prevalence was observed for rHev b 6.01 sIgE (76/97, 78%), followed by rHev b 6.02 (69/97, 71%), rHev b 2 (66/97, 68%) and rHev b 5 (59/97, 61%) (Fig. 1).

The range of IgE levels was very large for rHev b 5, rHev b 6.01 and rHev b 6.02 sIgE (0.1 to >100 kU/L), less extended for rHev b 2 sIgE (0.1-45 kU/L) and relatively small for the others (<20 kU/L).

Strong associations were observed between rHev b 6.01 and rHev b 6.02 sIgE (69 patients out of 76 [91%] who displayed rHev b 6.01 sIgE also displayed IgE against rHev b 6.02) and between rHev b 6.01 and rHev b 2 sIgE (65 patients out of 66 [98%] who had IgE against rHev b 2 also displayed IgE against rHev b 6.01). No monosensitization profile was observed with rHev b 6.02 or with rHev b 2. Interestingly, rHev b 6.01 and rHev b 5 sIgE had never been found in non allergic patients. Moreover, we showed a strong correlation between latex SPT and rHev b 6.01 reactivity: 65 cutaneous tests out of the 67 performed were positive in patients with rHev b 6.01 sIgE (63 with prick-tests and 2 with the glove test).

In the 97 latex allergic patients, 7 were mono-sensitized to rHev b 5. Out of these 7 patients, 5 were occupationally ex-

**Figure 1** - Prevalence (bars) and mean (squares) of specific IgE to recombinant latex allergens in the allergic population (97 patients).



posed to latex and, remarkably, 3 SPT of 6 performed were negative with both Stallergènes and Allerbio extracts.

Some particularities have been observed in the perianaesthetic anaphylactic shock subgroup (n=35): rHev b 1, rHev b 3 and rHev b 5 were more frequently recognized compared to the rest of the allergic population (Figure 2). Furthermore, mean levels of rHev b 1, rHev b 3 and rHev b 5 sIgE are statistically significantly higher (p=0.026, p=0.047 and p=0.007 respectively). sIgE response to rHev b 1 and rHev b 3 was highly correlated in this subgroup (9 patients out of the 12 who displayed rHev b 1 sIgE also displayed IgE against rHev b 3 and 9 patients out of the 11 who displayed rHev b 3 sIgE also displayed IgE against rHev b 1).

*Pattern of IgE reactivity against RLA in the asymptomatic sensitized population (n=33)*

In this population, NRL sIgE levels were significantly lower

than in the allergic population (Table1). None had a positive SPT.

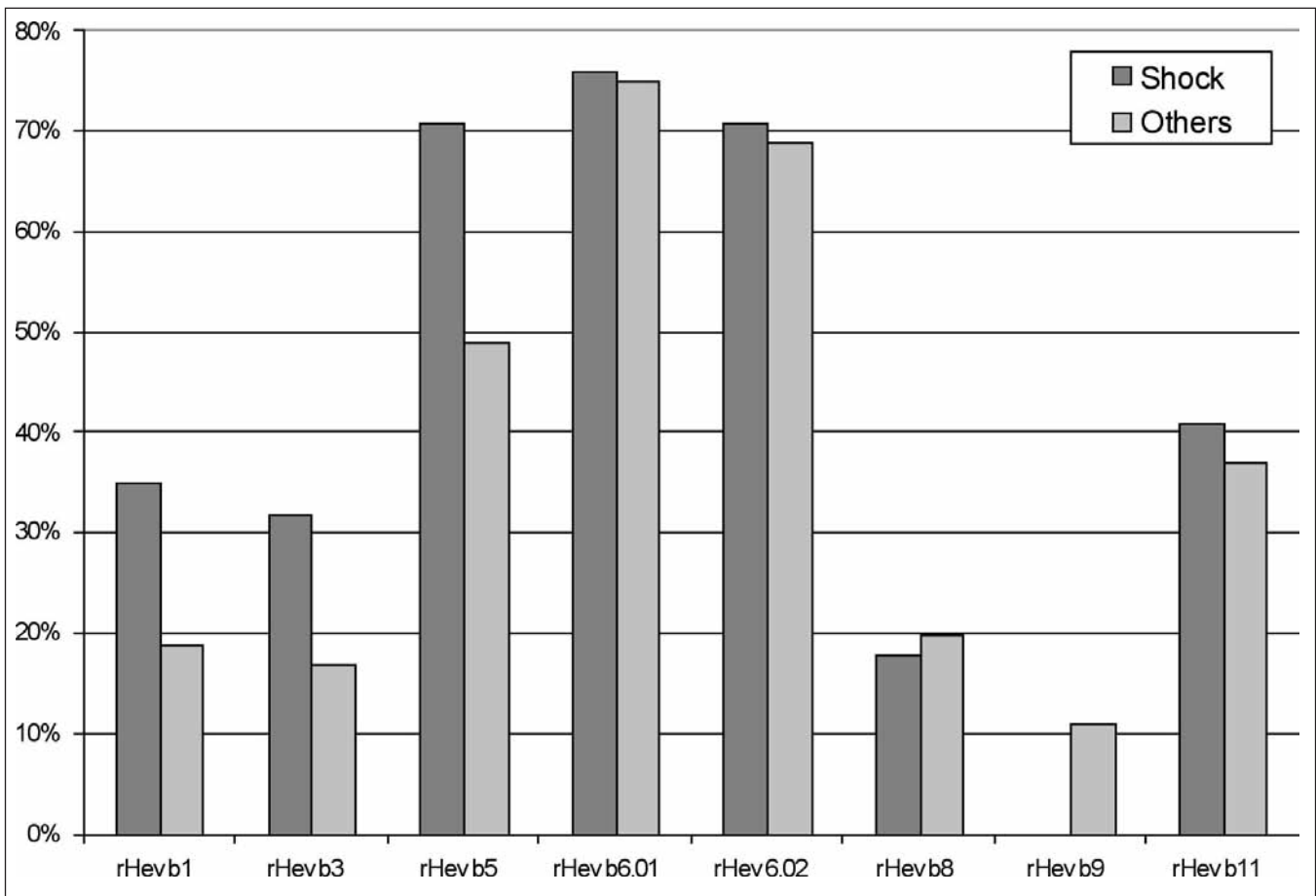
26 patients were monosensitized to the profilin rHev b 8. All of them were allergic to pollen. In contrast, among the 43 patients allergic to latex but not to pollen, only one had IgE against rHev b 8.

The other 7 patients were negative for all RLA but all of them present anti-CDD IgE which are certainly responsible for NRL sIgE positivity.

## Discussion

In recent years, a molecular approach has appeared to be very important in the understanding of allergic reactions. Indeed, allergenic extracts are made of numerous proteins and only few of them, named allergens, are responsible for allergic reaction. Furthermore, allergen concentration in su-

**Figure 2** - Comparison of prevalence of specific IgE against recombinant latex allergen between patients with a perianaesthetic anaphylactic shock due to latex (shock, n=35) and the other latex allergic patients (others, n=62).



ch extracts highly depends on the source material and preparation method, leading to a lack of standardization in allergy diagnosis. The cloning and sequencing of allergens permit their industrial production which improves the accuracy of diagnosis, particularly for latex allergy (9, 12). This study demonstrates the importance of determination of sIgE reactivity profiles using RLA in patients sensitized to NRL.

*rHev b 6.01, rHev b 6.02, rHev b 2 and rHev b 5 are the major allergens in symptomatic latex allergic patients*

Among a large population of 130 patients presenting with NRL sIgE, 97 were diagnosed as allergic to latex. In these allergic individuals, the positivity of IgE against rHev b 6.01, 6.02, 2 and 5 was the most frequently found (78, 71, 68 and 61% respectively). These results are in good agreement with literature (8, 10, 13-15) (except for rHev b 2 which will be discussed below). Indeed, Kurup et al. tested the sera of 26 latex allergic HCW against 11 latex allergens (three native purified proteins nHev b 2, 4 and 13 and eight RLA rHev b 1, 3, 5, 6, 7, 8, 9 and 10) using ELISA tests; they concluded that Hev b 2, 5, 6 and 13 (this latter not tested in our study) showed significant reactivity with patients sera and that Hev b 6 was the major allergen (sensitivity: 65%) (8). Similarly, Mari et al. explored 21 patients sera positive to NRL extracts with the ImmunoCAP® system using the 9 RLA commercialized by Phadia as in our study: the majority of sera reacted with rHev b 6.01 and 6.02 (71%) (13). Another study, performed in 23 latex allergic children, without spina bifida, showed that IgE against rHev b 6.01, 6.02 and 5 were found in respectively 70, 65 and 43% of these patients (14). These *in vitro* results were confirmed by 2 *in vivo* studies. In the first one, Bernstein et al. performed SPT with nHev b 1, 2, 3, 4, 6.01, 7.01, 13 and rHev b 5 allergens in 62 HCW with NRL allergy: they demonstrated that nHev b 2, 6.01, 13 and rHev b 5 were the major allergens (16). Yip et al. made SPT in 29 latex allergic patients with rHev b 2, 3, 5, 6, 7 and 8 recombinant allergens and found that 66% of patients reacted with rHev b 6 and 62% with rHev b 5 (17).

The high frequency of rHev b 6.01 sIgE in the latex allergic population from our study and from literature, and the strong correlation between *in vitro* (rHev b 6.01 sIgE) and *in vivo* tests (latex SPT) confirm that this allergen is of major interest for the diagnosis of latex allergy (7-9, 16, 17). Furthermore, in our series, IgE against rHev b 6.01 have never been detected in non allergic patients.

Concerning rHev b 2, our data, detecting a 68% positivity in the allergic population, are not consistent with the studies of Mari et al. (13) and Sanz et al. (14). Indeed, these groups found no IgE reactivity to rHev b 2 in the sera of their latex allergic population. Hev b 2 molecule exhibits a beta-1,3-glucanase activity. This allergen has several carbohydrates recognition sites (18). The presence of carbohydrates cross-reactivity determinant (CCD) in the natural Hev b 2 molecule could explain the difference of reactivity observed between natural and recombinant Hev b 2 in different studies. As an illustration, *in vivo* studies showed a 63% positivity with nHev b 2 (16) and only 7% with rHev b 2 (17). Nevertheless, as demonstrated by Barre et al. (19), the majority of the IgE binding epitopes are different from the N-glycosylation sites which is an argument for a limited contribution of the glycosylation in the allergenicity of Hev b 2. Our data, consistent with the results of Beaudoin et al. (20) who found rHev b 2 sIgE (with ImmunoCAP® reagent, such as us) in 71% of latex allergic patients, shown that rHev b 2 is a major allergen. This suggests also that variability in the conformation of the allergen proteic core could cause differences in IgE recognition. Currently, rHev b 2 is no longer marketed for *in vitro* diagnosis. Nevertheless, the diagnostic interest of Hev b 2 appears marginal, since it is strongly correlated with rHev b 6.01.

In line with our results on rHev b 5, Yeang et al. showed that more than half of the subjects mono-sensitized to rHev b 5 were falsely skin test negative with freeze-thawed latex serum antigen (analogous to the Stallergenes latex reagent) (21). For these authors, the concentration of Hev b 5 in SPT preparations is insufficient to reach the threshold for skin reactivity. Thus, the determination of IgE against rHev b 5 is of highest importance when clinicians are facing discrepancies between clinical signs and SPT.

*rHev b 5, rHev b 1 and rHev b 3 are helpful markers for the investigation of perianaesthetic anaphylactic shock and the management of multi-operated patients*

rHev b 5 is of special interest in allergic patients having experienced a perianaesthetic anaphylactic shock. The sera of these patients reacted more frequently with rHev b 5 and also with rHev b 1 and rHev b 3 compared with the rest of the allergic population (Fig. 2). Furthermore, IgE against rHev b 5 had a statistically higher mean in this population. Similar results have been described in children with multiple surgeries or with spina bifida (7, 9). Another study pointed out a positive correlation between sensitization to rHev



b 5 and the number of interventions in latex allergic children (14).

Until now, rHev b 1 and rHev b 3 have been described as major allergens only in spina bifida patients (9, 11), who were multi-operated. This is in line with two studies showing IgE against rHev b 1 and rHev b 3 only in children with two or more operations (7, 14).

#### *rHev b 8 and CCD as markers of asymptomatic latex sensitization*

Hev b 8 has been described as a profilin which highly cross-reacts with other plant profilins. For example, there is a 75% homology between the birch (Bet v 2) and the latex (Hev b 8) profilins (22). Vallier et al. first described this profilin as an IgE binding component in latex, but were dubious about its clinical relevance since only 2 patients out of 19 latex allergic patients displayed detectable IgE antibodies to profilin (23). Ganglberger et al. observed that rHev b 8 sIgE are only found in sera of latex sensitized patients which have a pollen or food associated allergy; thus, they concluded that this sensitization takes place via pollen or food profilin more than via latex (24). Our present results are quite similar since only one out of the 43 latex allergic, but non pollinic patients had IgE against rHev b 8; this patient was food allergic. Accordingly, Sanz et al. reported only four latex allergic children out of 23 with IgE against rHev b 8; these four patients were pollinic (14). Ebo et al. demonstrated that plant allergic patients with false positive IgE for latex had a significantly higher prevalence of profilin IgE than latex allergic patients (11/21 versus 0/17) (25). The clinical irrelevance of latex profilin was also demonstrated in a recent study showing that, in a population of patients monosensitized to Hev b 8, latex glove wearing tests were negative and that it is possible to achieve normal (non latex safe) surgical settings in these patients (26).

In our series of 33 clinically irrelevant latex positive sera, 7 were negative for the nine RLA tested. The positivity of latex CAP FEIA was explained by the presence of IgE against CCD. CCD have been identified as highly cross-reactive IgE binding structures and were particularly frequent in the sera of patients suffering from plant allergy or sensitized to venom. As a result, CCD yielded false positivity of IgE against latex and the in vitro diagnosis of latex allergy might benefit from the use of preparations without CCD such as recombinant allergens (25, 27).

Finally, 1 patient allergic to latex had IgE against latex which cannot be explained by the nine RLA tested, nor by bromelain. Using the same recombinants, Mari et al. also reported

three patients out of 21 negative to bromelain and to all RLA tested (13). It is worth mentioning that among the 13 latex allergens identified, five were not tested in our study, i.e. Hev b 4, 7, 10, 12 and 13. Hev b 10 and Hev b 12 are known to be minor allergens and to cross-react with molds and plant-derived foods respectively. In vitro (8) and in vivo (16) studies, in HCW, demonstrated the low clinical value of Hev b 4 and Hev b 7 compared to Hev b 2, 5, 6 and 13. In contrast, Hev b 13 yielded a prevalence of 63–75% in latex allergic spina bifida patients and of 83% in latex allergic HCW in a study from Raulf-Heimsoth et al. (9). In this study, 6 patients out of 53 who were negative to the same recombinants as ours had IgE against nHev b 13. As a consequence, testing Hev b 13 could be helpful for the diagnosis of latex allergy.

#### **Conclusion**

In conclusion, in a latex sensitized population, the introduction of RLA seems of major interest, since the positivity of specific IgE against NRL often leads to an overestimation of latex allergy. Indeed, analysis of RLA profiles allows discrimination between overt allergy and asymptomatic sensitization in most cases. From this study, the most relevant recombinant allergens to diagnose latex allergy are rHev b 6.01 and rHev b 5. Both represent major latex allergens: rHev b 6.01 is strongly correlated with in vivo tests while rHev b 5 is particularly useful when a disagreement exists between clinical history and cutaneous tests. In our series, taken together, these two allergens identified 90% of latex allergic patients with a perfect specificity (100%). Concerning rHev b 8, in our study, isolated positive IgE against this allergen were always associated with clinically irrelevant latex allergy. As a result, rHev b 8 is helpful to identify cross-reactivity between latex and pollen. This could lead to the development of reagents containing a mixture of latex allergens such as rHev b 6.01, rHev b 5 and potentially Hev b 13 for the future diagnosis of latex allergy. On the other hand, a new tool, using microarray technology, which allows multiple analysis in a single measurement, is being evaluated and seems to be promising in the diagnosis of latex allergy (10, 15).

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