

Successful and safe use of royal jell with careful attention to its cross reactivity to certain allergens

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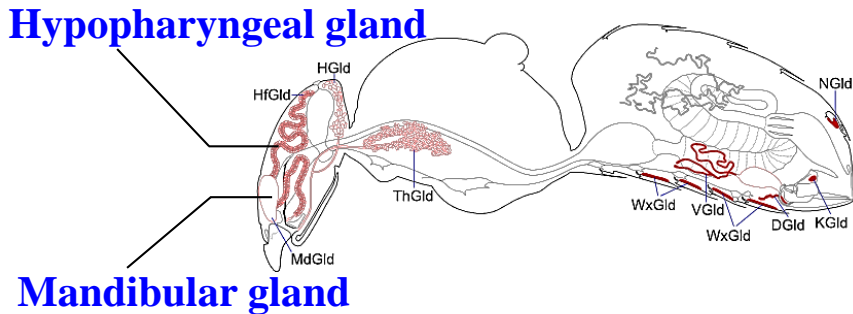
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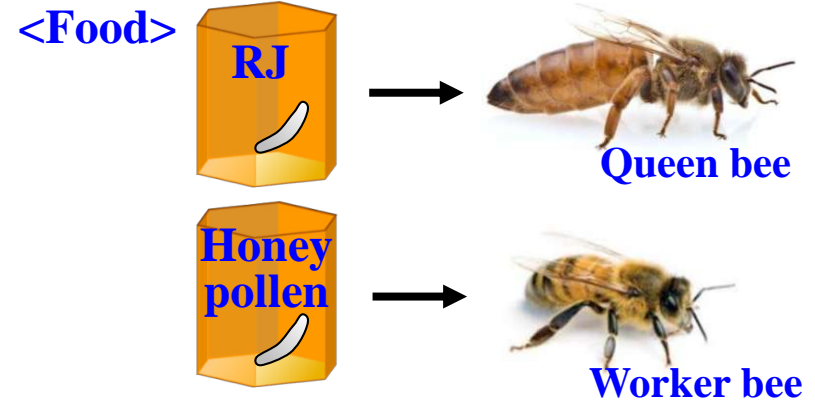
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What's "Royal jelly"?

secreted from hypopharyngeal and mandibular gland of worker bees.

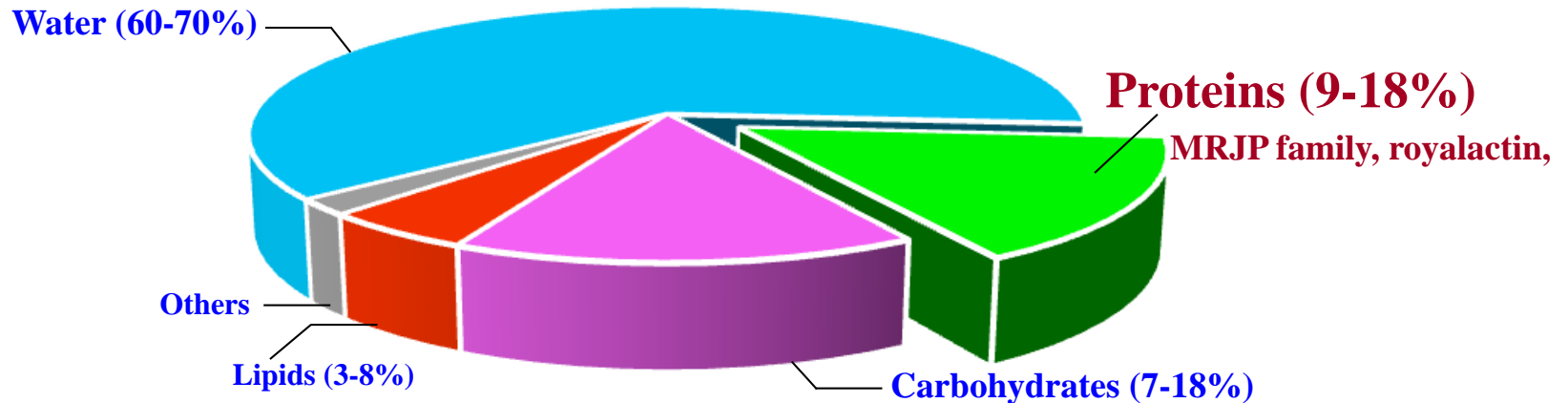


the key substance responsible for queen bee differentiation.



contains various nutritional components.

Proteins account for approx. 50% of dry weight.



The use of RJ

- RJ has various beneficial effects on fatigue, menopausal symptoms, and fat metabolism etc.
- RJ has been used for medicine, health supplement, beverages, and cosmetics worldwide.
- On the other hand, RJ includes a warning indication for consumers who have allergic diathesis.



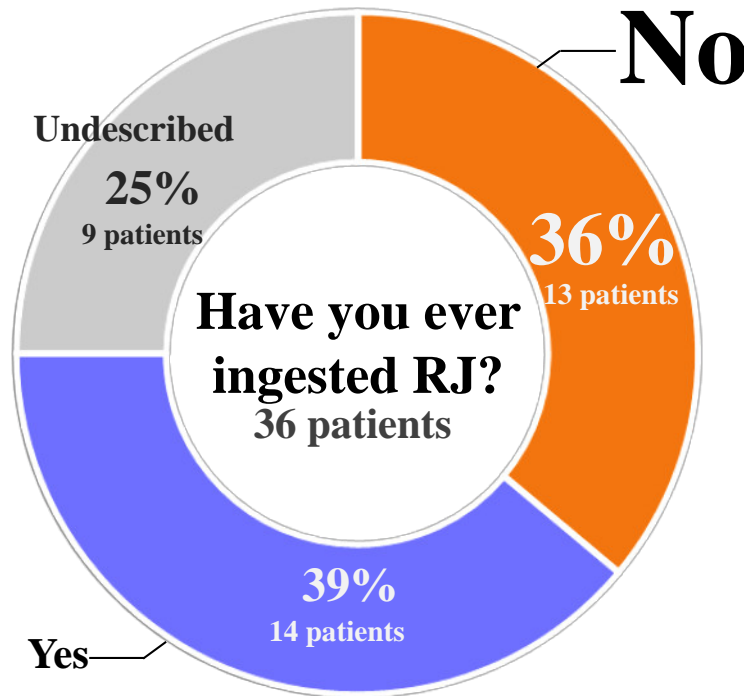
“This product may cause **severe allergic reactions** in asthma and allergy sufferers.”

Case reports of RJ-induced allergy

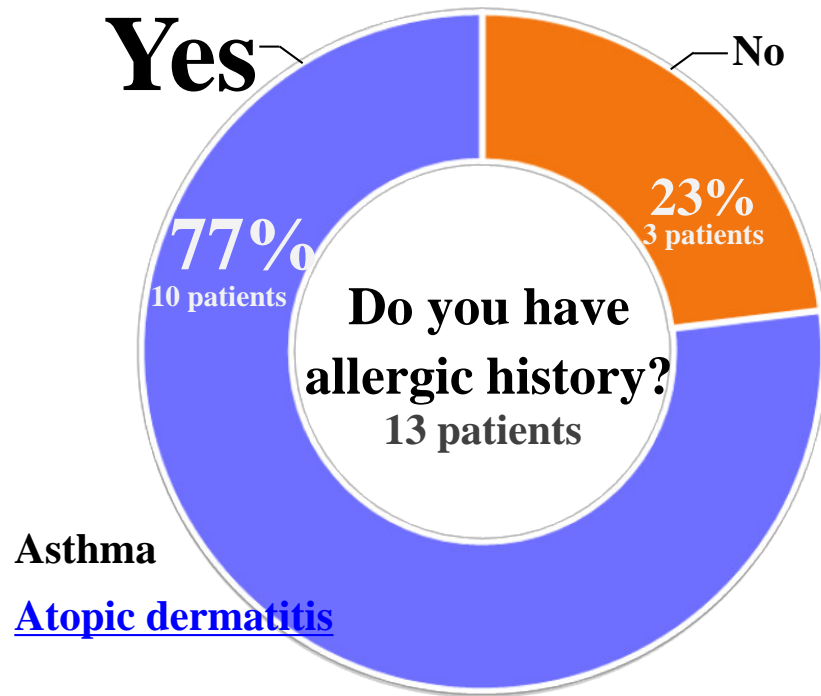


Year : 1986-2018
Data base : PubMed, J-global
Language : English, Japanese
Case reports : 22 reports
Patients data : [36 patients](#) data

Sex : 23 female, 12 male
Age : 7 – 66 year old (ave.27, median 23.5)
Country : Australia, Italy, Spain, UK, NZ, JPN, CN
Symptom : erythema, angioedema, pruritus, bronchospasm, [death \(1 case\)](#)



➤ Thirty-six percent of the patients have [never](#) been exposed to RJ.



➤ Most of the them had allergic history (asthma, atopic dermatitis).

Possible explanation

“Why do some allergy patients show allergic reaction after the first exposure to RJ?”

There are two possibilities.

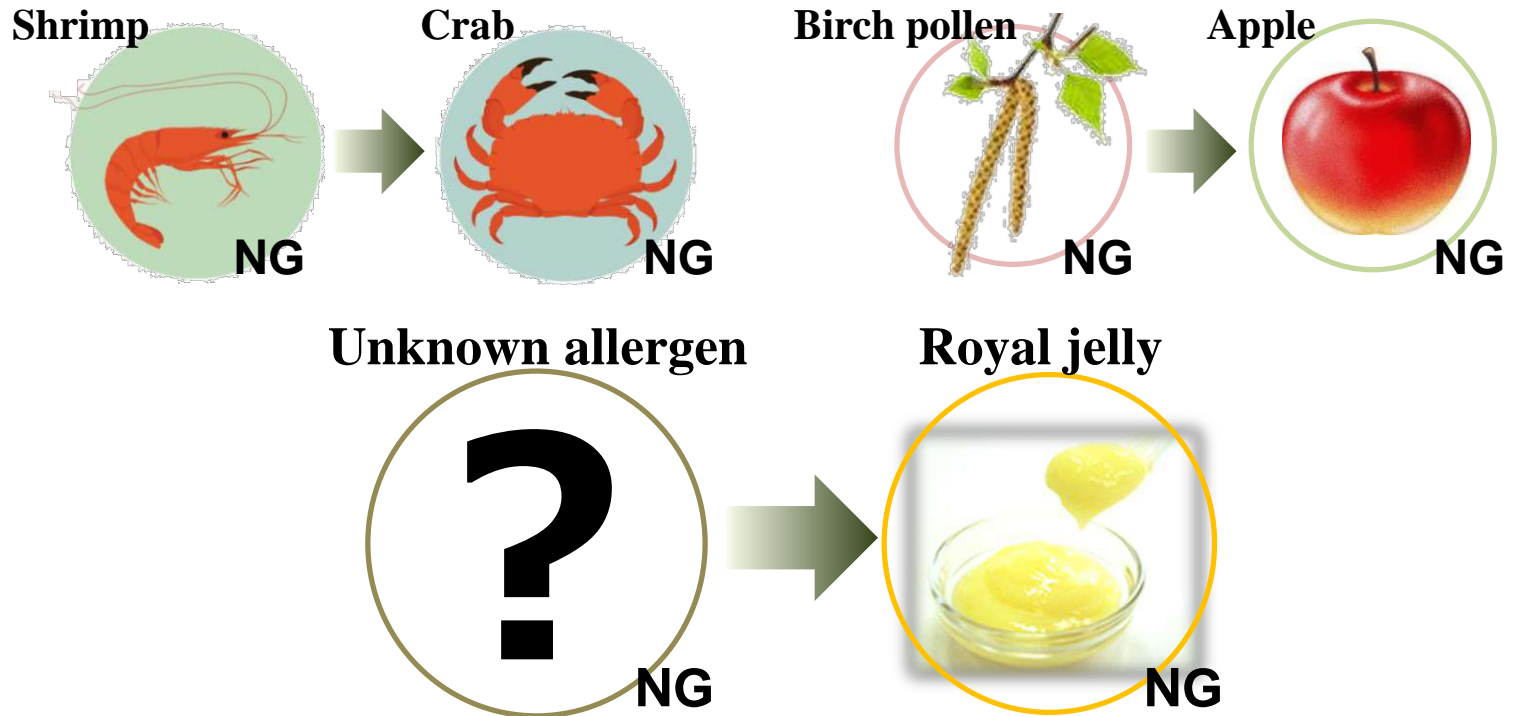
- 1) they have already been sensitized with RJ and really have RJ-specific antibody.**
- 2) they have cross-reactive antibodies against RJ.**

Cross-reactivity of RJ

- **What's cross-reactivity?**

Cross-reactivity occurs when an antibody raised against one specific antigen recognizes two or more antigens that have similar structural regions.

Therefore, a person who has allergy to some food may be positive to other foods with similar proteins.



The purpose of our study



Why does allergy occur, even though the first ingestion of RJ, in some allergy patients?

Study 1: examination of the RJ-specific antibody in atopic dermatitis patients

Study 2: examination of cross-reactive allergens of RJ

Study 1

Examination of the RJ-reactive antibody in atopic dermatitis patients

Subjects

We obtained serum samples from atopic dermatitis outpatients in Gifu university hospital.

Subjects : Atopic dermatitis (AD) patients

Number : 30 patients (no.31-60)

Age : 20 to 63 (median 32)

Sex : 14 female, 16 male

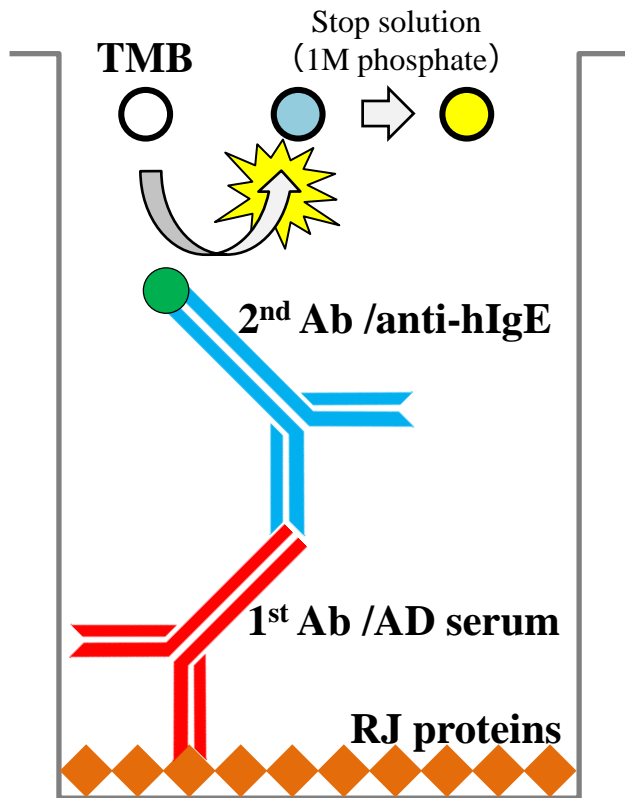
Country : Japanese

➤ These patients have **never** been exposed to RJ.

Methods

- **RJ-applied ELISA**

Coating: 7.5 $\mu\text{g/mL}$ of RJ, Blocking : EzBlockChemi
 1st Ab: serially diluted sera, 2nd Ab: HRP conjugated anti-human IgE antibody, Detection : TMB reaction



- **Antibody titration**

Serial dilutions of the serum were used for measuring antibody titer. The titer was expressed as the highest dilution rate in which positive reaction was observed.

e.g., Antibody titer is “4”

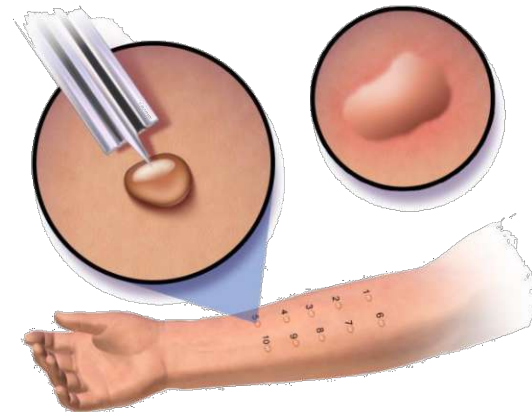
2-fold dilution : **Positive**

4-fold dilution : **Positive ***

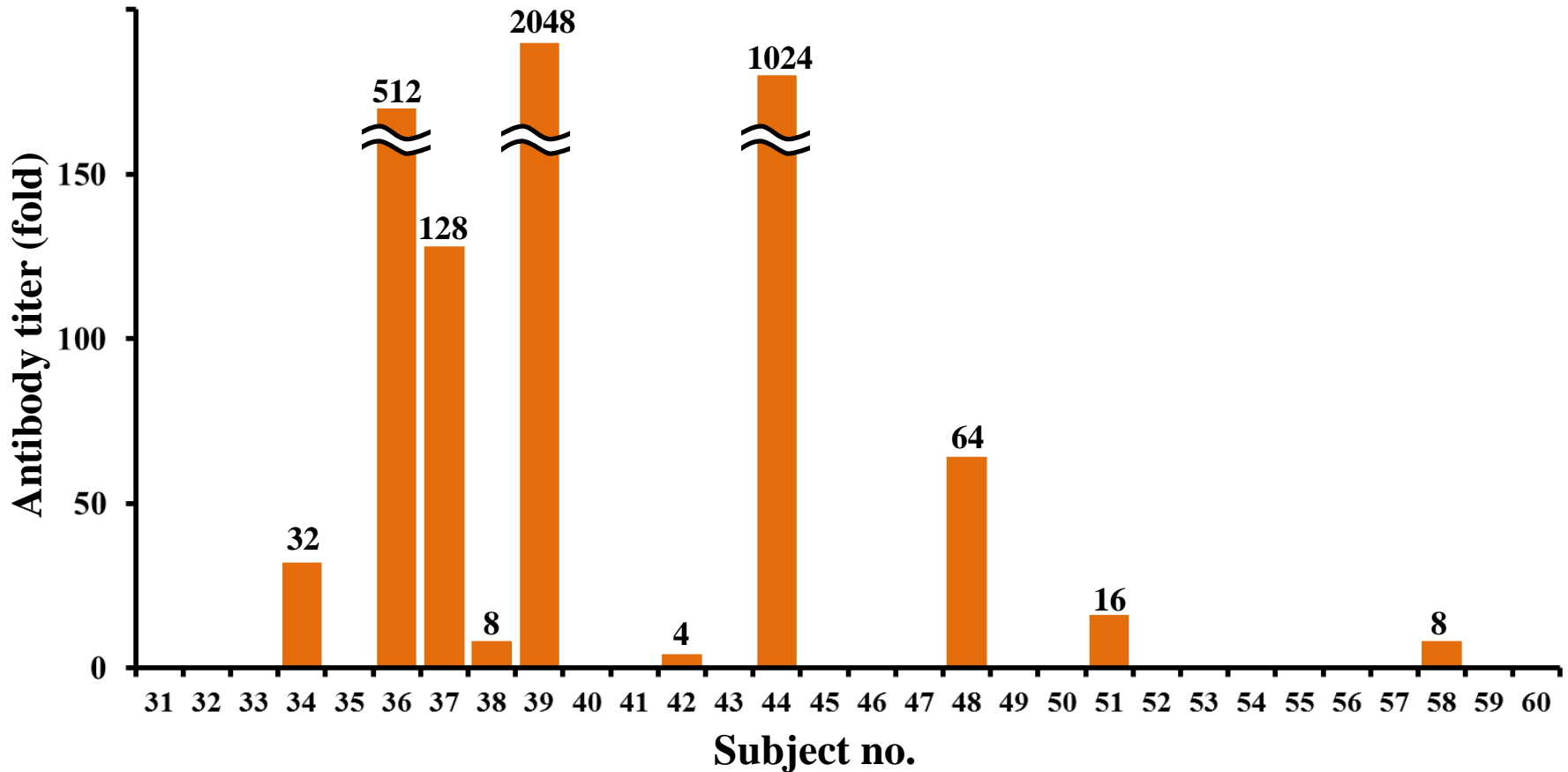
8-fold dilution : **Negative**

- **Skin-prick test**

Skin-prick test (SPT) was performed with undiluted, 10-fold diluted and 100-fold diluted RJ solutions to subject No.38, No.44, and No.48.



AD patients having RJ-reactive IgE



➤ **Ten out of thirty (33%) AD patients had RJ-reactive IgE.**

Skin-prick test in AD patients having the RJ antibody



	No.44	No.38	No.48
Positive Control			
RJ 1/1			
RJ 1/10		N.D.	
RJ 1/100		N.D.	
Negative Control	N.D.	N.D.	N.D.

➤ All the three patients showed positive reaction against undiluted RJ.

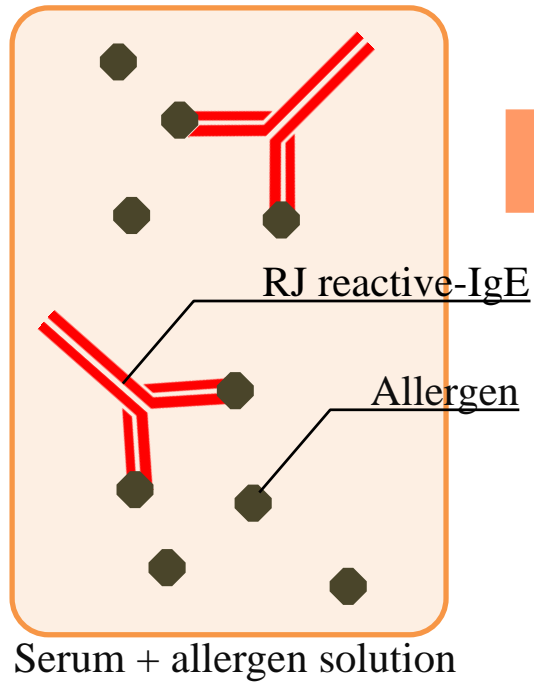
Study 2

Examination of cross-reactive allergens of RJ

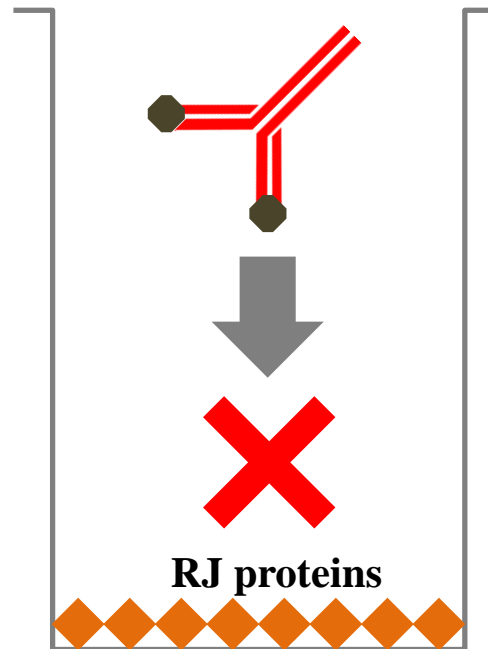
Methods

● ELISA-inhibition assay

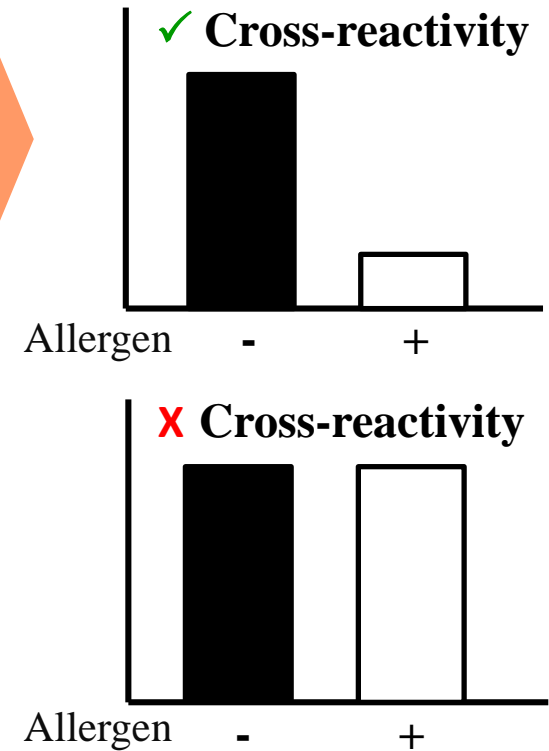
1) Pre-incubation



2) ELISA



3) Result



Methods

● Candidates of allergens



European house dust mite (HDM)



Timothy grass pollen



Peanut



American house dust mite (HDM)



Japanese mugwort pollen



Buckwheat



Alaskan pink shrimp



Japanese cedar pollen



Cat dander



Edible crab



German cockroach



Bee venom

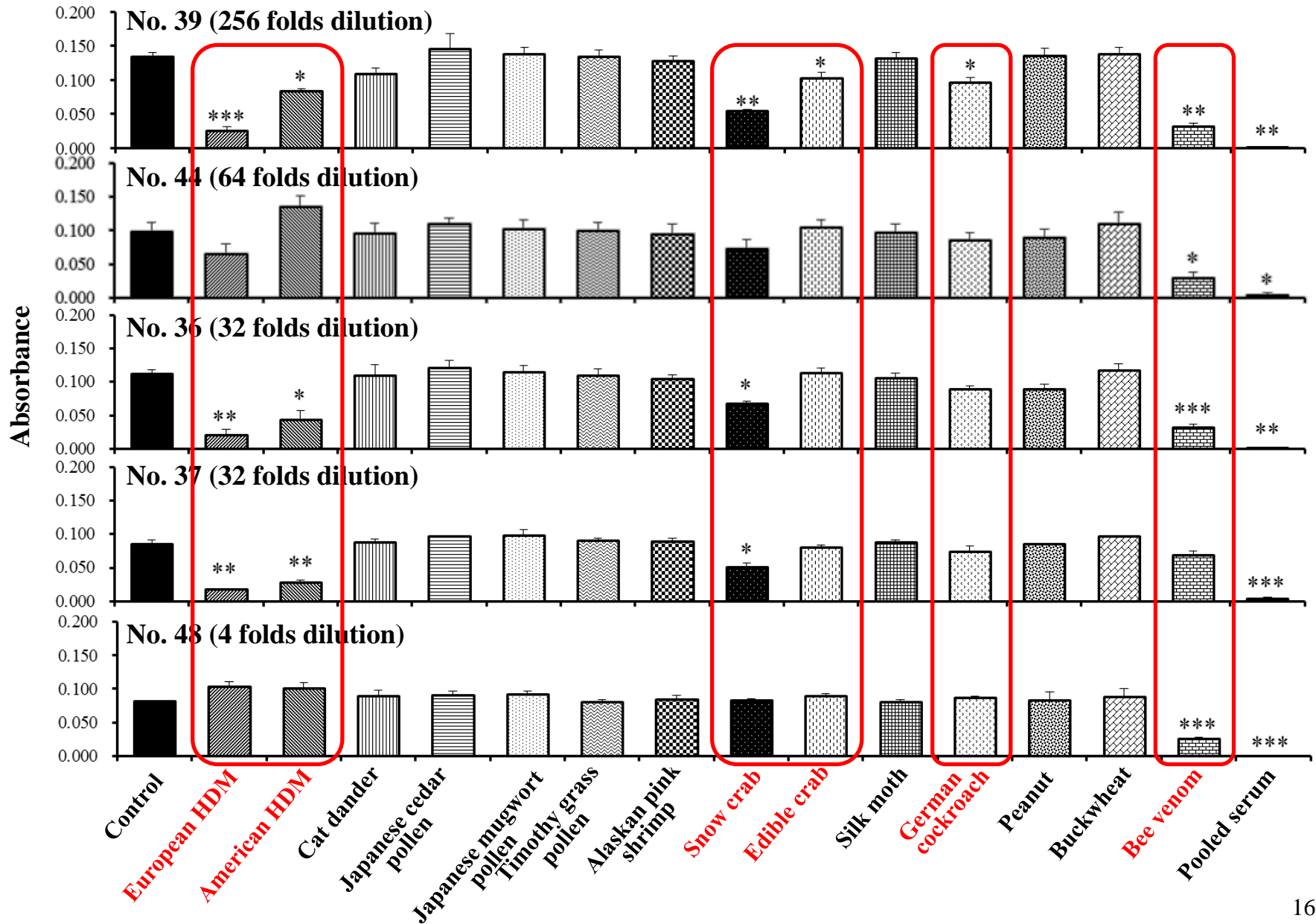


Snow crab



Silk moth

Cross-reactive allergens to RJ



A summary of cross-reactive allergen test



Subject no.	36	37	39	44	48	Positive rate
European HDM	**	**	***		0.058	3 / 5
American HDM	*	**	*			3 / 5
Cat dander			0.077			0 / 5
Japanese cedar						0 / 5
Mugwort						0 / 5
Timothy grass						0 / 5
Alaskan pink shrimp						0 / 5
Snow crab	*	*	**			3 / 5
Edible crab			*		0.082	1 / 5
Moth						0 / 5
German cockroach	0.053		*		0.055	1 / 5
Peanut	0.084					0 / 5
Buckwheat						0 / 5
Bee venom	***		**	*	***	4 / 5

HMD means house dust mite. * p<0.05, ** p<0.01, ***p<0.001 and the number shows p-value

- **Cross-reaction was observed with European HDM (3/5), American HDM (3/5), snow crab (3/5), German cockroach (1/5), edible crab (1/5), and bee venom (4/5) .**

Conclusion

1. In our study, about **33% of AD patients** who have never exposed to RJ had the RJ-reactive antibody.
2. **House dust mite, crab, cockroach, and bee venom** were thought to be the cross-reactive allergens to RJ.
3. Thus, RJ is not recommended for people who have allergy against house dust mite, crab, cockroach, and bee venom to avoid severe allergic reactions and **safe use** of RJ.
4. In addition, further studies are needed to define common epitopes of these allergens.

Conflict of Interest (COI)

The authors declare no COI directly relevant to the content of this presentation.

Statement of Ethics

The human blood experiments were approved by Gifu University Hospital Independent Ethics Committee, and written, informed patient consent was obtained (29-030, 30-034).

Acknowledgement

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*Thank you very much
for your kind attention.*



Member of Nagaragawa Research Center, 2019/08/22