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ORIGINAL ARTICLE

Patterns of sensitization to peanut allergen components in Taiwanese Preschool children

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Background/Purpose: Peanut allergy is very common in Western countries, although it is seldom encountered in Eastern countries. Peanuts are comprised of at least 11 components, but the contribution to clinical symptoms by each component in each individual is not known. This study investigated the distributions of sensitivity to peanut allergen components among Taiwanese children who were sensitized to peanuts and followed the evolution of sensitization patterns to these components.
Methods: We enrolled 29 preschool children (age $= 2.11 \pm 1.36$ years) who were sensitized to peanuts above class 3. Serum was analyzed for specific immunoglobulin E (IgE) antibodies to recombinant Ara h 1, Ara h 2, Ara h 3, Ara h 8, and Ara h 9. Allergen component-specific IgE ≥ 0.35 kU_A/L was defined as positive. Eighteen children were retested 22.64 ± 5.1 months later. Peanut allergy symptoms were recorded from detailed questionnaires.
Results: The percentages of children sensitized to Ara h 1, 2, 3, 8, and 9 were, respectively, 51.8%, 65.5%, 62.1%, 13.8%, and 24.1%. Regarding changing patterns of peanut component sensitization at follow-up, children with clinical symptoms to peanuts had persistent elevations of Ara h 2-specific IgE: 12.6 ± 1.01 up to 34.15 ± 19.4 kU_A/L; $p = 0.144$. In contrast, Ara h 2 concentrations decreased significantly in children without clinical symptoms. Ara h 8 and 9 were nonspecific for children with or without symptoms.
Conclusion: Ara h 1, Ara h 2, and Ara h 3 were major components contributing to peanut sensitization in Taiwanese children. Ara h 2 was probably the most important component that contributed to clinical symptoms and remained steady in children who had peanut allergy.
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Introduction

Allergy to peanuts is one of the leading causes of fatal allergic reactions. The prevalence of peanut allergy has increased dramatically in the last decade. It currently affects about 1.15%–1.5% of these populations, and there is an estimated threefold increase in reported peanut allergies among Westernized countries.[1–4] However, peanut allergy is not common in Asia, and its reported prevalence is about 0.4%–0.6%.[5] Children with allergies to milk or egg whites usually develop tolerance and become asymptomatic as they grow older. In contrast, peanut allergy symptoms are usually lifelong, but a minority of patients may outgrow the reactions over time.[6] Consuming peanut-containing products can lead to shock and even death among those with severe peanut allergies.[7,8] Therefore, it is very important to diagnose peanut allergy at an early stage.

The current clinical gold standard for diagnosing peanut allergy is an oral food challenge test (OFC),[9] but it is time-consuming, expensive, and extremely risky in clinical practice.[10] Therefore, a skin prick test or testing for serum levels of peanut-specific immunoglobulin E (IgE) are currently used as replacements in the clinic.[11,12] However, people who are positive by peanut-specific IgE tests can only be classified as having a peanut sensitization.[13] Evidence is required from a patient's clinical history of peanut contact experience for a diagnosis of peanut allergy. It has also been reported that only a skin prick result larger than 8 mm or a peanut-specific IgE level higher than 15 kU_A/L had a high predictive value for clinical peanut allergy.[14]

A possible reason for the ambiguity between peanut sensitization and peanut allergy is that the allergens used in test kits are derived from crude peanut protein extracts, which contain both allergenic and nonallergenic molecules. In addition, some of these molecules may cross-react with pollens or other allergens in foods.[15,16] Overall, this leads to discrepancies in test results and clinical diagnoses.

At least 11 different allergen components have been found to be associated with peanut allergy. These are designated Ara h 1-11 (*Arachis hypogaea*). Among these, Ara h 1, Ara h 2, and Ara h 3 are the major peanut allergen components based on their protein ratios and cellular activities. These are seed storage proteins comprised of vicilin, conglutin, and glycinin, respectively.[17] It was reported that American patients who became allergic around 1 year of age presented more frequently with IgE antibodies to rAra h 1 to 3 (56.7%–90.0%) than Swedish patients (37.1%–74.3%), followed by Spanish patients (16%–42%).[18] Ara h 4 and Ara h 3 are nearly identical isoforms,[19] and, additionally, Ara h 5 and Ara h 8 are both related to pollen allergy and are not seed storage proteins. Ara h 5 is a profilin protein in peanuts, which presents low quantity in peanuts and leads to a cross-reaction with Bet v 2, the birch pollen profilin[20] and Ara h 6 and Ara h 7 are proteins homologous to Ara h 2.[21] Ara h 8, a homologous protein of Bet v 1, the major allergen in birch pollen, is heat sensitive and labile to digestion, and usually results in clinical symptoms associated with oral allergy syndrome.[22] Ara h 9 is a nonspecific lipid-transfer protein (LTP), with properties of heat and acid resistance. Its clinical symptoms include systemic allergy and oral allergy. People in Mediterranean countries often have LTP allergy due to the high consumption of vegetables and fruits, among which Ara h 9 is the major causative allergen and is more relevant than Ara h 1-3.[23] Ara h 10 and Ara h 11 are both plant protein oleosins that were obtained from oil bodies from peanut and were not realized until their clinical relevance was present.

Peanut allergy has different clinical and immunologic patterns in different areas of the world. We investigated whether the uncommon presentation of peanut allergy in Taiwanese preschool children could be related to a different sensitization pattern to peanut allergen components.

Methods

Study population

From April 2007 to April 2009, 3936 children with allergic diseases had been tested for serum levels of peanut-specific IgE in the Pediatric Allergy and Asthma Center of Chang-Gung Memorial Hospital. Among these children, 215 were tested as positive (peanut-specific IgE levels $\geq$0.35 kU_A/L). There were only 29 preschoolers (age between 6 months to 6 years) out of 215 test-positive children who met our criteria by having peanut-specific IgE levels higher than 3.5 kU_A/L (or ImmunoCAP above class 3); then, their blood samples were tested for peanut component-specific IgE. After 1.5 to 2 years, they returned for follow-up blood tests for peanut component-specific IgE and parents completed a questionnaire about the child's allergic symptoms. The questionnaire included items such as the patient's consumption of peanut-containing products during the follow-up period. If peanut exposure was confirmed, we specifically inquired about the occurrence of allergic symptoms, including skin rash, eyelid swelling, cough, mouth numbness, heart palpitations, and difficulty breathing when the child consumed peanut-containing products. Written informed consent were obtained from the main caregiver for all study patients.

Determination of sensitization

Serum was analyzed for specific IgE antibodies to peanut-recombinant Ara h 1, Ara h 2, Ara h 3, Ara h 8, and Ara h 9 by ImmunoCAP (Phadia, Sweden). An allergen-specific IgE level $\geq$0.35 kU_A/L was defined as positive. Levels between 0.35 and 100 kU_A/L were recorded.

Statistics

A Wilcoxon Signed Rank Test was used to compare changes of specific IgE levels with peanut allergen components between two time points. A p value $<$0.05 was considered statistically significant.

Results

Baseline results

The average age of the 29 children with peanut sensitization was 2.11 $\pm$ 1.36 years (range: 0.53–5.7 years), and all of them were also sensitized to egg white; 23 were sensitized to milk, 12 were sensitized to shrimps and crabs, and nine were sensitized to cod. Their clinical histories showed that 26 children also suffered from allergic rhinitis, 25 children had atopic dermatitis, and 15 children had asthma (data not shown). Results for serum concentrations of peanut allergen component-specific IgE for these 29 children were: 15.24 ± 2.02 kU_A/L for peanut, 3.17 ± 5.64 for Ara h 1, 8.96 ± 2.02 for Ara h 2, 2.74 ± 6.14 for Ara h 3, 0.44 ± 1.48 for Ara h 8, and 1.24 ± 3.68 for Ara h 9 (Fig. 1).

As shown in Table 1, among these 29 children who were positive for peanut sensitization, the percentages that also tested positive for peanut allergen components were: 51.8% for Ara h 1, 65.5% for Ara h 2, 62.1% for Ara h 3, 13.8% for Ara h 8, and 24.1% for Ara h 9.

Table 1 Positive rates to peanut allergen components (total n = 29)

Class	rAra h 1 n (%)	rAra h 2 n (%)	rAra h 3 n (%)	rAra h 8 n (%)	rAra h 9 n (%)
6+	0	1 (3.5)	0	0	0
5+	0	0	0	0	0
4+	1 (3.5)	4 (13.8)	1 (3.5)	0	0
3+	7 (24.1)	5 (17.3)	4 (13.8)	1 (3.5)	2 (6.8)
2+	6 (20.7)	7 (24.1)	10 (34.5)	1 (3.5)	4 (13.8)
1+	1 (3.5)	2 (6.8)	3 (10.3)	2 (6.8)	1 (3.5)
0	14 (48.2)	10 (34.5)	11 (37.9)	25 (86.2)	22 (75.9)
≥1+	15 (51.8)	19 (65.5)	18 (62.1)	4 (13.8)	7 (24.1)

Reference ranges for Allergen IgE tests: Class 0 is < 0.35 kU_A/L or absent; Class 1 is ≥ 0.35 kU_A/L but < 0.7 kU_A/L; Class 2 is ≥ 0.7 kU_A/L but < 3.5 kU_A/L; Class 3 is ≥ 3.5 kU_A/L but < 17.5 kU_A/L; Class 4 is ≥ 17.5 kU_A/L but < 50 kU_A/L; Class 5 is ≥ 50 kU_A/L but < 100 kU_A/L; Class 6 is ≥ 100 kU_A/L.

Follow-up results

Eighteen of the 29 children (16 boys and two girls) had follow-up serum tests for peanut allergen component-specific antibodies. Their average age was 2.27 ± 1.39 years when they first had peanut allergen tests, and their average age at follow-up tests was 4.15 ± 1.44 years old. After a mean interval of 22.64 ± 5.1 months, the serum level of IgE against peanut changed from 8.42 ± 8.00 kU_A/L to 7.84 ± 15.49 kU_A/L ($p = 0.094$), and the positive rate for peanut sensitization declined from 100% to 77.8% (data not shown).

Ara h 1-specific IgE levels declined from 2.59 ± 4.75 kU_A/L to 1.89 ± 5.59 kU_A/L ($p = 0.043$), and the positive rate decreased from 44.4% to 33.3% (data not shown). Ara h 2-specific IgE levels increased from 3.37 ± 6.68 kU_A/L to 7.83 ± 16.62 kU_A/L ($p = 0.523$), while the positive rate decreased from 55.6% to 38.9% (data not shown). Ara h 3 specific-IgE levels changed from 1.50 ± 1.74 kU_A/L to 0.56 ± 1.26 kU_A/L ($p = 0.02$), and the positive rate declined from 61.1% to 22.2% (data not shown). IgE levels against Ara h 8, a pollen allergy-related allergen, and Ara h 9, the major peanut allergen in the Mediterranean region, decreased from 0.20 ± 0.41 kU_A/L and 0.24 ± 0.36 kU_A/L to 0.08 ± 0.09 kU_A/L ($p = 0.023$) and 0.06 ± 0.05 kU_A/L ($p = 0.001$), respectively. The positive rates to these components declined to 0% from 11.1% and 16.7% (data not shown), respectively (Fig. 2).

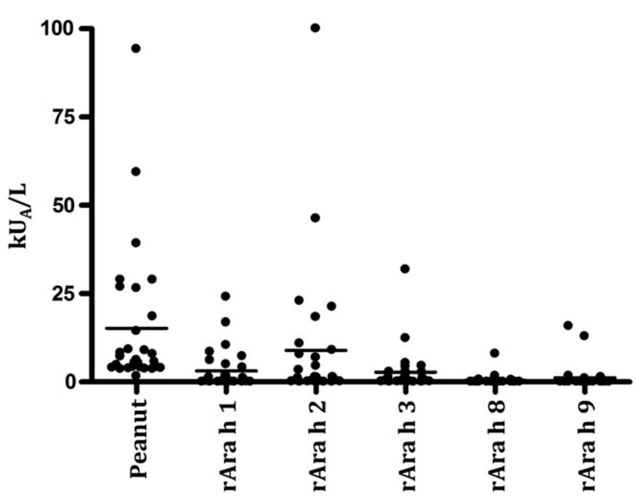

Figure 1. IgE levels of peanut allergen components in all peanut-sensitized children. Serum concentrations of IgE against recombinant Ara h 1, Ara h 2, Ara h 3, Ara h 8, and Ara h 9 in 29 children allergic to peanuts. Horizontal lines indicate mean values.

Questionnaires were given to the parents of these 18 children who were sensitive to peanuts to investigate whether they had consumed peanut-containing products during the follow-up period. If positive exposure history was confirmed, we further inquired about the occurrence of the associated allergic symptoms. Four children had shown allergic symptoms, such as a rash, eyelid swelling, cough, or itching over the body, while the other 14 children showed no allergic symptoms (seven children consumed peanut-containing products while the other seven children avoided peanut-containing products). The first and the follow-up values of peanut allergen component specific IgE in these two groups of children were compared.

In the group of children with allergic symptoms ($n = 4$), although serum IgE levels against these peanut allergen components changed at the follow-up tests, they did not show statistically significant differences. For these children, serum IgE levels against peanut allergen changed from 13.88 ± 10.75 kU_A/L to 27.98 ± 25.15 kU_A/L ($p = 0.465$). The detailed results were shown in Table 2.

By contrast, for these asymptomatic children ($n = 14$), overall the concentrations of IgE against peanut components decreased significantly and the positive rate also decreased. For these children, serum IgE levels against peanut allergen declined from 6.85 ± 6.72 kU_A/L to 2.09 ± 2.69 kU_A/L ($p = 0.001$); serum IgE levels against Ara h 1 declined from 1.44 ± 3.03 kU_A/L to 0.47 ± 1.04 kU_A/L ($p = 0.002$); serum IgE against Ara h 2 decreased from 0.73 ± 0.88 kU_A/L to 0.31 ± 0.57 kU_A/L ($p = 0.033$); and serum IgE against Ara h 3 decreased from 1.37 ± 1.58 kU_A/L to 0.29 ± 0.40 kU_A/L [$p = 0.001$ (Table 2)].

We further divided the asymptomatic group ($n = 14$) into two subgroups: peanut-avoiding and tolerant group. In the tolerant subgroup ($n = 7$), the levels of IgE against peanut components decreased significantly. However, in

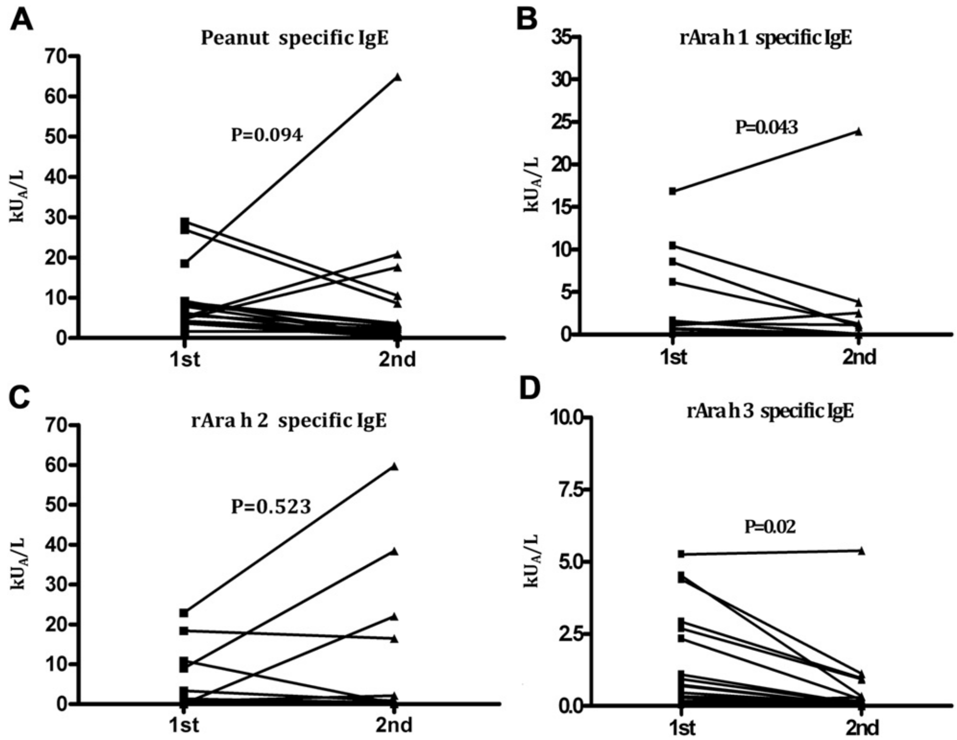

Figure 2. Changes of IgE levels. Serum specific IgE levels to (A) crude peanut; (B) rAra h 1, (C) rAra h 2; and (D) rAra h 3 were determined for 18 peanut-sensitized children at baseline and at an average of 22 months later. A Wilcoxon Signed Rank Test was used to compare changes of IgE levels to peanut allergen components between two time points, and a p value <0.05 was considered statistically significant.

the peanut-avoiding subgroup ($n = 7$), the levels of IgE against peanut components also decreased significantly, except those of Ara h 2 and Ara h 8 (Table 3).

Discussion

The prevalence of peanut allergy in Western countries has been increasing in recent years and is usually accompanied by severe allergic reactions that may lead to death. Therefore, most of the studies on peanut allergy are from Europe and North America.[18] By contrast, the prevalence and mortality rate due to peanut allergy in Asia are relatively low and have been less investigated in the literature. Even children who live in Asia but who were born in Western countries were at a higher risk of peanut and tree nut allergy compared with those born in Asia.[5] Our study showed that in children with allergic diseases in Taiwan, the incidence of peanut sensitization was low, and the number with a genuine peanut allergy was even lower.

The Ara h 1, 2 and 3, which are the major components of peanut allergy, play an important role in symptomatic patients in Western countries.[24] Chiang and colleagues[25] investigated peanut allergen component distributions in Singapore. Their results indicated that the positive rates to native Ara h 1, native Ara h 2, and recombinant Ara h 3 in children who were hypersensitive to peanuts were 87.1%, 87.1%, and 54.8%, respectively, suggesting that Ara h 1-3

Table 2 Baseline and follow-up serum specific IgE levels

Reported symptoms to peanut sensitization	Yes (N=4)					No (N=14)				
	1st		2nd		P	1st		2nd		P
	n	IgE(kUA/L)	n	IgE		n	IgE	n	IgE	
peanut	4	13.88 ± 10.75	4	27.98 ± 25.15	0.465	14	6.85 ± 6.72	10	2.09 ± 2.69	0.001
rAra h 1	3	6.60 ± 7.78	3	6.85 ± 11.41	0.715	5	1.44 ± 3.03	3	0.47 ± 1.04	0.002
rAra h 2	3	12.6 ± 1.01	4	34.15 ± 19.4	0.144	7	0.73 ± 0.88	3	0.31 ± 0.57	0.033
rAra h 3	2	1.96 ± 2.43	1	1.51 ± 2.59	1.000	9	1.37 ± 1.58	3	0.29 ± 0.40	0.001
rAra h 8	2	0.60 ± 0.80	0	0.18 ± 0.13	0.273	0	0.09 ± 0.07	0	0.05 ± 0.04	0.022
rAra h 9	2	0.50 ± 0.61	0	0.08 ± 0.06	0.273	1	0.17 ± 0.24	0	0.05 ± 0.05	0.002

"n" means numbers of patients positive for testing peanut component allergens.
P-value was derived from Wilcoxon Signed Rank Tests, and p-value <0.05 was considered significant.

Table 3 Changes of IgE levels in the asymptomatic group

sensitization	peanut-tolerant subgroup (N=7)					peanut-avoiding subgroup (N=7)				
	1st		2nd		P	1st		2nd		P
	n	IgE(kUA/L)	n	IgE		n	IgE	n	IgE	
peanut	7	5.39 ± 2.80	4	1.21 ± 1.24	0.018	7	8.32 ± 9.22	6	2.97 ± 3.51	0.018
rAra h 1	2	1.68 ± 3.85	1	0.58 ± 1.42	0.018	3	1.21 ± 2.23	2	0.36 ± 0.56	0.043
rAra h 2	3	0.50 ± 0.46	0	0.09 ± 0.04	0.028	4	0.96 ± 1.16	3	0.53 ± 0.76	0.398
rAra h 3	4	0.83 ± 0.92	1	0.19 ± 0.33	0.028	5	1.90 ± 1.98	2	0.39 ± 0.47	0.018
rAra h 8	0	0.09 ± 0.05	0	0.05 ± 0.05	0.017	0	0.09 ± 0.09	0	0.05 ± 0.04	0.225
rAra h 9	1	0.22 ± 0.32	0	0.05 ± 0.05	0.028	0	0.12 ± 0.11	0	0.05 ± 0.06	0.028

"n" means numbers of patients positive for testing peanut component allergens.
P-value was derived from Wilcoxon Signed Rank Tests, and p-value <0.05 was considered significant.

was also a major allergen for Asian peanut-sensitized children.[25] After examining the major allergen components that caused peanut sensitization in preschool children, we found that the major contributing peanut allergen components in Taiwan were also Ara h 1-3, although the sensitivity rate to each component was lower. Of these three components, the levels of IgE against Ara h 2 were the highest, followed by Ara h 1 and Ara h 3. In a previous study, Ara h 2 was considered to be the most important component because the threshold for inducing basophil-degranulation and histamine release for Ara h 2 was lower than that of Ara h 1 and Ara h 3, which may be associated with the ability of peanut allergen components to induce basophil degranulation and histamine release.[26]

Moreover, we compared the positive rates with Ara h 9, the major peanut allergen in the Mediterranean area, and Ara h 8, a pollen allergy-associated allergen. Our study showed that the positive rates to Ara h 8 and Ara h 9 were only 13.8% and 24.1 %, respectively, and the avidity only had an epitope valence of 1 to 3. However, a study showed that the prevalence of pollen allergy was less than 2% in a population of primary school—children aged 7—8 years in Taiwan.[27] This indicated that the proportion of children with pollen allergy was very low in Taiwan, and our results suggested that the proportion caused by cross-reactivity of a pollen allergen and peanut allergen was also very low. Although 45.2% of the Mediterranean population that is allergic to peanuts is hypersensitive to Ara h 9, our investigation indicated that Ara h 9 was not a major allergen causing peanut sensitization in Taiwan. It is possible that the children in our study were too young to have been exposed to a variety of foods, which could have minimized the possibility of peanut allergy caused by cross-reactions with LTP in other foods.

It has been reported that peanut allergy lingers throughout life.[6] Therefore, we kept track of the peanut-sensitized children to see if their peanut sensitization was ameliorated as these children grew older. Our result showed that both crude peanut and Ara h 2 specific IgE had no statistical difference between initial and the follow-up test results. This indicated that the progression of peanut sensitization did not vary with age, which was attributed to Ara h 2 instead of other components. Furthermore, our questionnaire results indicated that there were four children consuming peanut-containing products who developed allergic symptoms. Their Ara h 2 level remained steady year apart, and it indicated that Ara h 2 was probably associated with peanut-induced allergy in Taiwanese children. Furthermore, in our asymptomatic group, the levels of peanut-specific or peanut allergen components-specific IgE were both decreased and statistically significant at 2-year follow-ups, which suggested that serum peanut allergen components-specific IgE gradually diminished if no symptoms occurred. Analysis of peanut-avoiding and tolerant subgroups also showed that the titer of Ara h 2 specific IgE decreased slower than other specific IgE in peanut-avoiding subgroup, implying that Ara h 2 IgE is relatively more stable compared with those of other allergen components. Interestingly, Ara h 2 levels and the positive rate of sensitization were lower in the group without allergy than in the group with allergy at the initial test results. This could be related to the cut-off value for peanut- or Ara h 2-specific IgE. If we set the peanut specific IgE level at 15 kU_A/L, we had a higher predictive value for clinical peanut allergy.[14]

According to a study by Asarnolj and others,[28] 97% of children 8 years of age who were hypersensitive to both Ara h 2 and Ara h 1 or Ara h 3 developed more severe allergic symptoms than children who were only hypersensitive to Ara h 2. In our study, we found that in the allergic group, the levels of sIgE against peanut and Ara h 2 were increased and the positive rate was 100%. There were also three children with sensitized Ara h 2 who had concomitant IgE reactivity to Ara h 1 or Ara h 3. By contrast, the levels of sIgE against Ara h 8 and Ara h 9 decreased to be unremarkable after follow-up in the allergic children.

This study revealevd that the levels of serum sIgE against Ara h 1, 2, and 3 either remained constant or increased in Taiwanese children who were allergic to peanuts. Based on the positive rates and serum levels, we found that Ara h 2 was the major contributing allergen, which was similar to results by Flinterman and others in 2007.[29] They showed that the Ara h 2 IgE expression level was higher than those of Ara h 1 and Ara h 3 in peanut-allergic children by IgE immunoblotting. They also showed that 20 months after food stimulation Ara h 1-3 IgE levels remained unchanged. However, that study investigated positive rates, while our study further analyzed variation on IgE levels. In addition, our study suggested that Ara h 8 and Ara h 9 may not be associated with peanut allergy in Taiwan.

In conclusion, Ara h 1, Ara h 2, and Ara h 3 were found to be major components of peanut sensitization in children in Taiwan. Ara h 2 was probably the most important component that contributed to clinical symptoms and remained at steady levels in children who were allergic to peanuts.

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