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Concordance of CAP-RAST responses for food and indoor allergens between sibling pairs with atopic dermatitis

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Abstract

Aim: To examine the concordance of positive response to food and indoor allergens between siblings with atopic dermatitis (AD) and factors related to their response to allergens.

Methods: Study subjects were 338 Japanese children (169 sibling pairs) diagnosed with AD. A questionnaire was administered to the patients' parents to collect information on medical history and environmental factors for both the patients and the parents in June and July, 2006. The questionnaire asked about the allergic disease histories of the patients' parents, the patients' birth weight, way of feeding, and weaning age, the presence of pets in the home, and other environmental factors, including parents' smoking and alcohol drinking habits. Sera from patients were subjected to CAP radio-allergosorbent test (CAP-RAST) to examine responses to 8 food (egg, cow's milk, soybean, peanut, sesame, wheat, buckwheat, and rice) and 2 indoor (house dust and mite) allergens.

Results: Positive reactions to egg, cow's milk, wheat, sesame, peanut, and soybean were found in 48% (160/335), 21% (70/334), 14% (46/333), 14% (38/280), 10% (28/285), and 8% (28/333) of children, respectively. Less than 6% of the children were positive for allergies to buckwheat and rice. The frequencies of positive response to house dust and to mites were 46% (105/228) and 47% (106/227), respectively. We examined Spearman's rank correlation coefficients among all CAP-RAST scores for first- and second-born children, separately. There were significant and strong positive associations among CAP-RAST scores of oil seeds (soybean, peanut, and sesame), and all of their correlation coefficients were higher than 0.700. In the next step, we examined the Spearman's rank correlation coefficient between the first- and second-born children. There were significant associations between sibling's CAP-RAST scores for some of the same food allergens, cow's milk (r = 0.178), soybean (r = 0.227), peanut (r = 0.166), sesame (r = 0.186), and wheat (r = 0.192). We observed more than 0.25 of correlation coefficients among CAP-RAST responses of the first-born children's soybean and peanut, and the second-born children's soybean and sesame except the combination of the same allergen.

Conclusion: The concordance for allergen-specific positive response between siblings was observed only for oil seeds in this study.

Key words: atopic dermatitis, food allergy, indoor allergy, siblings

Introduction

Atopic diseases, including atopic dermatitis (AD), food allergy, allergic rhinitis, and asthma, are the most frequent chronic diseases in developed countries[1)] and affect up to 20% of children in industrialized countries[2)]. Recent epidemiologic studies suggest that the prevalence of allergic diseases has increased among children and young adults[3)]. Although the development of those allergic disorders is attributed to the complex interplay of immune and psychoneurotic responses to environmental factors[4)], genetic background is also an important consideration. Detailed analyses of family history in atopic patients show that 50-75% of patients harbor family histories of atopic diseases[1)]. In addition, the concordance rates of having asthma, AD, and bronchial hyper-responsiveness in monozygous twin pairs are found to be higher than in dizygous twin pairs[5]. However, the mechanism involved in the inheritance of allergic disease is not fully understood .

Some common genetic backgrounds are involved in the pathogeneses of different atopic disorders. In fact, recent genome-wide screens for AD, conducted in four different populations[6], show that the susceptibility gene regions for AD overlap with those for asthma. Interestingly, some genomic regions related to AD also overlap with susceptibility regions for psoriasis, another chronic skin disease[6, 7]. These findings suggest that AD pathogenesis involves genes expressed in the skin in addition to genes influencing atopic diathesis. More importantly, recent studies show that an epidermal barrier is important for preventing AD[4]. However, these genetic factors cannot fully explain the increase of allergic diseases in the last 30 years[3, 8]. Thus, it is quite likely that gene-environmental interactions play a role in the development of AD. Suggested environmental factors are prenatal or childhood exposure to foods, endotoxins, indoor pollutants including tobacco smoke, and viruses[3, 8].

AD often represents the beginning of the so-called "allergic march", which leads to the development of asthma and allergic rhinitis. Half of AD patients will develop asthma and two-thirds will develop allergic rhinitis[9]. In addition, AD is closely related to food allergy. Nearly 80% of children with AD in Japan[10] and 70% in the US[11] suffer from food allergies. Some studies indicate that children with both AD and food allergy, especially in the case of IgE-mediated food allergy, are prone to developing reactions to inhalant allergens and the allergic march[12, 13]. Thus, clarification of risk factors for food allergy is extremely important to prevent the progression of the allergic march among children with AD[13].

The CAP radioallergosorbent test (CAP-RAST) measures allergen-specific IgE levels, and is the most popular test to evaluate allergic responses objectively. Although sibling pairs are expected to share similar CAP-RAST responses, especially between sibling pairs with AD, there was no report showing associations in the CAP-RAST responses for various allergens between sibling pairs in Japan. In addition, it is not well known which factors more strongly affect the CAP-RAST responses if discrepant CAP-RAST responses were observed between sibling pairs.

In the present study, thus, we examined the concordance of positive response to food and indoor allergens between siblings with AD and factors related to their response to allergens.

Materials and methods

From April 2004 to June 2006, around 6,000 children were diagnosed with AD at Sanrigi Skin Allergy Clinic in Kumamoto. All patients were diagnosed by a single doctor according to the criterion of Japanese Dermatological Association. In brief, a patient showing the following 3 symptoms is considered as AD: 1) eczematous dermatitis, 2) the dermatitis is observed in symmetric lesion, and 3) he or she shows chronic and repetitive course (more than 2 and 6 months for children under a year old and others, respectively). For the study subjects, we listed all sibling pairs who were diagnosed with AD and already examined for their IgE levels using the CAP-RAST, and 218 sibling pairs, 436 children, satisfied the inclusion criteria. Since sibling size and birth order are potential confounders of food or indoor allergies[14], we limited to sibling pairs without other brothers and sisters.

In the present study, we used existing results of the CAP-RAST. When each child was diagnosed with AD for the first time, he or she was asked to undergo the CAP-RAST, which measures allergen-specific IgE levels, using 0.3 ml of serum per allergen. Sixty-four percent of the study subjects were diagnosed with AD for the first time at Sanrigi Skin Allergy Clinic, and the CAP-RAST for these children was performed at a commercial medical laboratory center, FALCO Biosystems Ltd., in Japan. The FALCO Biosystems has 2 multi-allergen tests for food-allergy screening as follows: 1) egg, cow's milk, wheat, soybean, and peanut, and 2) wheat, buckwheat, rice, sesame, and sweet corn. If a patient is positive for at least one of the multi-allergen tests, he or she will be asked to undergo each allergen-specific test again. Test for sweet corn is not included since the frequency of sweet-corn allergy is not so common among children. Furthermore, allergen tests for mite and house dust are also recommended for children after one year old. Regarding the rest children whose first AD diagnoses were made at other clinics, we used results of the CAP-RAST when they were diagnosed with AD for the first time. Although we did not obtain the information of selection criteria for allergen test at other clinics, most of the children were examined their IgE levels using the CAP-RAST for common food allergens such as egg and cow's milk. All study subjects have been examined for their allergen-specific IgE levels using the CAP-RAST at least for two allergens of eight food items (egg, cow's milk, soybean, peanut, sesame, wheat, buckwheat and rice) and two inhalant allergens (house dust and mites). None of them showed any clinical symptoms of food allergy when they were examined for their IgE levels using the CAT-RAST. The results of CAP-RAST are routinely reported as scores ranging from 0 to 6, and a score of 1 or higher (0.35 UA/ml ≦) was categorized as positive. Subjects with a CAP-RAST score of 0 were categorized as negative for the corresponding allergen. The lower boundary values of CAP-RAST scores of 2, 3, 4, 5, and 6, which are common among commercial medical laboratories, are 0.70, 3.50, 17.50, 50.00, and 100.00 UA/ml, respectively.

In June and July of 2006, we conducted a questionnaire survey to obtain information about allergy histories, and 170 sibling pairs (78%) visited the clinic during that period. The questionnaire asked about the allergic disease histories of the patients' parents (allergic conjunctivitis, allergic rhinitis, pollen allergy, urticaria, asthma, and AD); the patients' birth weight, way of feeding, and weaning age; the presence of pets in the home, and other environmental factors, including parents' smoking and alcohol drinking habits. The present study was approved by the Institutional Review Board of Kagoshima University Graduate School of Medical and Dental Sciences, Japan, and at least one parent of each study subject gave informed consent.

Spearman's rank correlation coefficients were calculated using CAP-RAST scores to examine the associations among food or indoor allergies within individuals and between sibling pairs. Because the frequency of clinical symptoms of food allergy does not always increase with the CAP-RAST scores[15, 16], we decided to use the CAP-RAST score as binomial variable (positive or negative) for the following analyses. We conducted unconditional logistic regression analyses to examine associations between the CAP-RAST result (positive / negative) of each antigen and corresponding siblings' CAP-RAST results (positive / negative). Age at the first AD diagnosis and sex, and birth order were always included as covariates in the models. Furthermore, separate analyses by birth order were conducted using age at the first AD diagnosis, sex, and allergic disease history of parents as covariates. Maximum likelihood estimates of odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated using STATA9.2 statistical software (Stata Corporation, USA). Trend tests for age at the first AD diagnosis and weaning age were conducted using original data as continuous variables. We categorized the parents' allergic disease histories into three groups: "neither", "either", and "both", depending on whether none, one, or both parents, respectively, had a history of allergic disease, and used it as a categorical variable. All *P* values presented are two-sided.

Results

Out of 170 sibling pairs who visited the clinic during the study period, one sibling pair refused to participate in the survey. In addition, one child did not undergo CAP-RAST for any food allergens examined in the present study and was excluded from our data analysis. Thus, the study subjects consisted of 337 children. In the analysis of sibling pairs, 168 pairs were used for analysis. Among of them, there were 125 (37%) children whose first diagnoses of AD were made at other clinics. Table 1 shows the characteristics of the subjects in the present study. Mean ages (standard errors) at the first AD diagnosis for the first- and second-born children were 3.3 (0.14) and 1.0 (0.10) years, respectively, and the difference was statistically significant in logistic regression analysis adjusting for the effect of sex (P<0.001). The prevalence of sibling pairs consisting of both brothers, an elder brother and a younger sister, an elder sister and a younger brother, and both sisters, were 28%, 21%, 31%, and 20%, respectively. The first-born children tended to start eating weaning foods earlier than the second-born children, and the difference was marginally significant (*P* for trend =0.050). Mothers breast-fed their second-born child more frequent than their first-born child although the difference was not significant. Children's birth weights and parents' smoking habits in the first year of a child's life showed no significant difference between the first- and second-born children (data not shown). Each sibling pair in this study was living together after birth. Regarding allergic disease histories of the siblings' parents, we could obtain the information on 160 mothers and 155 fathers. Numbers of mothers with histories of allergic conjunctivitis, allergic rhinitis, pollen allergy, urticaria, asthma, and AD, were 44 (28%), 66 (41%), 40 (25%), 16 (10%), 16 (10%), and 47 (29%), respectively. Numbers of siblings' fathers with allergic

Table 1. Characteristics and the distribution of weaning age, feeding, and mothers' diet of the study subjects.

	first-born child number	%	second-born child number	%	P value*
All	169	100	169	100	
Age(year)[†]					
0-1	21	12	117	69	*P* for trend<0.001
2-3	81	48	40	24	
4-	67	40	12	7	
Sex					
Boy	83	49	101	60	0.748
Girl	86	51	68	40	
Weaning age (month)[‡]					
<6	72	44	51	31	0.384
6-	92	56	113	69	
Mother has restricted her diets through breast feeding [§]					
Yes	14[‖]	9	24[¶]	15	0.873
No	141	91	135	85	
Smoking during pregnancy					
Father					0.606
Yes	66	40	59	36	
Stop	27	16	24	15	
No	72	44	82	50	
Mother					0.167
Yes	3	2	4	2	
Stop	13	8	5	3	
No	149	90	156	95	
Mother's alcohol drinking during pregnancy					0.395
Yes	4	2	7	4	
No	162	98	159	96	
Mother's alcohol drinking through breast feeding [§]					
Yes	7	5	9	6	0.098
No	144	95	146	94	

＊: P values were obtained by logistic regression models in which age and sex. were always included as covariates.
†: Age at the first AD diagnosis
‡: Means of weaning age (standard errors) for the first- and second-born child were 5.9 (0.12) and 6.4 (0.14) months, respectively.
§: The subjects were limited to children whose mothers have given breast feeding.
‖: egg (n=4), milk (n=2), egg and milk (n=5), egg, milk, and soybean (n=1), egg, milk, and peanut (n=1), egg, milk, soybeans, wheat, and shrimp (n=1).
¶: egg (n=8), milk (n=2), milk and egg (n=8), egg, milk, and shrimp (n=1), egg and buckwheat (n=1), sesame (n=1), egg, wheat, and soybean (n=1), unknown (n=2).

conjunctivitis, allergic rhinitis, pollen allergy, urticaria, asthma, and AD, were 19 (12%), 66 (43%), 44 (28%), 9 (6%), 14 (9%), and 23 (15%), respectively. There were 122 mothers (76%) and 109 fathers (70%) who had at least one of the allergic diseases, and 42 mothers (26%) and 35 fathers (23%) had more than 2 allergic diseases' history.

The numbers of the first-born (second-born) children who were examined for their IgE levels for egg, cow's milk, soybean, peanut, sesame, wheat, buckwheat, rice, house dust, and mites were 167(168), 166(168), 165(168), 135(150), 130(150), 165(168), 150(163), 145(152), 142(86), and 141(86), respectively. There were 256 children who underwent CAP-RAST for all food allergens, and 130 (51%) out of them showed a positive response to at least one food allergen. All study subjects were examined for their IgE levels at least for two food allergens. Regarding indoor allergens, 231 children underwent CAP-RAST for house dust or mites. Among them, 109 (47%) children reacted positively to either house dust or mites. Table2 shows the proportions of CAP-RAST-positive cases for each allergen by age at the first AD diagnosis and sex. the positive frequencies of CAP-RAST for soybean, peanut, sesame, and buckwheat were higher among girls than boys in some age groups among all study subjects (Table 2). The frequencies of CAP-RAST-positive cases tended to increase with age for all allergens except egg among all children (Table 2).

We examined Spearman's rank correlation coefficients among all CAP-RAST scores for first- and second-born children, separately (Table 3). The two most common food allergens, egg and cow's milk, were moderately associated with other allergens in the first-born children (Table 3, upper-right half). On the other hand, there were significant and strong positive associations among CAP-RAST scores of oil seeds (soybean, peanut, and sesame), and all of their correlation coefficients were higher than 0.700. Soybean and sesame were also strongly related to buckwheat [correlation coefficients (r) > 0.700]. Furthermore, relatively strong positive associations were observed among grain foods and between oil seeds and grain foods. On the other hand, house dust and mites were strongly correlated with each other (r = 0.996). Regarding the second-born child, significant associations among the CAP-RAST scores of oil seeds were also observed although their correlation coefficients were relatively lower than those in the first-born child (Table 3, lower-left half). Grain foods were also related to each other and to oil seeds, and house dust and mites were strongly correlated with each other (r = 0.973). On the other hand, the associations between indoor allergies and common food allergies such as egg, cow's milk, and wheat, were relatively weak.

In the next step, we examined the Spearman's rank correlation coefficient between the first- and second-born children (Table 4). There were significant associations between sibling's CAP-RAST scores for some of the same food allergens, cow's milk (r = 0.178, P = 0.010), soybean (r = 0.227, P < 0.001), peanut (r = 0.166, P = 0.035), sesame (r = 0.186, P = 0.020), and wheat (r = 0.192, P = 0.005). Significant associations among the CAP-RAST scores of oil seeds were also observed although the correlation coefficients were relatively low (from 0.161 to 0.341). Furthermore, we observed more than 0.25 of correlation coefficients among CAP-RAST responses of the first-born children's soybean and peanut, and the second-born children's soybean and sesame except the combination of the same allergen. In addition, the CAP-RAST scores

Table 2. The age- and sex-specific proportions of CAP-RAST* positive cases among all study subjects.

		Number of positive cases / Number of subjects who were examined									
year	number	Egg	Cow's milk	Soybean	Peanut	Sesame	Wheat	Buckwheat	Rice	House dust	Mite
Boy											
All	183	99 / 182	43 / 182	18 / 181	18 / 156	26 / 151	29 / 172	11 / 168	10 / 158	59 / 112	58 / 110
		54%	24%	10%	12%	17%	17%	7%	6%	53%	53%
Age group (year)											
0	61	30 / 61	7 / 61	4 / 61	3 / 51	3 / 51	5 / 61	1 / 59	1 / 54	2 / 14	2 / 13
		49%	11%	7%	6%	6%	8%	2%	2%	14%	15%
1	32	19 / 32	12 / 32	3 / 32	2 / 29	7 / 27	7 / 32	4 / 32	2 / 31	10 / 21	9 / 21
		59%	38%	9%	7%	26%	22%	13%	6%	48%	43%
2	32	18 / 32	8 / 32	3 / 32	5 / 27	5 / 26	4 / 32	1 / 30	2 / 26	16 / 28	15 / 27
		56%	25%	9%	19%	19%	13%	3%	8%	57%	56%
3	19	14 / 19	6 / 19	3 / 19	3 / 19	5 / 19	6 / 19	3 / 18	1 / 16	10 / 13	11 / 13
		74%	32%	16%	16%	26%	32%	17%	6%	77%	85%
4-	39	18 / 38	10 / 38	5 / 37	5 / 30	6 / 28	7 / 37	2 / 29	4 / 31	21 / 36	21 / 36
		47%	26%	14%	17%	21%	19%	7%	13%	58%	58%
P for trend†		0.771	0.141	0.066	0.085	0.018	0.057	0.260	0.084	0.134	0.123
Girl											
All	154	61 / 153	27 / 152	10 / 152	10 / 129	12 / 129	17 / 152	6 / 145	6 / 139	45 / 115	47 / 116
		40%	18%	7%	8%	9%	11%	4%	4%	39%	41%
Age group (year)											
0	29	12 / 29	1 / 29	1 / 29	1 / 24	2 / 25	1 / 29	0 / 28	0 / 27	0 / 10	0 / 11
		41%	3%	3%	4%	8%	3%	0%	0%	0%	0%
1	16	8 / 16	4 / 16	2 / 16	2 / 15	2 / 15	3 / 16	0 / 15	1 / 16	1 / 7	1 / 6
		50%	25%	13%	13%	13%	19%	0%	6%	14%	17%
2	44	19 / 44	9 / 44	2 / 44	2 / 36	2 / 36	4 / 44	0 / 42	0 / 37	16 / 35	18 / 36
		43%	20%	5%	6%	6%	9%	0%	0%	46%	50%
3	26	13 / 26	7 / 25	1 / 25	2 / 20	2 / 19	4 / 24	1 / 24	1 / 23	10 / 26	10 / 26
		50%	28%	4%	10%	11%	17%	4%	4%	38%	38%
4-	39	9 / 38	6 / 38	4 / 38	3 / 34	4 / 34	5 / 39	5 / 36	4 / 36	18 / 37	18 / 37
		24%	16%	11%	9%	12%	13%	14%	11%	49%	49%
P for trend†		0.114	0.603	0.238	0.258	0.368	0.282	0.007	0.024	0.483	0.389

＊: Radio-allergosorbent test
† : P values were obtained by logistic regression models in which age was used as a continuous variable after adjusting for the effects of birth order and sex.

Table 3. Spearman's rank correlation coefficients among all CAP-RAST* scores.

	Correlation coefficients and P values of first-born child (numbers of the subjects examined)									
	(167)	(166)	(165)	(135)	(130)	(165)	(150)	(145)	(142)	(141)
	Egg	Cow's milk	Soybean	Peanut	Sesame	Wheat	Buckwheat	Rice	House dust	Mite
Egg		0.539†	0.408†	0.313†	0.343†	0.470†	0.312†	0.241‡	0.338†	0.316†
Cow's milk	0.400†		0.354†	0.249‡	0.307†	0.344†	0.276†	0.104	0.289†	0.286†
Soybean	0.414†	0.335†		0.706†	0.738†	0.623†	0.790†	0.561†	0.367†	0.351†
Peanut	0.313†	0.184§	0.625†		0.703†	0.591†	0.607†	0.588†	0.363†	0.362†
Sesame	0.412†	0.223‡	0.667†	0.605†		0.673†	0.700†	0.617†	0.325†	0.323†
Wheat	0.489†	0.451†	0.548†	0.519†	0.461†		0.612†	0.537†	0.395†	0.399†
Buckwheat	0.203§	0.105	0.403†	0.376†	0.487†	0.274†		0.690†	0.198§	0.166
Rice	0.284†	0.394†	0.671†	0.609†	0.450†	0.492†	0.441†		0.221§	0.220§
House dust	0.069	0.061	0.207	0.315‡	0.437†	0.148	0.291‡	0.246§		0.996†
Mite	0.061	0.036	0.107	0.254	0.305‡	0.087	0.276§	0.227	0.973†	
	Egg	Cow's milk	Soybean	Peanut	Sesame	Wheat	Buckwheat	Rice	House dust	Mite
	(168)	(168)	(168)	(150)	(150)	(168)	(163)	(152)	(86)	(86)
	Correlation coefficients and P values of second-born child (numbers of the subjects examined)									

* : Radio-allergosorbent test
†: P<0.001
‡: P＜0.01
§: P<0.05

Table 4. Spearman's rank correlation coefficients among all CAP-RAST* scores between all sibling pairs.

		first-born child									
		Egg	Cow's milk	Soybean	Peanut	Sesame	Wheat	Buckwheat	Rice	House dust	Mite
second-born child	Egg	0.081	0.091	0.054	0.128	0.121	0.048	0.053	0.081	-0.089	-0.085
	Cow's milk	0.035	0.178§	-0.064	0.073	0.049	-0.072	-0.029	-0.003	-0.117	-0.113
	Soybean	0.151§	0.200‡	0.227†	0.262†	0.243‡	0.218‡	0.152§	0.104	0.096	0.095
	Peanut	0.075	0.182§	0.231‡	0.166§	0.161§	0.183§	0.140	0.070	0.268	0.081
	Sesame	0.118	0.196‡	0.284†	0.341†	0.186‡	0.209‡	0.203‡	0.107	0.122	0.120
	Wheat	0.207‡	0.212‡	0.129	0.155§	0.166§	0.192‡	0.153§	0.193‡	-0.022	-0.026
	Buckwheat	-0.020	-0.003	0.042	0.031	0.018	0.073	0.053	0.067	0.022	0.020
	Rice	0.039	0.068	0.049	0.036	0.151	0.064	0.081	0.081	-0.049	-0.051
	House dust	-0.028	0.033	0.019	0.097	0.063	0.077	0.154	0.100	0.140	0.123
	Mite	-0.069	-0.012	-0.011	0.079	0.122	0.068	0.150	0.136	0.089	0.103

＊: Radio-allergosorbent test
†: P<0.001
‡: P<0.01
§: P<0.05

Table 5. Association between allergic response to egg and potential risk factors : results of multivariate logistic regression analyses*

	egg allergy of 1st and 2nd born child		egg allergy of first-born child		egg allergy of second-born child	
	−/+	OR (95%CI)	−/+	OR (95%CI)	−/+	OR (95%CI)
Age (year)†						
0	48 / 42	1.00 (referent)	3 / 4	1.00 (referent)	45 / 38	1.00 (referent)
1	21 / 27	1.36 (0.64-2.87)	8 / 6	0.76 (0.10-6.05)	13 / 21	2.10 (0.90-4.92)
2-3	57 / 64	1.35 (0.68-2.69)	32 / 49	2.65 (0.46-15.2)	25 / 15	0.80 (0.35-1.84)
4-	49 / 27	0.61 (0.27-1.37)	41 / 24	0.93 (0.16-5.37)	8 / 3	0.48 (0.11-2.05)
		P for trend= 0.254		*P* for trend= 0.395		*P* for trend= 0.301
Sex						
Girl	92 / 61	1.00 (referent)	50 / 35	1.00 (referent)	42/ 26	1.00 (referent)
Boy	83 / 99	1.81 (1.14-2.87)	34 / 48	2.08 (1.09-4.00)	49 / 51	1.62 (0.83-3.12)
Allergic disease history of parents						
No	21 / 13	1.00 (referent)	12 / 5	1.00 (referent)	9 / 8	1.00 (referent)
Either	57 / 57	1.73 (0.77-3.87)	30 / 27	2.47 (0.74-8.23)	27 / 30	1.22 (0.40-3.78)
Both	85 / 84	1.71 (0.79-3.70)	38 / 46	3.51 (1.10-11.2)	47 / 38	0.86 (0.29-2.56)
Birth weight (g)						
< 2500	19 / 11	1.00 (referent)	13 / 4	1.00 (referent)	6 / 7	1.00 (referent)
2500-	60 / 58	2.46 (1.01-5.95)	24 / 33	8.89 (2.09-37.9)	36 / 25	0.74 (0.22-2.51)
3000-	79 / 61	1.71 (0.72-4.04)	39 / 33	5.49 (1.34-22.5)	40 / 28	0.61 (0.18-2.06)
3500-	16 / 29	3.39 (1.23-9.34)	7 / 13	8.56 (1.67-43.9)	9 / 16	1.38 (0.34-5.57)
		P for trend= 0.326		*P* for trend= 0.164		*P* for trend= 0.868
Weaning age (month)						
<6	66 / 57	1.00 (referent)	35 / 37	1.00 (referent)	31 / 20	1.00 (referent)
6-	103 / 100	1.15 (0.72-1.85)	47 / 44	0.91 (0.47-1.76)	56 / 56	1.43 (0.71-2.90)
Feeding						
Breast	67 / 73	1.00 (referent)	29 / 36	1.00 (referent)	38 / 37	1.00 (referent)
Mixed	96 / 77	0.74 (0.47-1.18)	48 / 41	0.66 (0.34-1.31)	48 / 36	0.83 (0.43-1.60)
Bottle	9 / 9	1.13 (0.41-3.12)	6 / 5	0.79 (0.21-2.99)	3 / 4	1.94 (0.38-10.0)
Restriction of diets through breast feeding‡						
No	149 / 125	1.00 (referent)	73 / 67	1.00 (referent)	76 / 58	1.00 (referent)
Yes	12 / 25	2.53 (1.18-5.42)	3 / 10	3.37 (0.85-13.4)	9 / 15	1.94 (0.75-4.97)

＊: Age, gender, birth order, and allergic disease history of parents were always included in the models as covariates.
† : Age at first AD diagnosis
‡ : The subjects were limited to children whose mothers have given breast feeding.

Table 6. Association between allergic response to house dust and potential risk factors : results of multivariate logistic regression analyses.*

	house-dust allergy of 1st and 2nd born child		house-dust allergy of first-born child		house-dust allergy of second-born child	
	−/+	OR (95%CI)	−/+	OR(95%CI)	−/+	OR(95%CI)
Age (year)†						
0	22 / 2	1.00 (referent)	2 / 0	-	20 / 2	1.00 (referent)
1	17 / 11	5.55 (1.03-29.9)	7 / 4	1.00 (referent)	10 / 7	13.8 (1.75-108)
2-3	50 / 52	10.2 (2.08-50.1)	26 / 40	4.83 (1.09-21.3)	24 / 12	11.4 (1.48-87.3)
4-	34 / 40	9.28 (1.79-48.2)	30 / 33	2.87 (0.64-12.9)	4 / 7	42.0 (3.69-478)
		P for trend= 0.074		*P* for trend= 0.832		*P* for trend= 0.001
Sex						
Girl	70 / 45	1.00 (referent)	39 / 36	1.00 (referent)	31 / 9	1.00 (referent)
Boy	53 / 60	2.13 (1.20-3.80)	26 / 41	1.73 (0.87-3.44)	27 / 19	6.22 (1.66-23.3)
Allergic disease history of parents						
No	12 / 12	1.00 (referent)	7 / 8	1.00 (referent)	5 / 4	1.00 (referent)
Either	46 / 36	1.74 (0.53-5.74)	26 / 23	1.39 (0.29-6.73)	20 / 13	5.24 (0.68-40.1)
Both	63 / 49	1.30 (0.42-4.03)	31 / 41	2.49 (0.54-11.6)	32 / 8	0.94 (0.15-5.78)
Birth weight (g)						
< 2500	17 / 5	1.00 (referent)	13 / 2	1.00 (referent)	4 / 3	1.00 (referent)
2500-	44 / 37	5.30 (1.49-18.8)	22 / 24	18.9 (2.16-166)	22 / 13	0.84 (0.12-5.87)
3000-	49 / 49	5.06 (1.47-17.3)	25 / 40	24.2 (2.89-203)	24 / 9	0.46 (0.06-3.29)
3500-	13 / 14	7.22 (1.73-30.2)	5 / 11	41.5 (3.91-440)	8 / 3	0.77 (0.08-7.24)
		P for trend= 0.066		*P* for trend= 0.002		*P* for trend= 0.507
Pregnancy week						
<38	19 / 12	1.00 (referent)	9 / 8	1.00 (referent)	10 / 4	1.00 (referent)
38-41	89 / 68	1.34 (0.56-3.21)	50 / 48	1.52 (0.49-4.73)	39 / 20	1.82 (0.36-9.15)
42-	3 / 6	3.51 (0.67-18.4)	2 / 5	4.11 (0.56-30.0)	1 / 1	4.03 (0.14-114)
Weaning age (month)						
<6	45 / 44	1.00 (referent)	27 / 33	1.00 (referent)	18 / 11	1.00 (referent)
6-	75 / 54	0.72 (0.40-1.30)	37 / 40	0.85 (0.42-1.72)	38 / 14	0.27 (0.07-1.00)
Feeding						
Breast	43 / 45	1.00 (referent)	21 / 34	1.00 (referent)	22 / 11	1.00 (referent)
Mixed	69 / 51	0.64 (0.35-1.15)	38 / 36	0.54 (0.26-1.13)	31 / 15	0.86 (0.27-2.67)
Bottle	10 / 7	0.65 (0.21-2.02)	5 / 6	0.76 (0.20-2.87)	5 / 1	0.53 (0.05-6.17)

＊: Age, gender, birth order, and allergic disease history of parents were always included in the models as covariates.
† : Age at diagnosis of AD.

of oil seeds and wheat in the second-born children were significantly related to those for various food allergens (from 4 to 8 food allergens) in the first-born children. On the other hand, there was no significant correlation in the CAP-RAST for egg, buckwheat, rice, house dust, and mite between sibling pairs.

We conducted logistic regression analyses to examine associations between environmental factors and the CAP-RAST results. Table 5 summarizes the results of logistic analyses, examining factors related to CAP-RAST results for egg. The leftmost column shows the results obtained from the analysis using the data of first- and second-born children. The central and rightmost columns are for the results of the first- and second-born children, respectively. There were 37 mothers who refrained from consuming eggs and/or cow's milk, and one mother eliminated sesame from her diet during the period of breastfeeding. We analyzed the association between maternal dietary restriction during breastfeeding and egg allergy. A significantly increased OR of 2.53 (95%CI=1.18-5.42) was observed for children whose mothers refrained from consuming eggs and/or cow's milk during the period of breastfeeding. In addition, boys showed an increased frequency of egg allergy (OR=1.81, 95%CI=1.14-2.87). In the analysis conducted separately for the first-born children (central column of Table 5), boys (OR=2.08, 95%CI=1.09-4.00) and histories of allergic disease in both parents (OR=3.51, 95%CI=1.10-11.2) increase the risk of egg allergy. No other significant relationship was observed. On the other hand, among second-born children, no factor was significantly associated with egg allergy.

Similar analyses were also conducted for other frequent food allergens: cow's milk, soybean, peanut, sesame, and wheat. Bottle feeding significantly increased the frequency of allergic response to cow's milk (OR=3.56, 95%CI = 1.19-10.6). Unlike egg, the frequency of allergy to cow's milk, soybean, peanut, sesame, and wheat increased significantly with the advancement of age. The prevalence of positive CAP-RAST against other food allergens was more frequent among boys than among girls (data not shown).

Table 6 summarizes the results of logistic analysis for house dust. When the data for first- and second-born children were combined, the frequency of house-dust allergy increased with age (*P* for trend= 0.074) and among boys (OR=2.13 95%CI=1.20-3.80). In the analysis conducted separately for first- and second-born children, the risk of house-dust allergy among second-born children was strongly related to age (*P* for trend=0.001) and sex (OR=6.22 95%CI=1.66-23.3). We observed similar tendencies among the first-born children, although there was no statistical significance. On the other hand, the risk of house-dust allergy significantly increased with birth weight among first-born children (*P* for trend=0.002). Among second-born children, however, there was no association between the CAP-RAST for house dust and birth weight. No other significant relationship was observed. The results of logistic analysis for mites were similar to those for house dust (data not shown).

Discussion

In this study, we examined the associations of positive responses to foods, house dust, and mite allergens in an individual and between sibling pairs. Spearman's rank correlation coefficients using CAP-RAST scores suggested strong associations among all food allergens, and the correlations were stronger among oil seeds. CAP-RAST scores for two indoor allergens, house dust and mite, were also strongly related to each other. However, associations between food and indoor allergies were relatively weak.

The prevalence of positive response to oil-seed allergens was associated with the presence of positive response to various food allergens between siblings. On the other hand, only weak correlations between siblings were observed for egg and cow's milk. Interestingly, positive response to indoor allergens showed no association between siblings at all. The absence of a strong association between siblings with respect to positive response to indoor allergens suggests that the involvement of genetic backgrounds is weak. Indeed, inheritance of positive response to indoor allergens is considered to be unlikely, although genetic backgrounds may influence defensive mechanisms in the membranes of the respiratory organs[17]. Since food allergy is closely related to AD of the infants[10], positive reactions to the CAP- RAST of oil seeds among AD children may help predict positive responses to oil seeds for their younger siblings. This suggests a possibility of prevention against AD in younger siblings of children with AD.

Since each sibling pair in this study was living together after birth, it is quite likely for them to share most environmental factors. In fact, there was no environmental factor related to positive response to oil seed allergens in our survey. Other possible explanations for the strong association of positive response to oil-seed allergens between siblings were genetic backgrounds. However, it is not entirely clear to what extent genetic backgrounds regulate antigen-specific immune responses to oil seeds, including peanuts[18] although systematic immune response is known to be affected by genetic backgrounds[19]. Two major genetic factors related to allergic responses against oil seeds can be considered, polymorphisms of HLA and enzyme(s) to control allergic response(s). Howell *et al.*[20] suggested that an HLA class II genetic polymorphism may be involved in the susceptibility to peanut allergy. However, this association is inconclusive as recent reports are contradictory[21]. On the other hand, allergic response is thought to be triggered by an imbalance between n-6 and n-3 fatty acids[22]. Oil seeds are known to be rich in linoleic acid, an n-6 fatty acid[23], which is metabolized into arachidonic acid, a source of prostaglandin E2 (PGE2) and leukotriene B4, both of which enhance immune response[24]. Recently, genetic polymorphisms of enzymes involving metabolism of the arachidonic cascade were reported[25]. These genetic polymorphisms may explain the strong concordance between siblings for positive response to oil-seed allergens.

In the present study, frequencies of positive response to food allergens tended to increase among breast-fed children although the associations were not statistically significant. It is reported that children with strong atopic backgrounds before weaning are more easily sensitized to allergens consumed by their mothers and secreted into breast milk[26]. A study of children aged 2-6 months shows that breast-fed children had higher levels of antibody against cow's milk than bottle-fed children[8]. However, many studies report the contrary: breast-fed children are less likely to develop AD or food allergy[8]. A possible explanation for the apparent conflict is the presence of two antagonizing mechanisms: allergens absorbed into the maternal blood stream are efficiently released into breast milk by IgA contained in the breast milk during very early childhood (the first 6 months). However, IgA antibody in breast milk inhibits absorption of allergens from the alimentary tract. In other words, breastfeeding promotes allergy in the very early childhood but, in a long run, it inhibits food allergy.

Children with lower birth weights are known to be more likely to develop allergy[8]. In the present study, however, higher birth weight in first-born children was related to positive CAP-RAST results for house dust and mites. Since we did not collect in-depth information to explain these observations, we can not draw any conclusion at this moment. It is necessary to conduct extensive studies to establish the association between birth weights and allergy.

In the present study, we applied CAP-RAST scores to determine the cases of food/indoor allergies using a cut-off point of 0.35 UA/ml, following the previous reports [27]. A positive CAP-RAST score for egg or cow's milk is thought to indicate the presence of clinical symptom(s) of cow's milk allergy during infancy[28]. However, this is not true in the case of other food items, although positive CAP-RAST scores are frequently related to the presence of those food allergies[16]. In addition, the frequency of clinical symptoms of food allergy does not always increase with the CAP-RAST scores[16,28].

In the present study, we could not analyze the CPA-RAST results of all food allergens and all indoor allergens for 24% of the children because most of them have been examined for their IgE levels at other clinics where all food and indoor allergens were not always examined. Since some of those children might change or restrict their diets after the CAP-RAST, we used the existing results at the first AD diagnosis. However, these missing information might not induce bias in our results since none of the study subjects showed any clinical symptoms of food allergy when they had the first CAP-RAST, and it is unlikely that the study subjects restricted their diets before the CAP-RAST.

The mean age at the first AD diagnosis in first-born children was relatively high (3.3 years old) in the present study. The difference in dates of the first AD diagnosis between sibling pairs indicated that more or less 20-25% of parents brought their elder children to clinics after AD diagnoses of their younger children. One of the reasons for the delay of their visit to clinics was that those first-born children tended to show mild symptoms in their early childhood.

In summary, the present study showed that siblings with AD had an antigen-specific concordance of positive response only for oil seeds allergen. Further studies for genetic polymorphisms including non-AD children are warranted.

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アトピー性皮膚炎に罹患している同胞対における食物と室内抗原CAP-RASTの関係の検討

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【目的】同胞共にアトピー性皮膚炎に罹患している小児の食物と室内抗原に対する同胞間のアレルギー反応の相違を比較検討した。

【方法】対象はアトピー性皮膚炎に罹患している同胞で，2004年４月から2006年６月の間に熊本県内の皮膚科専門クリニックを受診している218組（436人）の同胞対のうち，2006年６月～７月の間に同クリニックを受診した10歳未満の同胞対169組（338人）である。患児の保護者に，外来にて自記式質問票による調査を行った。質問票では患児の性，年齢，出生時体重，離乳食の開始時期，授乳形態，両親のアレルギー既往歴，妊娠中・授乳期の両親の喫煙習慣，妊娠中・授乳期の母親の飲酒習慣，ペットの有無などについて質問した。対象者は，初診時にCAP radio-allergosorbent test（CAP-RAST）を測定しており，８つの食物抗原（卵白，牛乳，大豆，ピーナツ，ゴマ，小麦，そば，米）と２つの室内抗原（ハウスダスト，ダニ）に対するアレルギー反応結果を解析に使用した。

【結果】CAP- RAST陽性の割合は卵が48％と最も高く，続いて牛乳21％，小麦14％，ゴマ14％，ピーナツ10％，大豆８％，そば５％，米５％であった。またハウスダスト，ダニのCAP- RAST陽性の割合はそれぞれ46％，47％であった。Spearmanの順位相関で第一子，第二子それぞれでCAP- RASTスコアと抗原間の関係をみた場合，第一子において，特にoil seeds（大豆・ピーナツ・ゴマ）間で相関係数0.700以上の強い相関がみられた。次に同胞間のCAP- RASTスコアの関係を，Spearmanの順位相関を用いて検討した。牛乳（相関係数0.178），大豆（相関係数0.227），ピーナツ（相関係数0.166），ゴマ（相関係数0.186），小麦（相関係数0.192）において有意に同胞間で相関が認められた。また第一子の大豆，ピーナツと第二子の大豆，ゴマとの相関係数はいずれも0.25以上で，その他の抗原の相関係数と比べ高く，特に第一子のピーナツと第二子のゴマの相関係数は0.341と最も強い相関を示した。

【結論】本研究ではoil seedsのCAP- RASTスコアにのみ同胞間の強い相関が認められた。