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Genetic and environmental susceptibility to food allergy in a registry of twins

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Clinical Implications

- In a study of 80 twin pairs we demonstrate that genetic factors play a major role in the development of food allergy and that atopic dermatitis is a significant risk factor. Eczema control might reduce the risk of food allergy.

TO THE EDITOR:

A food allergy poses a substantial burden in many countries and the prevalence of food-induced anaphylaxis is increasing.[1-3] It is likely that gene-environment interactions, rather than genetic factors solely, play a major role in the development of food allergy. Effective prevention of allergic diseases requires understanding of the factors that contribute to the development of allergy.

We aimed to evaluate the concordance rate for food allergy in pairs of MZ and DZ twins for the most common food allergies. Moreover, we aimed to investigate the effect of zygosity, sex, comorbidities, and lifestyle habits on the development of food allergy.

Twins were recruited during the period 2014 to 2018 through Food Allergy Canada, Multiple Births Canada, BC Children's Hospital allergy clinic, and the Montreal Children's Hospital allergy clinic. Only participants with an allergist-diagnosed food allergy AND the presence of convincing clinical history and positive confirmatory test results were included in this registry.

Interested participants were sent a consent form and a questionnaire, based on previous validated food allergy questionnaires[4] and the International Study of Asthma and Allergies in Childhood.[5] The principal investigator and study coordinator independently reviewed participants' data.

DNA was collected through salivary samples, which were collected on all consenting and eligible participants to determine zygosity by genetic testing (GenePrint24 kit).

To assess twin concordance, we calculated probandwise concordance rates between pairs of MZ and DZ twins (defined as $2C/(2C + D)$) where C is the number of all twin pairs who are both allergic to the specific food [concordant pairs] and D is the number of all discordant pairs). The probandwise rate is preferred over the pairwise rate because the probandwise concordance serves to forecast risk at the level of the individual rather than at the level of the pair. Furthermore, pairwise concordance may underestimate the genetic effect.[6]

Univariable and multivariable logistic regression models were used to evaluate the association between genetic and environmental factors and the development of food allergy.

Statistical analysis was performed using R version 3.4.3 (Microsoft R Open 3.4.3, Boston, MA; November 30, 2017). The McGill Research Ethics Boards approved the study (ethics reference no. 13-034 PED).

For this study, we recruited 80 twin pairs of which 34 were MZ and 46 DZ. The median age of the patients was 4.8 years (range, 0.59-35.8 years). Fifty-nine percent of the patients were boys and 41% were girls.

Among 19 pairs of MZ and 30 pairs of DZ twins for peanut allergy, the concordance rate was 0.59 and 0.29, respectively (difference, 0.31; 95% CI, 0.04-0.58). Among 8 pairs of MZ and 8 pairs of DZ twins for pistachio allergy, the concordance rate was 0.55 and 0.00, respectively (difference, 0.55; 95% CI, 0.14-0.95) (Table I).

Among 5 pairs of MZ and 6 pairs of DZ twins for walnut allergy, the concordance rate was 0.57 and 0.00, respectively (difference, 0.57; 95% CI, 0.05-1.00). Among 5 pairs of MZ and 4 pairs of DZ twins for sesame allergy, the concordance rate was 0.75 and 0.00, respectively (difference, 0.75; 95% CI, 0.26-1.00) (Table I).

When investigating the risk of allergy to any food, the odds ratio of the atopic dermatitis was 6.74 (95% CI, 2.29-19.83; $P =$ .001) in the univariable regression model and 6.41 (95% CI, 1.93-21.28; $P = .02$) in the multivariable regression model when adjusted for sex, zygosity, atopic dermatitis, and use of more than 4 courses of antibiotics. The same was observed for peanut allergy: odds ratio of the atopic dermatitis was 8.42 (95% CI, 2.09-33.99; $P = .003$) in the univariable regression model and 8.3 (95% CI, 1.80-38.27; $P = .007$) in the multivariable regression model (Table II).

There was only 1 previous study on clinical food allergy (ie, food allergy that was established through corroborating clinical symptoms of reaction with a positive confirmatory test result) in twins. This study has shown a higher concordance rate for peanut allergy among MZ twins than among DZ twins (0.64 vs 0.07).[7] The present study shows similarly significant higher concordance rate of peanut allergy among MZ twins, strengthening the evidence of heritability of peanut allergy. In addition, for the first time, we have shown a similar genetic effect among patients allergic to pistachio, walnut, sesame, and fish. It is possible that genetic factors play a more important role among certain tree nuts in the development of allergy.

Our study is unique because it identifies atopic dermatitis as a significant risk factor for food allergy, independent of genetic factors. This highlights the importance of atopic dermatitis control among children because this may reduce the risk of food allergy.

This study is novel, because this is the largest twin study evaluating the concordances of phenotyped food allergies among

TABLE I. Specific food allergy concordances (*C* is the number of twin pairs who are both allergic to the specific food [concordant pairs], and *D* is the number of discordant pairs)

Food item	No. of MZ pairs	No. of DZ pairs	Concordant pairs *C*	Discordant pairs *D*	MZ Concordance (2*C*/2*C* + *D*)	DZ Concordance (2*C*/2*C* + *D*)	Difference (95% CI)
Almond	4	0	0	4	0.00		
Brazil nut	2	0	0	2	0.00		
Cashew	8	10	4	14	0.55	0.18	0.36 (−0.10 to 0.82)
Codfish	1	1	1	1	1.00	0.00	**1.00 (0.25 to 1.00)**
Egg	12	13	7	18	0.50	0.38	0.13 (−0.28 to 0.53)
Fish	3	3	3	3	1.00	0.00	**1.00 (0.75 to 1.00)**
Haddock	0	1	0	1		0.00	
Hazelnut	6	6	1	11	0.29	0.00	0.29 (−0.20 to 0.78)
Kiwi	2	0	0	2	0.00		
Lentil	1	0	1	0	1.00		
Milk	5	4	1	8	0.33	0.00	0.33 (−0.25 to 0.92)
Peanut	19	30	13	36	0.59	0.29	**0.31 (0.04 to 0.58)**
Peas	1	0	1	0	1.00		
Pecan	5	2	1	6	0.33	0.00	0.33 (−0.38 to 1.00)
Pinenut	0	1	0	1		0.00	
Pistachio	8	8	3	13	0.55	0.00	**0.55 (0.14 to 0.09)**
Salmon	1	2	1	2	1.00	0.00	**1.00 (0.5 to 1.00)**
Sesame	5	4	3	6	0.75	0.00	**0.75 (0.26 to 1.00)**
Shellfish	4	1	1	4	0.40	0.00	0.40 (−0.43 to 1.00)
Shrimp	2	0	2	0	1.00		
Soy	2	1	0	3	0.00	0.00	0.00
Sunflower	1	0	1	0	1.00		
Treenut	7	9	3	13	0.44	0.20	0.24 (−0.27 to 0.76)
Trout	0	1	0	1		0.00	
Tuna	1	0	1	0	1.00		
Walnut	5	6	2	9	0.57	0.00	**0.57 (0.05 to 1.00)**
Wheat	2	1	0	3	0.00	0.00	0.00
Pistachio/ cashew	9	12	4	17	0.50	0.15	0.35 (−0.77 to 0.07)
Walnut/ pecan	6	6	2	10	0.50	0.00	**0.50 (0.01 to 0.99)**
Any food	34	46	23	57	0.58	0.49	**0.10 (0.05 to 0.46)**

Bold values are statistically significant.

MZ and DZ twins. In one previous study, the sample size was larger but included only sensitization (not phenotyped food allergy).[8] In another study, food allergy was based on parental report in contrast to our study when the presence of convincing history and positive confirmatory test results were required as well.[9] In addition, in contrast to previous studies, zygosity of the twin pairs was verified by genetic testing. The inclusion of all common food allergies is also a major strength of the study.

The present study has some limitations. First, some information may be subjected to recall bias. Second, some twins may have outgrown, for example, milk allergy. Moreover, the diagnosis was not confirmed by a food challenge in most children. However, given that all cases were established by the presence of convincing history, confirmatory tests, and allergist's diagnosis, we believe that any misclassification bias would be minimal. Finally, our sample size might have been too small to capture concordance differences and the effects of other factors on the risk of developing all major food allergies.

In summary, in this study including 80 twin pairs with a median age of 5 years, we showed that genetic factors play a major role in the development of food allergies. This study showed that even when controlling for genetics, atopic dermatitis is a significant risk factor for food allergy. Further studies are needed to assess whether other risk factors (along with atopic dermatitis) will be identified as influencing the development of food allergies.

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TABLE II. An association between genetic and environmental factors to the development of food allergy by logistic regression model.

				Univariate			Multivariable		
Allergy	**Variable**		**No. of pairs**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Any food	Zygosity	Di	46	1			1		
		Mono	34	2.54	0.93-6.95	.068	0.90	0.23-3.43	.86
	Same sex	No	24	1			1		
		Yes	56	3.60	0.95-13.59	.059	3.17	0.56-18.05	.19
	Eczema	(N)one	51	1			1		
		Both	29	**6.74**	**2.29-19.83**	**.001**	**6.41**	**1.93-21.28**	**.02**
	Antibiotics	(N)one	76	1			1		
		Both	4	9.00	0.88-91.76	.064	9.99	0.88-113.80	.064
Peanut	Zygosity	Di	46	1			1		
		Mono	34	2.52	0.74-8.55	.137	0.65	0.14-3.15	.60
	Same sex	No	24	1			1		
		Yes	56	6.27	0.77-51.30	.087	5.84	0.53-64.09	.15
	Eczema	(N)one	51	1			1		
		Both	29	**8.42**	**2.09-33.99**	**.003**	**8.3**	**1.80-38.27**	**.007**
	Introduction	(N)one	25	1			1		
		Both	55	1.03	0.28-3.72	.967	1.18	0.28-4.91	.82
	Antibiotics	(N)one	76	1			1		
		Both	4	1.31	0.14-12.79	.815	0.93	0.079-10.77	.95

OR, Odds ratio.
Bold values are statistically significant.

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