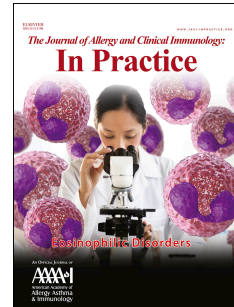


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Genetic and Environmental Susceptibility to Food Allergy in a Registry of Twins

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43 **Clinical Implications statement**

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

47

48 **To the Editor:**

49 A food allergy poses a substantial burden in many countries and the prevalence of food
50 induced anaphylaxis is increasing¹⁻³. It is likely that gene-environment interactions, rather
51 than genetic factors solely, play a major role in the development of food allergy. Effective
52 prevention of allergic diseases requires understanding of the factors that contribute to the
53 development of allergy.

54

55 We aimed to evaluate the concordance rate for food allergy in pairs of MZ and DZ twins, for
56 the most common food allergies. Moreover, we aimed to investigate the effect of zygosity,
57 gender, co-morbidities and lifestyle habits on the development of food allergy.

58

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

63

64 Interested participants were sent a consent form and a questionnaire, based on previous
65 validated food allergy questionnaires⁴ and the ISAAC (International Study of Asthma and
66 Allergies in Childhood)⁵. The Principal Investigator and study coordinator independently
67 reviewed participants' data.

68

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

71

72 To assess twin concordance, we calculated probandwise concordance rates between pairs of
73 MZ and DZ twins (defined as $2C/(2C+D)$) where C is the number of all twin pairs that are
74 both allergic to the specific food (concordant pairs), and D is the number of all discordant
75 pairs). The probandwise rate is preferred over the pairwise rate as the probandwise
76 concordance serves to forecast risk at the level of the individual rather than at the level of the
77 pair. Further, pairwise concordance may underestimate the genetic effect⁶.

78
79 Univariable and multivariable logistic regression models were conducted to evaluate the
80 association between genetic and environmental factors and the development of food allergy.

81
82 Statistical analysis was performed using R version 3.4.3 (2017-11-30). The McGill
83 Research Ethics Boards approved the study (ethics reference number: 13-034 PED).

84
85 For this study, we recruited 80 twin pairs of which 34 were MZ, and 46 DZ. The median age
86 of the patients was 4.8 years (range 0.59 – 35.8 years). Fifty-nine percent of the patients were
87 boys and 41 % were girls.

88
89 Among 19 pairs of MZ and 30 pairs of DZ twins for peanut allergy, the concordance-rate was
90 0.59 and 0.29 respectively [difference= **0.31 (95%CI 0.04, 0.58)**]. Among 8 pairs of MZ and
91 8 pairs of DZ twins for pistachio allergy, the concordance-rate was 0.55 and 0.00 respectively
92 [difference= **0.55 (95%CI 0.14, 0.95)**]. (Table 1)

93
94 Among 5 pairs of MZ and 6 pairs of DZ twins for walnut allergy, the concordance-rate was
95 0.57 and 0.00 respectively [difference= **0.57 (95%CI 0.05, 1.00)**]. Among 5 pairs of MZ and

96 4 pairs of DZ twins for sesame allergy the concordance-rate was 0.75 and 0.00 respectively
97 [difference= **0.75 (95%CI 0.26, 1.00)**]. (Table 1)

98

99 When investigating the risk of allergy to any food, the odds ratio of the atopic dermatitis was
100 6.74 (**95%CI 2.29, 19.83, p=0.001**) in the univariable regression model and 6.41 (**95%CI**
101 **1.93, 21.28, p=0.02**) in the multivariable regression model when adjusted for gender,
102 zygosity, atopic dermatitis and use of more than 4 courses of antibiotics. The same was
103 observed for peanut allergy: odds ratio of the atopic dermatitis was 8.42 (**95%CI 2.09, 33.99,**
104 **p=0.003**) in the univariable regression model and 8.3 (**95%CI 1.80, 38.27, p=0.007**) in
105 multivariable regression model. (Table 2)

106

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

115

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

119

120 This study is novel, since this is the largest twin study evaluating the concordances of
121 phenotyped food allergies among MZ and DZ twins. In one previous study, the sample size
122 was larger but included only sensitization (not phenotyped food allergy)⁸. In another study,
123 food allergy was based on parental report in contrast to our study when the presence of
124 convincing history and positive confirmatory tests were required as well⁹. In addition, in
125 contrast to previous studies, zygosity of the twin pairs was verified by genetic testing. The
126 inclusion of all common food allergies is also a major strength of the study.

127
128 The present study has some limitations. First, some information may be subjected to recall
129 bias. Second, some twins may have outgrown e.g. milk allergy. Moreover, the diagnosis was
130 not confirmed by a food challenge in the majority of children. However, given that all cases
131 were established by the presence of convincing history, confirmatory tests and allergist's
132 diagnosis, we believe that any misclassification bias would be minimal. Finally, our sample
133 size might have been too small to capture concordance differences and the effects of other
134 factors on the risk of developing all major food allergies.

135
136 In summary, in this study including 80 twin pairs with median age of 5 years, we showed that
137 genetic factors play a major role in the development of food allergies. This study showed that
138 even when controlling for genetics, atopic dermatitis is a significant risk factor for food
139 allergy. Further studies are needed to assess whether other risk factors (along with atopic
140 dermatitis) will be identified as influencing the development of food allergies.

141

142

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145 with recruitment.

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148 **References**

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Table 1. Specific food allergies concordances (C is the number of twin pairs that are both allergic to the specific food (concordant pairs), and D is the number of discordant pairs).

	Number of MZ pairs	Number of DZ pairs	Concordant pairs C	Discordant pairs D	MZ Concordance (2C/2C+D)	DZ Concordance (2C/2C+D)	Difference (95% Confidence Interval)
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, 0.82)
Codfish	1	1	1	1	1.00	0.00	1.00 (0.25, 1.00)
Egg	12	13	7	18	0.50	0.38	0.13 (-0.28, 0.53)
Fish	3	3	3	3	1.00	0.00	1.00 (0.75, 1.00)
Haddock	0	1	0	1		0.00	
Hazelnut	6	6	1	11	0.29	0.00	0.29 (-0.20, 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, 0.92)
Peanut	19	30	13	36	0.59	0.29	0.31 (0.04, 0.58)
Peas	1	0	1	0	1.00		
Pecan	5	2	1	6	0.33	0.00	0.33 (-0.38, 1.00)
Pinenut	0	1	0	1		0.00	
Pistachio	8	8	3	13	0.55	0.00	0.55 (0.14, 0.09)
Salmon	1	2	1	2	1.00	0.00	1.00 (0.5, 1.00)
Sesame	5	4	3	6	0.75	0.00	0.75 (0.26, 1.00)
Shellfish	4	1	1	4	0.40	0.00	0.40 (-0.43, 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, 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, 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, 0.07)
Walnut/ Pecan	6	6	2	10	0.50	0.00	0.50 (0.01, 0.99)
Any food	34	46	23	57	0.58	0.49	0.10 (0.05, 0.46)

Table 2. An association between genetic and environmental factors to the development of food allergy by logistic regression model.

Allergy		n of pairs	Univariate				Multivariable				
			OR	95% CI		P-value	OR	95% CI		p-value	
Any food	Zygoty	di	46	1			1				
		mono	34	2.54	0.93	6.95	0.068	0.90	0.23	3.43	0.86
	Same gender	no	24	1			1				
		yes	56	3.60	0.95	13.59	0.059	3.17	0.56	18.05	0.19
	Eczema	(n)one	51	1			1				
		both	29	6.74	2.29	19.83	0.001	6.41	1.93	21.28	0.02
	Antibiotics	(n)one	76	1			1				
		both	4	9.00	0.88	91.76	0.064	9.99	0.88	113.80	0.064
Peanut	Zygoty	di	46	1			1				
		mono	34	2.52	0.74	8.55	0.137	0.65	0.14	3.15	0.60
	Same gender	no	24	1			1				
		yes	56	6.27	0.77	51.30	0.087	5.84	0.53	64.09	0.15
	Eczema	(n)one	51	1			1				
		both	29	8.42	2.09	33.99	0.003	8.3	1.80	38.27	0.007
	Introduction	(n)one	25	1			1				
		both	55	1.03	0.28	3.72	9.967	1.18	0.28	4.91	0.82
Antibiotics	(n)one	76	1			1					
	both	4	1.31	0.14	12.79	0.815	0.93	0.079	10.77	0.95	

Antibiotics = 4 or more courses of antibiotics, Introduction = Age of introduction to peanut (less than 1 year or more than 1 year)