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Breastfeeding Might Have Protective Effects on Atopy in Children With the CD14C-159T CT/CC Genotype

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Breastfeeding is widely recommended to reduce risk of sensitization, eczema and asthma. However, the role of breastfeeding in prevention of allergic diseases is uncertain. We aimed to investigate whether the relationship between breastfeeding and sensitization to aeroallergens is modified by cluster of differentiation 14 (CD14) genotype. This study included 1,828 school children aged 9-12. We administered a detailed questionnaire and genotyped the CD14C-159T polymorphism. Skin prick tests for 12 aeroallergens were performed. School children who had been breastfed were less likely sensitized to aeroallergens (adjusted odds ratio [aOR] 0.712, 95% confidence interval [CI]: 0.555-0.914). There was no significant association between CD14C-159T genotype and atopy. Breastfeeding was associated with a decreased risk of atopic sensitization in children with CT/CC genotype (aOR 0.667, 95% CI: 0.463-0.960). Our data might identify the gene-environment interaction between the CD14C-159T polymorphism and breastfeeding in relation to aeroallergen sensitization.

Key Words: Breastfeeding; cluster of differentiation 14 (CD14); gene-environmental interaction; sensitization to aeroallergens

INTRODUCTION

Breastfeeding is widely recommended to reduce the risk of sensitization, eczema, and asthma.[1] However, the role of breastfeeding in the prevention of allergic diseases is uncertain, with some studies reporting favorable outcomes associated with breastfeeding and others reporting no effects. *Cluster of differentiation 14* (*CD14*) is a well-established susceptibility gene for atopic sensitization,[2] but it has demonstrated inconsistent results in its relationship with atopy and breastfeeding.

CD14C-159T is the promoter region of the *CD14* gene. Previous genetic studies have indicated that CD14C-159T polymorphisms might interact with environmental factors and contribute to the development of atopy and allergic diseases.[3] Although the mechanisms of gene-environmental factor interactions are largely unknown, a polymorphism in the promoter region of a gene might exert its effect by modulating gene expression.[4] Recent reports have shown that the effect of breastfeeding on food sensitization can be modified by single nucleotide polymorphisms in the IL-12 receptor β1, toll-like receptor 9, and thymic stromal lymphopoietin receptor genes.[5] However, to date there is no evidence that the effect of breastfeeding on sensitization to aeroallergens is modulated by the CD14C-159T genotype. Therefore, we investigated whether the relationship between breastfeeding and sensitization to aeroallergens is modified by the *CD14* genotype.

MATERIALS AND METHODS

We distributed questionnaires pertaining to breastfeeding to the homes of 1,828 schoolchildren aged 9-12 years from 10 elementary schools in urban (Seoul) and rural areas (Jeongeup) of Korea. Of the 1,828 potential subjects, 1,749 (95.7%) returned the questionnaires. Demographics and information on wheth-

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er the child breastfed and for how long were obtained through the following questions: "Did you breastfeed your child?" and "How long did you breastfeed?". A breastfed child was defined as having been breastfed for ≥4 months. Skin prick tests for 12 aeroallergens were performed: *Dermatophagoides pteronyssinus* (*D. pteronyssinus* [*D.p*]), *Dermatophagoides farinae* (*D. farinae* [*D.f*]), dog epithelium, cat epithelium, cockroach, grass, mixed tree pollen -1 and -2, *alternaria*, *aspergillus*, ragweed, and mugwort. Atopy was defined as a positive skin reaction (wheal diameter, ≥3 mm after subtraction of a negative control). Genotyping of the *CD14* polymorphism (-159C/T, rs2569190) was performed using the TaqMan fluorogenic 5' nuclease assay (ABI, Foster City, CA, USA). Genotyping was performed on 1,227 (67%) schoolchildren for whom parental consent for genetic studies was obtained.

The study was approved by the human ethics committees of Hallym University and Ulsan University. Written informed consent was obtained from the parents of all children.

Data were categorized and analyzed using SPSS version 14.0 (SPSS, Inc., Chicago, IL, USA). Multivariate models evaluating the effects of breastfeeding and genetic factors on atopy were adjusted for predefined covariates, including sex, age, place of residence, parental history of allergic disease, income, and body mass index. A *P* value of less than 0.05 was considered significant.

Table 1. Subject characteristics

	Atopic	Non-atopic	*P* value
No. (%)	506	721	
Age (yr)	11.2±0.89	11.2±0.86	>0.05
Sex (M/F)	281/225	323/398	<0.001
BMI	19.4±3.01	18.8±3.04	0.006
Allergic diseases of parents	137/491 (27.9%)	158/696 (22.7%)	0.041
Delivery mode			
Vaginal delivery	338/503 (67.2%)	480/714 (67.2%)	>0.05
Cesarean section	163/503 (32.8%)	234/714 (32.8%)	
Breastfeeding (Yes/%)*	277 (54.7%)	460 (63.8%)	0.002
Pet ownership (Yes/%)	69/505 (13.6%)	106/716 (14.8%)	>0.05
Exposure to smoking (Yes/%)	225/506 (46.0%)	327/704 (46.4%)	>0.05
CD14 genotype			
CC	77 (15.2%)	82 (11.4%)	>0.05
CT	226 (44.7%)	355 (49.2%)	
TT	203 (40.1%)	284 (39.4%)	
Residence			
Urban	242 (47.8%)	277 (38.4%)	0.003
Rural city	120 (23.7%)	186 (25.8%)	
Village	144 (28.5%)	258 (35.8%)	
Economic state (monthly income)			
Low (≤200 KWN)	108 (22.8%)	192 (28.7%)	0.003
Middle (200-500 KWN)	315 (66.6%)	438 (65.5%)	
High (≥500 KWN)	50 (10.6%)	39 (5.8%)	

*Breastfeeding was defined as a condition in which children had breastfed for ≥4 months.
BMI, body mass index; CD14, cluster of differentiation 14; KWN, Korean Won.

RESULTS

We analyzed data from 506 atopic children and 721 nonatopic children (Table 1). Overall, schoolchildren who had been breastfed were less likely to be sensitized to aeroallergens (adjusted odds ratio [aOR], 0.712; 95% confidence interval [CI]: 0.555-0.914). This effect was greatest in children breastfed for more than 4 months (aOR, 0.731; 95% CI: 0.555-0.962). There was no significant association between the CD14C-159T genotype and sensitization to aeroallergens. Breastfeeding was associated with a decreased risk of sensitization to aeroallergens in children with the CT/CC genotype (aOR, 0.667; 95% CI: 0.463-0.960) (Table 2).

DISCUSSION

To the best of our knowledge, this is the first study to show that the effect of breastfeeding on sensitization to aeroallergens varies according to the CD14C-159T polymorphism. Our results show that breastfeeding might have protective effects on sensitization to aeroallergens in children carrying the CD14C-159T CT/CC genotype.

Reduced soluble CD14 (sCD14) levels in breast milk have been associated with the development of atopy in 4-year-old children.[6] The CD14C-159T promoter genotype may alter gene transcription, thereby affecting sCD14 levels.[7] T allele homozygotes had higher circulating levels of sCD14 at baseline. However, following an inhalational challenge with low-dose endotoxin,[8] the levels of sCD14 increased more in individuals with the C allele, such that there was no difference in sCD14 levels between genotype groups after the challenge. This suggests that carriers of the C allele are more responsive than T allele homozygotes to endotoxin exposure. Therefore, it is possible that carriers of the C allele may react more effectively to breastfeeding.

Table 2. Relationship between CD14 genotype and breastfeeding with regard to sensitization to aeroallergens

	Schoolchildren			
	Atopic	Non-atopic	OR (95% CI)	*P* value
No BF/CD14 TT	96	111	1	
No BF/CD14 CT+CC	133	150	1.071 (0.721-1.589)	>0.05
Yes BF/CD14 TT	107	173	0.803 (0.541-1.192)	>0.05
Yes BF/CD14 CT+CC	170	287	0.667 (0.463-0.960)	0.029

Adjusted by age, sex, BMI, residence, parental allergic disease, and income. Multivariate logistic regression.
CD14, cluster of differentiation 14; BF, breastfeeding; OR, odds ratio; CI, confidence interval.

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The association between breastfeeding and sensitization to aeroallergens in childhood may vary significantly depending on the CD14C-159T genotype. Although our study included objective measurements such as genotyping and sensitization, the limitations of cross-sectional studies in elucidating biologic mechanisms are well recognized. Nevertheless, our results support the need for further investigation into the gene-environment interaction of the CD14C-159T polymorphism and breastfeeding in relation to aeroallergen sensitization.

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