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Filaggrin Mutation in Korean Patients with Atopic Dermatitis

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Purpose: Atopic dermatitis (AD) is a chronic, relapsing eczematous inflammatory skin disease. Mutations in the filaggrin gene (*FLG*) are major predisposing factors for AD. Ethnic differences exist between Asian and European populations in the frequency and spectrum of *FLG* mutations. Moreover, a distinct set of *FLG* mutations has been reported in Asian populations. The aim of this study was to examine the spectrum of *FLG* mutations in Koreans with AD. We also investigated the association of *FLG* mutations and clinical features of AD and compared the Korean *FLG* landscape with that of other East Asian countries.

Materials and Methods: Seventy Korean patients with AD were enrolled in this study. Fourteen *FLG* mutations previously detected in Korean, Japanese, and Chinese patients were screened by genotyping.

Results: Four *FLG* null mutations (3321delA, K4022X, S3296X, and S2889X) were identified in eleven patients (15.7%). The most commonly detected mutations in Korean patients with AD were 3321delA (n=6, 9.1%) and K4022X (n=3, 4.5%). *FLG* mutations were significantly associated with elevated IgE (≥200 KIU/L and/or MAST-CLA >3+, p=0.005), palmar hyperlinearity (p<0.001), and a family history of allergic disease (p=0.021).

Conclusion: This study expanded our understanding of the landscape of *FLG* mutations in Koreans and revealed an association between *FLG* mutations and AD phenotype.

Key Words: Atopic dermatitis, filaggrin mutation, Korean

INTRODUCTION

Atopic dermatitis (AD) is a chronic and relapsing pruritic inflammatory skin disease, often associated with elevated serum IgE levels and a family history of AD, allergic rhinitis, and asthma.[1,2] The prevalence of AD in industrialized countries has recently increased to 15 to 30% in children and 2 to 10% in adults.[3]

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AD has a complex etiology with genetic, immunological, and environmental aspects. Mutations in the filaggrin gene (*FLG*) are the most common and significant genetic defects identified to date causing AD, emphasizing the role of skin barrier alterations in AD pathogenesis.[1,4-6]

FLG was first identified by Dale[7] in 1977 as a highly insoluble, histidine-rich protein that was co-purified with keratin intermediate filament proteins in epidermal extracts. *FLG* monomers have been thought to promote corneocyte compaction by contributing to keratin pattern formation in the lower stratum corneum (SC).[4] *FLG* monomers are proteolyzed into natural moisturizing factors, which are necessary to maintain hydration of the upper SC and acidic pH of the skin surface.[1]

FLG mutations have been identified as the underlying cause of ichthyosis vulgaris[8] (IV; OMIM 146700), which is characterized by dry and scaly skin, palmar and plantar hyperlinearity, and keratosis pilaris.[9] Furthermore, *FLG* mutations have proved to be a major predisposing factor for AD in Europe and Asia.[6,10]

Patients with AD who carry *FLG* mutations have been reported to have more persistent and severe disease, a higher incidence of herpes virus infection, allergic sensitization, and a greater risk of multiple allergies than patients with AD without *FLG* mutations.[1,5]

Some *FLG* mutations (R501X, R1891X, 3321delA, S1405X, S1515X, W1947X, G2025X, E3070X, Q1701X, Y1767X, S3296X, and K4022X) have been identified in Korea.[11-14] This study aimed to examine the spectrum of *FLG*-null mutations in Koreans with AD to investigate the association between *FLG* mutations and clinical AD markers and to compare the landscape of Korean *FLG* mutations with that of other Asian countries.

MATERIALS AND METHODS

Clinical materials

Seventy Korean patients with AD whose parents and all four grandparents were recorded as ethnic Korean were enrolled. Diagnosis of AD was confirmed by experienced dermatologists using AD diagnostic criteria created by Hanifin and Rajka.[15] Patients were divided into three groups according to age of onset: early childhood onset (<8 years), late childhood onset (8–18 years), and adult onset (>18 years). AD disease severity was assessed using the SCORing Atopic Dermatitis (SCORAD) index, and patients with AD were grouped into mild (<15 points), moderate (15–40 points), and severe (>40 points) disease groups.[16] Peripheral blood samples were analyzed for total serum IgE levels and specific IgE levels for egg, milk, soybean, peanut, fish, wheat, mites (*Dermatophagoides pteronyssinus, Dermatophagoides farinae*), and cockroach by multiple allergosorbent test chemiluminescent assay (MAST-CLA; AdvanSureTM AlloStation, LG Life Science, Seoul, Korea). Total IgE concentrations ≥200 KIU/L and/or ≥3+ in three categories of the MAST-CLA test were arbitrarily defined as elevated IgE in this study.[17,18] Associated allergic diseases, including asthma and allergic rhinitis, were determined on the basis of the questionnaire and previous diagnoses by physicians. Patients provided written informed consent, which complied with the principles of the Declaration of Helsinki. This study was approved by the Institutional Review Board (IRB No. 3-2014-0027) of Gangnam Severance Hospital, Seoul.

Mutation analysis

Genomic DNA was extracted from peripheral blood leukocytes with a DNA extraction kit (QIAamp DNA Blood Midi kit, Qiagen, Hilden, Germany). Patients with AD were screened for fourteen *FLG* mutations that have been identified in Korea, Japan, and China (R501X, 3321delA, S1695X, Q1701X, Q1745X, Y1767X, Q1790X, S2554X, S2889X, S3296X, 3222del4, S1515X, Q2417X, and K4022X) by direct DNA sequencing as described previously.[19,20]

Statistical analysis

Descriptive statistics for quantitative values were expressed as means [±standard deviation (SD)] in accordance with the data distribution. Frequencies and percentages were used to describe categorical variables. We used Fisher's exact test to assess the associations between *FLG* mutations and AD, as well as AD-associated phenotypes, including age of onset of AD, SCORAD index, allergic AD, family history of AD, and associated allergic diseases like asthma and allergic rhinitis. The strength of associations was estimated by calculating odds ratios and 95% confidence intervals. The level of statistical significance was established at $\alpha<0.05$. Statistical analyses were performed using SPSS version 19 (SPSS Inc., Chicago, IL, USA).

Table 1. Clinical Characteristics of Korean Patients with AD in This Study

Characteristics	Number of patients (%)
Total AD patients	70
Mean age (yrs)	19.3 (range 0–63)
Sex	
Male	48 (68.6)
Female	22 (31.4)
Elevated IgE*	44 (62.8)
Hyperlinear palms	17 (24.2)
Age of onset (yrs)	
Early childhood (<8)	53 (75.7)
Late childhood (8–18)	10 (14.3)
Adult (>18)	7 (10.0)
Family history	28 (40.0)
Allergic disease association†	25 (35.7)
Severity (SCORAD index)	
Mild (<15 points)	13 (18.6)
Moderate (15–40 points)	25 (35.7)
Severe (>40 points)	32 (45.7)

AD, atopic dermatitis; SCORAD, SCORing Atopic Dermatitis.
*Total IgE ≥200 KIU/L and/or specific IgE ≥3+, †Allergic disease: allergic rhinitis and/or asthma.

Table 2. Atopic Dermatitis Association Analysis for *FLG* Null Variants in Korea

Genotype	R501X	3321delA	Y1767X	S1695X	Q1701X	Q1745X	Q1790X	S2554X	S2889X	S3296X	K4022X	3222del4	S1515X	Q2417X
AA	70	64	70	70	70	70	70	70	69	68	67	70	70	70
Aa	0	6	0	0	0	0	0	0	1	2	3	0	0	0
aa	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	70	70	70	70	70	70	70	70	70	70	70	70	70	70

FLG, filaggrin gene.

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RESULTS

Clinical features

The clinical characteristics of patients with AD are presented in Table 1. A total of 70 patients were enrolled in this study. The mean age was 19.3 years (range 0 to 63, SD=13.14), and 68.6% of patients were male. Thirteen patients had mild AD, 25 had moderate, and 32 had severe AD, as determined by the SCORAD index. Fifty-seven (81.4%) patients had moderate to severe disease. In the AD cohort, 24.3% of patients had hyperlinear palms.

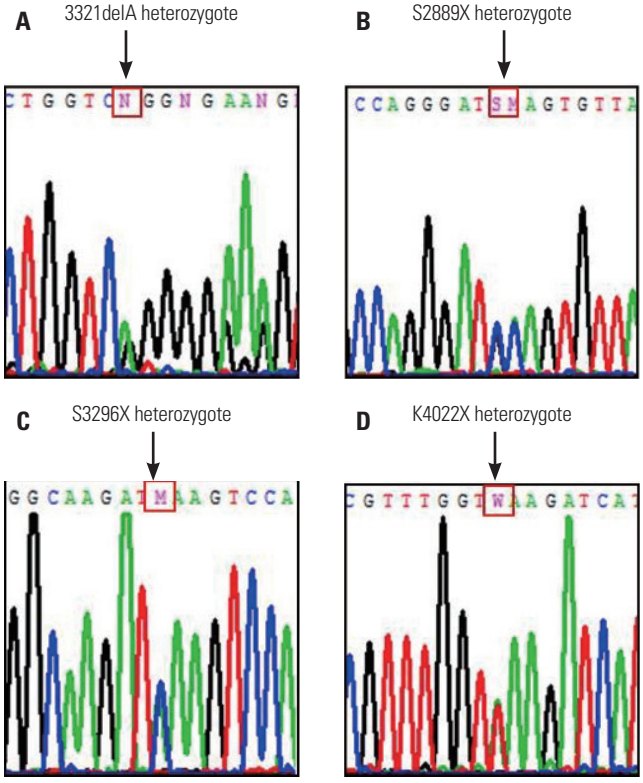

Fig. 1. *FLG* mutations detected in patients with atopic dermatitis. (A) A heterozygous deletion mutation, 3321delA, in *FLG* repeat 2 in exon 3 was identified in patient no. 28. (B) Two heterozygous transition mutations, c.8666C→G and c.8667C→A, in patient no. 11 resulted in S2889X. (C) A heterozygous transition mutation, c.9887C→A, in patient no. 66 resulted in S3296X. (D) A heterozygous transition mutation, 14011A→T, in patient no. 40 resulted in nonsense mutation K4022X. *FLG*, filaggrin gene.

FLG mutations in AD patients

Among the fourteen mutations screened, four, S2889X, S3296X, 3321delA, and K4022X, were identified in our AD patients (Table 2, Fig. 1). Eleven patients had *FLG* mutations, and all were heterozygous for the mutation. All patients with *FLG* mutations had moderate to severe AD (Fig. 2). Mutations 3321delA, K4022X, S3296X, and S2889X were carried by six (9.1%), three (4.5%), two (3.0%), and one (1.5%) individuals, respectively. One patient was a heterozygous carrier of two different *FLG* mutations. This study is the first time S2889X has been identified in Koreans with AD (Fig. 1).

Associations between *FLG* mutations and AD characteristics

FLG mutations were significantly associated with elevated IgE, palmar hyperlinearity, and a family history of allergic disease ($p<0.05$) (Table 3). All patients with *FLG* mutations had high IgE, and were positive for MAST-CLA or moderate to severe AD. Palmar hyperlinearity was present in eight patients (72.7%) with AD and *FLG* mutations. Eight patients (72.7%) with *FLG* mutations had a family history of allergic disease. Age of onset was not significantly associated with *FLG* mutation. AD severity was not statistically significantly associated with *FLG* mutation ($p=0.115$).

Clinical phenotype differences among each *FLG* mutations are shown in Table 4 and Fig. 3. Although clinical severity and phenotypic expression tended to differ among mutation types, statistical significance was not reached since the number of patients was too small.

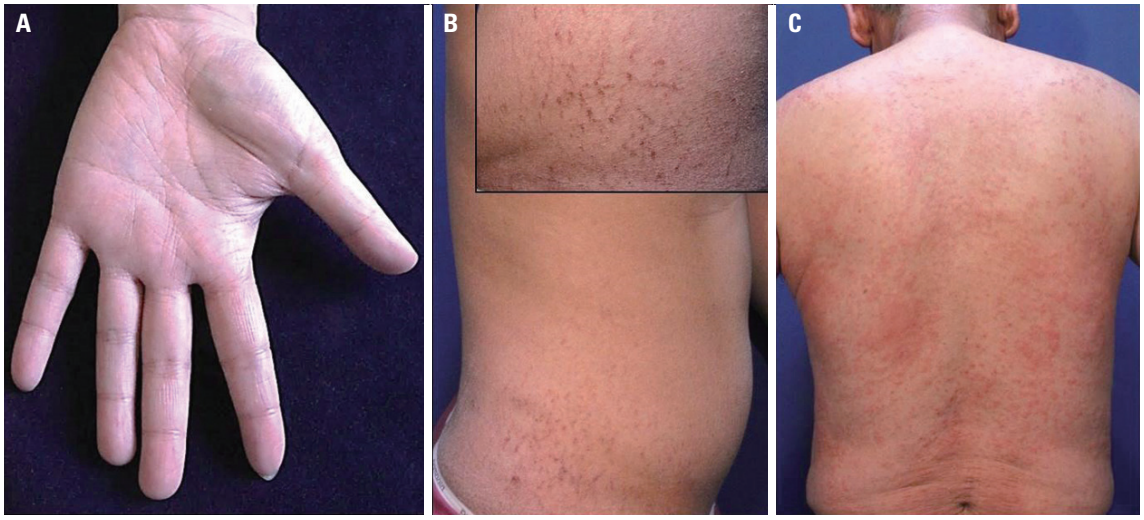

Fig. 2. Clinical features of patients with atopic dermatitis. (A) Palmar hyperlinearity of an atopic dermatitis patient with mutation K4022X. (B) Fine scales and xerosis on the trunk of a patient with mutations S2889X and S3296. (C) Erythematous papules and a patch on the back of a patient with mutation 3321delA.

DISCUSSION

Since two *FLG* mutations, R501X and 2282del4, were identified in Europeans with AD, many replication studies have reported the prevalence and frequency of mutations in the *FLG* in individuals with AD.[9,10] New *FLG* mutations associated with AD have been widely reported in European and non-European cohorts. Previous reports have also shown variations in *FLG* mutations among individuals with AD in different ethnic groups. The most prevalent *FLG* mutations are R501X and 2282del4 and have been reported to be present in up to 48% of Europeans with AD.[1,5] The mutation landscape in Asians with AD cohorts has been reported to vary, and the frequency was reported to be much lower than that in Europeans. Although many European countries have a similar *FLG* mutation landscape, Asian countries have been reported to have distinct *FLG* mutation landscapes. Among the Asian-specific *FLG* null mutations identified in Japan, China, Taiwan, and Singapore, only 3321delA was common. In a Japanese AD cohort, the S2554X and S2889X mutations were the most prevalent, followed by 3321delA and S3296X.[21,22] 3321delA and K4671X were the most common *FLG* mutations in an AD cohort in China.[23,24] Hsu, et al.[25] identified three *FLG* mutations, 3321delA, Q2417X, and E1795X, in Taiwanese families with ichthyosis vulgaris. The 3321delA mutation was the most prevalent *FLG* mutation in Singapore.[26]

In this study, fourteen *FLG* mutations, R501X, 3321delA, S1695X, Q1701X, Q1745X, Y1767X, Q1790X, S2554X, S2889X,

Table 3. Clinical Characteristics of Korean Patients with AD and with or without *FLG* Mutations

Characteristic	AD with *FLG* mutations (%)	AD without *FLG* mutations (%)	*p* value
Number of patients	11	59	-
Age (range), yrs	28 (0–63)	18 (0–43)	-
Sex			
Male	8 (72.7)	40 (67.8)	-
Female	3 (27.3)	19 (32.2)	-
Elevated IgE*	11 (100)	33 (55.9)	0.005
Hyperlinear palms	8 (72.7)	9 (15.3)	<0.001
Age of onset (yrs)			0.545
Early childhood (< 8)	8 (72.7)	45 (76.3)	
Late childhood (8–18)	1 (9.1)	9 (15.3)	
Adult (>18)	2 (18.2)	5 (8.5)	
Family history of allergic disease	8 (72.7)	20 (33.4)	0.021
Allergic disease association†	4 (36.4)	21 (35.6)	1.000
Severity (SCORAD index)			0.115
Mild (<15 points)	0 (0)	13 (22.0)	
Moderate (15–40 points)	3 (27.3)	22 (27.3)	
Severe (>40 points)	8 (72.7)	24 (40.7)	

FLG, filaggrin gene; AD, atopic dermatitis; SCORAD, SCORing Atopic Dermatitis.
*Total IgE ≥200 KIU/L and/or specific IgE ≥3+, †Allergic disease: allergic rhinitis and/or asthma.

Table 4. Clinical Characteristics of Korean Patients with Atopic Dermatitis and with *FLG* Mutations

FLG mutation	Patient number	Scorad score	Hyperlinear palm	Family history of allergic disease	Allergic disease association	IgE (KIU/L)	Age of onset (yrs)
3321delA	16	59	Yes	Yes	No	377	62
	24	28	No	Yes	No	68.4	0
	28	23	No	Yes	No	30.6	0
	34	36	Yes	Yes	Yes	>1000.0	8
	48	54	Yes	Yes	Yes	>1000.0	5
	63	50	Yes	Yes	Yes	4119	1
K4022X	5	57	No	No	Yes	>1000.0	0
	33	41	Yes	No	No	167	5
	40	69	Yes	No	No	>1000.0	31
S3296X	11	68	Yes	Yes	No	405	7
	67	49	Yes	Yes	No	2124	0
S2889X	11	68	Yes	Yes	No	405	7

FLG, filaggrin gene.

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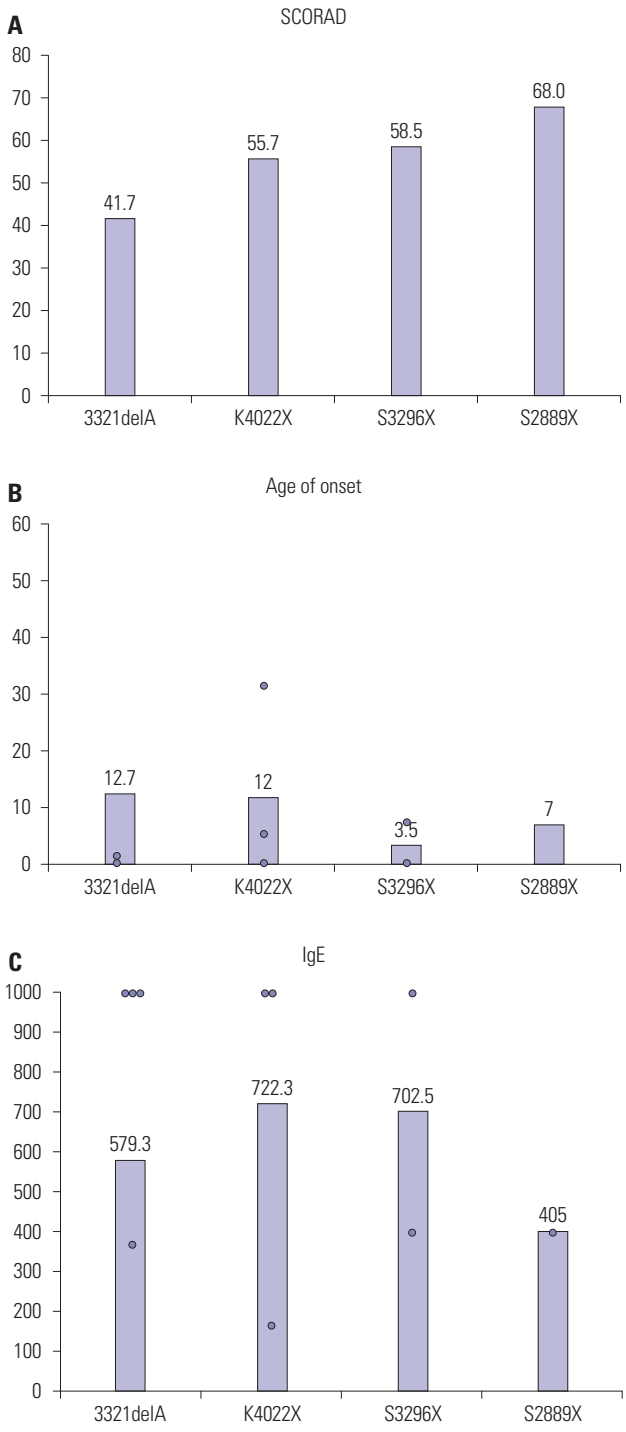

Fig. 3. Clinical phenotype difference among each *FLG* mutations. (A) SCORAD index. (B) Age of onset. (C) IgE level. *FLG*, filaggrin gene; SCORAD, SCORing Atopic Dermatitis.

S3296X, 3222del4, S1515X, Q2417X, and K4022X, which previously were reported in Asian AD cohorts, were selected for *FLG* mutation analysis. We demonstrated that 15.7% of Koreans with AD in our study had four *FLG* null mutations: S2889X, S3296X, 3321delA, and K4022X. 3321delA (n=6, 9.1%) was the most common *FLG* mutation in our AD cohort followed by K4022X (n=3, 4.5%). This prevalence is similar to that in China; 3321delA is one of the most prevalent mutations in Chinese patients with AD.[24] In a recent study, Park, et al.[14] screened 81 Korean AD patients and K4022X was the most common. We also found that K4022X was the second most common mutation in our cohort; therefore, K4022X is thought to be a common mutation in Koreans with AD. There were differences of prevalent *FLG* mutations and AD-associated phenotype between the previously published two studies. Park, et al.[14] reported new *FLG* mutations in Korean AD patients by analyzing coding exons, whereas we analyzed known mutations. The differences in *FLG* mutations and AD-associated phenotype may be the result of small sample size in both studies.

S2889X (n=1, 1.5%) and S3296X (n=2, 3.1%), which are common in Japanese patients with AD, were also detected in two Koreans in our study. S2554X, which was the most common *FLG* mutation in Japan, was not detected in our study. One patient who had two mutations, S2889X and S3296X, had hyperlinear palms, clinical features of IV, and severe AD. Notably, this study was the first to detect the S2889X mutation in Koreans. This study expanded our understanding of the landscape of *FLG*-null mutations in Koreans with AD.

The frequency of *FLG* mutation was 31.4% and 26.0% in Chinese patients with AD in previous reports.[23,24] A Japanese case–control study of eight *FLG* mutations demonstrated that about 27% of Japanese patients with AD carried at least one *FLG* mutation.[22] The frequency of *FLG* mutations was 20.2% in Singaporean Chinese patients with AD or IV.[26] In our study, the frequency of *FLG* mutations in Korean patients with AD (15.7%) was similar to that reported by Park, et al.[14] The frequency of *FLG* mutations in Koreans with AD seems to be lower than that in other Asian countries. The low frequency of *FLG* mutations in our study can be explained by the fact that AD is a multifactorial disease that is affected by genetic and environmental factors. Mutations in other barrier-related genes may contribute to AD in our cohort. In addition, decreased *FLG* expression in AD as a result of genetic mutations or skin inflammation can induce acquired *FLG* deficiency. Barrier impairment in AD patients with severe inflammation has been reported to be similar in patients with wild-type and mutant *FLG*. These *FLG* alterations due to inflammation can also explain the low *FLG* mutation frequency in individuals with AD.[5,27] The other important finding of our study is the association between *FLG* mutations and clinical features of AD in the Korean population. Palmar hyperlinearity and allergic sensitization with increased total IgE levels have been previously reported to be strongly associated with mutant *FLG*.[26,28] A significant association between palmar hyperlinearity and *FLG* mutations was also observed in our study. Previously, associations between *FLG* mutations and AD severity have been reported.[26] In contrast, other groups did not identify an association between *FLG* mutations and disease severity or skin barrier defects, characterized by high transepidermal water loss.[21,23,24] Although AD has been reported to be

more severe in patients with *FLG* mutations, there were no significant associations between *FLG* mutations and AD severity in our study. The lack of association between *FLG* mutations and AD severity maybe due to the fact that the SCORAD is a momentary variable that does not reflect overall disease activity.[29]

Any associated between early-onset AD and *FLG* mutations is still controversial. *FLG* mutations are related to early onset and persistent AD.[30] However, Meng, et al.[31] did not find an association between early-onset AD and the *FLG* mutation 3321delA. Age of onset was also not significantly associated with *FLG* mutations in the present study.

In conclusion, our study expands our understanding of the landscape of *FLG* mutations in Koreans by finding four *FLG* mutations, of which one has not previously been reported in Koreans with AD. We also found that the frequency of *FLG* mutations in Korean AD was lower than that of other Asian countries. The *FLG* mutation spectrum in our cohort was both distinct and partially overlapping with other Asian AD cohorts. We also demonstrated a significant association between *FLG* mutations and AD phenotype (elevated IgE, palmar hyperlinearity, and a family history of allergic disease).

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