Filaggrin mutation in Korean patients with atopic dermatitis

Hye Rang On

Department of Medicine

The Graduate School, Yonsei University

Filaggrin mutation in Korean patients with atopic dermatitis

Directed by Professor Soo-Chan Kim

The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

Hye Rang On

June 2015

This certifies that the Master's Thesis of
HYE RANG ON is approved.

Thesis Supervisor : Soo-Chan Kim

Thesis Committee Member#1 : Kyu Earn Kim

Thesis Committee Member#2 : Sang Eun Lee

The Graduate School
Yonsei University

June 2015

ACKNOWLEDGEMENTS

First of all, I very much appreciate my thesis supervisor, Professor Soo-Chan Kim, for giving me great advice and guidance that has been helpful for taking a degree. I thank him for his supervision and encouragement to study this subject

I also appreciate Professors Kyu Earn Kim and Sang Eun Lee who gave me expert advice and warm support. I wish to thank researcher Song-Ee Kim and Professor Toshifumi nomura for their bright ideas and unremitting effort. They make it possible to complete this valuable research.

And thanks to all members of our department for their helpful assistance and supports.

Finally, I would like to thank with all my heart to my entire family very much for their support and encouragement.

<TABLE OF CONTENTS>

ABSTRACT·····1

I. INTRODUCTION ·····3
II. MATERIALS AND METHODS ·····5
1. Clinical materials ·····5
2. Mutation analysis ·····5
A. DNA samples ·····5
B. Polymerase chain reaction (PCR) amplification ·····5
C. DNA sequence analysis ·····7
3. Statistical analysis ····· 7
III. RESULTS ·····8
1. Clinical features of the AD patients ·····8
2. Identifications of *FLG* mutations in AD patients ·····11
3. Associations between *FLG* mutations and AD characteristics ·····14
IV. DISCUSSION ·····16
V. CONCLUSION ·····19

REFERENCES ·····20
ABSTRACT(IN KOREAN) ·····24

LIST OF FIGURES

Figure 1. Clinical features of patients with atopic dermatitis· 9
Figure 2. *FLG* mutations detected in patients with atopic dermatitis ····· 12
Figure 3. Clinical features of patients with atopic dermatitis· 13
Figure 4. *FLG* null mutations found in Korean ichthyosis vulgaris and atopic dermatitis patients ····· 13

LIST OF TABLES

Table 1. The sequences of PCR primers ····· 6
Table 2. Clinical characteristics of patients with atopic dermatitis ····· 10
Table 3. Atopic dermatitis association analysis for *FLG* null variants in Korea ····· 12
Table 4. Clinical characteristics of AD patients with and without *FLG* mutations ····· 15

<ABSTRACT>

Filaggrin mutation in Korean patients with atopic dermatitis

HYE RANG ON

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Soo-Chan Kim)

Atopic dermatitis (AD) is a chronic, relapsing eczematous inflammatory skin disease. Filaggrin gene, *FLG*, mutation is a major predisposing factor for AD. Ethnic difference exists between Asian and European populations in the frequencies and prevalence of *FLG* mutations. Also, there is a difference in prevalent mutations among Asian countries. The aim of this study was to examine the spectrum of *FLG* mutations in Korean AD individuals; we also investigate the association of *FLG* mutations and clinical markers of AD, and compare the *FLG* landscape with other Asian countries.

Sixty-six patients who were diagnosed as AD were enrolled in this study. Eleven *FLG* mutations previously detected in Korean, Chinese and Japanese populations were screened by genotyping. The mean age of the patients with AD was 19.5 years and 71.2% were male. Four kinds of *FLG* null mutations (3321delA, S2889X, S3296X, and K4022X) were identified in total eleven patients (16.7%). One patient showed coexistence of two *FLG* mutations, S2889X and S3296X. There was a significant association between *FLG*

mutations and allergic type of AD, palmar hyperlinearity, and a family history of allergic disease.

Of these mutations, three mutations (K4022X, S2889X, and S3296X) were first identified in Korean AD populations. In conclusion, our study expanded the landscape FLG mutations in Korean AD population.

Key Words : Filaggrin, Atopic dermatitis, Korean

Filaggrin mutation in Korean patients with atopic dermatitis

HYE RANG ON

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Soo-Chan Kim)

Ⅰ. Introduction

Atopic dermatitis (AD), also known as atopic eczema, 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/or asthma.[1] The prevalence of AD have been increased in industrialized countries during the past three decades; 15 to 30% of children and 2 to 10% of adults.[2] The various observations of the disease indicate that AD has a complex etiology with genetic, immunological, and environmental aspects. Among them, mutation of the filaggrin (FLG) gene as a major genetic predisposing factor for AD has been investigated in many studies.[3-5]

FLG which was a highly insoluble, histidine-rich protein that co-purified with keratin intermediate filament proteins in epidermal extracts was identified by Beverly Dale in 1977.[6] The purified protein condensed and aligned keratin intermediate filaments in vitro and, accordingly, was named filaggrin (for filament

aggregating protein).[7] FLG monomers have been thought to promote the compaction of corneocytes by contributing to keratin pattern formation in the lower stratum corenum (SC).[3] FLG monomers are further proteolyzed into natural moisturizing factors (NMFs) which are necessary to maintain hydration of the upper SC and acidic pH of the skin surfaces.[4]

FLG mutation has been identified as the underlying cause of ichthyosis vulgaris[8] (IV; OMIM 146700) which is characterized clinically by dry and scaly skin, palmar and plantar hyperlinearity, and keratosis pilaris. Furthermore, *FLG* mutation has proved to be a major predisposing factor for AD in European and Asian populations.[9] There are differences in *FLG* mutations between European and Asian populations. R501X and 2282del4 mutations have been reported to be the most common *FLG* mutations in Europeans,[5] whereas 3321delA mutation appears to be the most common mutation in Chinese population and S2889X in Japanese population.[10,11]

There have been a few reports about FLG mutations (3321delA, R501X, Y1767X, and Q1701X) in Korean populations.[12-14] This study aimed to examine the spectrum of FLG-null mutations in Korean AD individuals, to investigate the association of FLG mutations and clinical markers of AD, and to compare the FLG landscape with other Asian countries.

Ⅱ. Materials and methods

1. Clinical materials

Blood samples were obtained from 66 patients with AD whose parents and all four grandparents were recorded as ethnic Korean. The diagnosis of AD was performed by experienced dermatologists using the AD diagnostic criteria by Hannifin and Rajka.[15] According to the age of onset, patients were divided into 3 groups; early childhood onset (< 8), late childhood onset (8-18), and adult onset (18<). AD disease severity was assessed by using the SCORing Atopic Dermatitis (SCORAD) index and the patients with AD were grouped into mild (<15 points), moderate (15-40 points) or severe (>40 points) disease groups. Peripheral blood samples analyzed for total serum IgE levels and specific IgE levels for egg, milk, soybean, peanut, fish, wheat, mite (Dermatophagoides pteronyssinus, Dermatophagoides farina), house dust, and coakroach by MAST-CLA (AdvanSureTM AlloStation, LG Life Science, Seoul, Korea). Total IgE concentrations ≥ 250 KIU/L and/or ≥ 3+ in 3 categories of MAST-CLA test were considered to be allergic type of AD. Patients gave written informed consent, which complies with all the Declarations of Helsinki Principles. This study was approved by the Institutional Review Board of Gangnam Severance Hospital, Seoul.

2. Mutation analysis

A. DNA samples

Genomic DNA was extracted from peripheral blood lymphocytes of patients using a DNA extraction kit (QIAamp DNA Blood Midi kit, Qiagen, Hilden, Germany).

B. Polymerase chain reaction (PCR) amplification

Gnomic DNA was used as templates for amplication of gnomic sequences of *FLG*

(GenBank NM_002016.1). Mutations R501X, 3321delA, S1695X, Q1701X, Q1745X, Y1767X, Q1790X, S2554X, S2889X, S3296X, and K4022X were amplified by PCR using pairs of oligonucleotide primers. PCR primers were described previously and were shown in Table1.[10,16,17] Amplification conditions were: 95°C for 10 min, followed by 35 cycles of 95°C for 30 s, 63°C for 30 s, and 72°C for 50s. The final extension was at 72°C for 7 min.

Table 1. The sequences of PCR primers

FLG exon3 repeats	Primer pairs
1-3	5' GCT GAT AAT GTG ATT CTG TCT G 3'
	5' GAC CCC GAT GAT TGT TCC TGT 3'
3-5	5' GCA AGC AGA CAA ACT CGT AAG 3'
	5' ACA TCA GAC CTT TCC TGG GAC 3'
4-7	5' GAC AAG ATT CAT CTG TAG TCG 3'
	5' CTG GCT AAA ACT GGA TCC CCA 3'
7-8	5' CCA CAC GTG GCC GGT CAG CA 3'
	5' CTA CCG AAT GCT CGT GGT GGT 3'
7-10	5' CCC AGG ACA AGC AGG AAC T 3'
	5' GCT TCA TGG TGA TGC GAC CA 3'
9-10	5' GAA ACG TCT GGA CAT TCA GGA 3'
	5' GCT TCA TGG TGA TGC GAC CA 3'
10	5' GCC CAT GGG CGG ACC AGG A 3'
	5' CTG CAC TAC CAT AGC TGC C 3'
FLG end	5' CTA GTA CCG CTA AGG AAC ATG G 3'
	5' TGG CTC CTT CGA TAT TTC TGA 3'

C. DNA sequence analysis

Sequence analyses were performed using Big Dye terminator technology (ABI 3100 Perkin-Elmer, Warrington, UK).

3. Statistical analysis

Descriptive statistics for quantitative values were expressed as mean (±SD) in accordance with the data distribution. Frequencies and percentages were used to describe the categorical variable data. The statistical significance of differences in genotype frequency among analyzed groups was assessed using Fisher's exact test. The strength of association was estimated by calculating the odds ratio (OR) with a 95% confidence interval (CI). The level of statistical significance was established at $\alpha < 0.05$. Statistical analyses were performed by using SPSS version 19.

Ⅲ. RESULTS

1. Clinical features of the AD patients

The clinical characteristics of the patients with AD are presented in Table 1 and Figure 1. Total sixty-six patients were enrolled in this study. Mean age of the patients were 19.5 years old (range 0 to 60, SD = 33.44) and 71.2% of the AD patients were male. AD patients showed various clinical features (Figure 1.). When AD severity was determined by generating objective SCORAD index, thirteen, twenty-three, and thirty of the patients with AD were found to have mild, moderate and severe disease, respectively. Fity-three (80.3%) of total patients presented moderate to severe SCORAD index. Total sixty-one patients (92.42%) were child-onset AD. Twenty-six patients (39.39%) had a family history of AD. Forty-one (61.22%) patients showed high IgE level. In this AD cohort, 24.2% of patients showed hyperlinear palm.

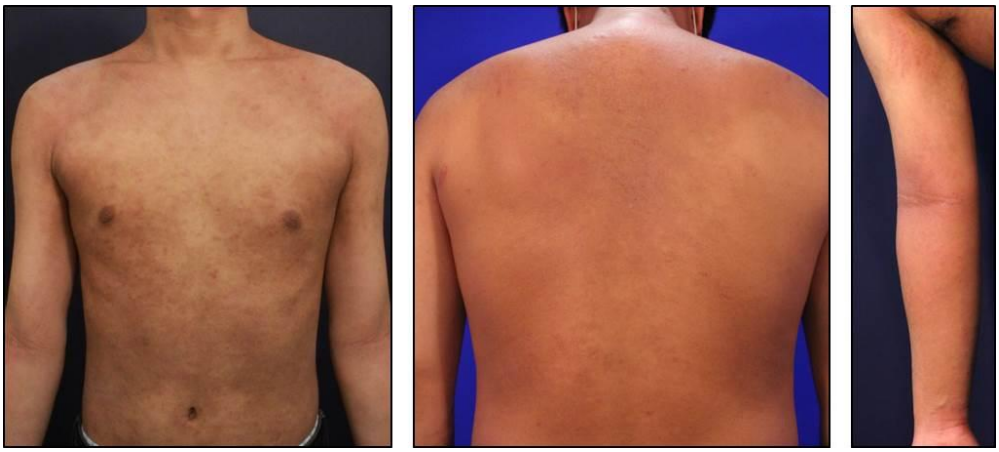

Figure 1. Clinical features of patients with atopic dermatitis. Erythematous scaly and lichenified patches on the trunk and extremities.

Table 2. Clinical characteristics of patients with atopic dermatitis

Characteristics	Number of patients (%)
Total AD patients	66 (100%)
Mean age	20 (range 0-63)
Sex	
Males	47 (71.2%)
Females	19 (28.8%)
Allergic AD*	31 (47.0%)
Hyperlinear palm	16 (24.2%)
Age of onset (year)	
Early childhood (< 8)	52 (78.8%)
Late childhood (8-18)	7 (10.6%)
Adult (18<)	7 (10.6%)
Family history	26 (39.4%)
Allergic disease association	23 (34.8%)
Severity (SCORAD index)	
Mild (<15 points)	13 (19.7%)
Moderate (15-40 points)	23 (34.8%)
Severe (>40 points)	30 (45.5%)

* Total IgE≥250 and/or Specific IgE ≥ 3+

2. Identifications of *FLG* mutations in AD patients

Among screened eleven mutations, four *FLG* mutations, S2889X, S3296X, 3321delA, and K4022X, were identified in AD patients (Table 2 and Figure 2). Total eleven patients were detected with *FLG* mutations and were all heterozygous for those mutations. All patients with *FLG* mutations showed moderate to severe clinical features of AD (Figure 3). Mutations S2889X, S3296X, 3321delA, and K4022X were found to be carried by 1 (1.5%), 2 (3.0%), 6 (9.1%), and 3 (4.5%) individuals. One patient was a heterozygous carrier of two different *FLG* mutations. Identification of S2889X, S3296X, and K4022X in this study is the first identification in Korean AD populations (Figure 4).

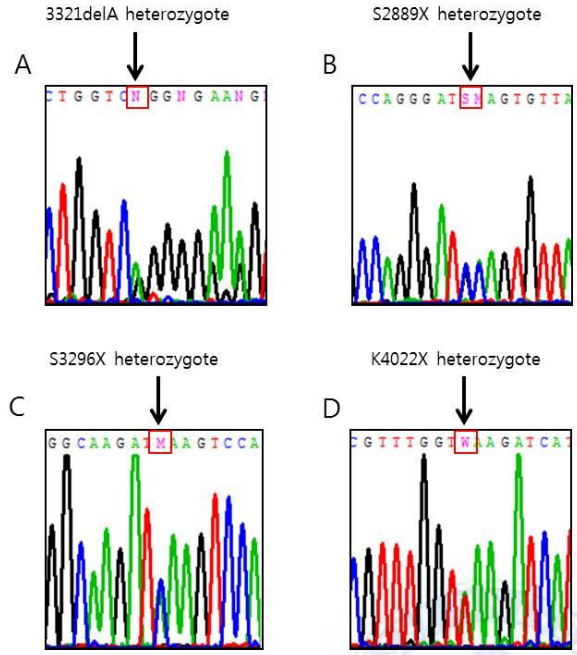

Figure 2. *FLG* mutations detected in patients with atopic dermatitis (A) Heterozygous deletion mutation in *FLG* repeat 2 in exon3 in patient no.28, 3321delA was identified. (B) Two heterozygous transition mutations c.8666C → G and c.8667C → A in patient no.11, resulting in S2889X. (C) A heterozygous transition mutation c.9887C → A in patient no.66, resulting in S3296X. (D) A heterozygous transition mutation 14011A → T in patient no.40, resulting in nonsense mutation K4022X

Table 3. Atopic dermatitis association analysis for *FLG* null variants in Korea

	R501X	3321delA	Y1767X	S1695X	Q1701X	Q1745X	Q1790X	S2554X	S2889X	S3296X	K4022X
Genotype											
AA	66	60	66	66	66	66	66	66	65	64	63
Aa	0	6	0	0	0	0	0	0	1	2	3
aa	0	0	0	0	0	0	0	0	0	0	0
Total	66	66	66	66	66	66	66	66	66	66	66

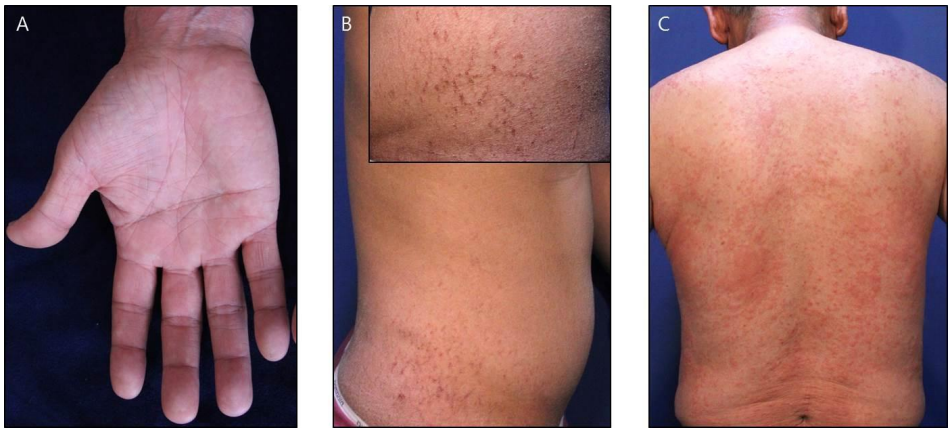

Figure 3. Clinical features of patients with atopic dermatitis (A) Palmar hyperlinearity of AD patient with K4022X mutation (B) Fine scales and xerosis on the trunk of AD patient with S2889X and S3296 mutations (C) Erythematous papules and patch on the back of AD patient with 3321delA mutation

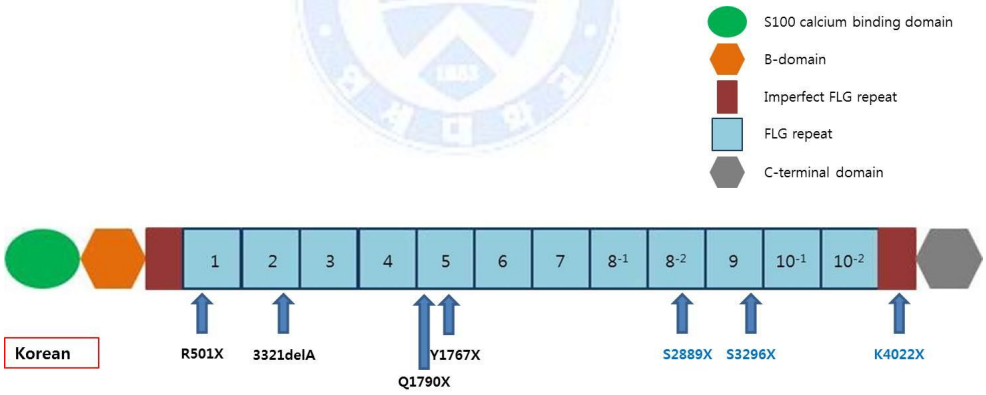

Figure 4. *FLG* null mutations found in Korean ichthyosis vulgaris (IV) and atopic dermatitis (AD). In total, seven *FLG*-null mutations have been detected in Korean IV and AD. Mutations in blue color were found in Korean populations for the first time from this study.

3. Associations between *FLG* mutations and AD chatacteristics (Table 3.)

FLG mutations were significantly associated with allergic type of AD, palmar hyperlinearity, and a family history of allergic disease ($p < 0.05$). Among AD patients with *FLG* mutations, a high percentage (90.9%) of patients showed high IgE level and/or positive for MAST-CLA. Palmar hyperlinearity was showed in eight patients (72.72%) of AD patients with *FLG* mutations. Eight patients (72.72%) had a family history of allergic disease. There was no significant association between onset age and *FLG* mutations. All patients with *FLG* mutations showed moderate to severe severity. Forty two patients (63.63%) in non-*FLG* mutation group showed moderate to severe severity. No significant association were detected between AD severity and *FLG* mutations statistically (p=0.088).

Table 4. Clinical characteristics of AD patients with and without *FLG* mutations

Characteristics	AD with FLG mutations (%)	AD without FLG mutations (%)	*p* value
Number of patients	11 (16.7)	55 (83.3)	-
Age (range)	28 (0-63)	19 (0-43)	-
Sex			
Males	8 (72.7)	39 (70.9)	-
Females	3 (27.3)	16 (29.1)	-
Allergic AD*	10 (90.9)	21 (38.1)	0.002
Hyperlinear palm	8 (72.7)	8 (14.5)	<0.001
Age of onset (year)			0.626
Early childhood (< 8)	8 (72.7)	44 (80.0)	
Late childhood (8-18)	1 (9.1)	6 (10.9)	
Adult (18<)	2 (18.2)	5 (9.1)	
Family history of allergic disease	8 (72.7)	19 (34.5)	0.040
Allergic disease association	4 (36.4)	19 (34.5)	1.000
Severity (SCORAD index)			0.088
Mild (<15 points)	0 (0)	13 (23.6)	
Moderate (15-40 points)	3 (27.3)	20 (36.4)	
Severe (>40 points)	8 (72.7)	22 (40.0)	

* Total IgE≥250 and/or Specific IgE ≥ 3+,

IV. Discussion

The human profilaggrin gene is located on chromosome 1q21 and consists of 3 exons of which exon 1 is noncoding and exon 2 encodes part of the S100 domain, and exon 3, one of the largest exons in the genome at more than 12.7 kb, encodes almost the entire profilaggrin protein.[4] In the final process of keratinocyte differentiation, profilaggrin is dephosphorylated and cleaved into 10–12 FLG peptide units. The liberated FLG subsequently and efficiently aggregates the keratin filament cytoskeleton, causing the collapse of the granular cells into flattened residual cells.[7] The collapsed cytoskeleton is crosslinked by transglutaminases to bind it to the cornified cell envelope.[9] FLG degradation products also contribute to moisture retention in the cornified layers as a natural moisturizing factor (NMF).[4] Thus, FLG is a key epidermal protein essential for the formation of a normal skin barrier. During the past few years, a strong association between FLG defects and allergic disorders has been observed in different populations.

Previous reports have identified *FLG* as the causative gene for IV but have highlighted that prevalence and frequency of *FLG* mutations in each populations are distinct.[10,11,16,18-22] The most prevalent *FLG* mutations in the U.K. population are R501X and 2282del4 which are not commonly found mutations in Asian populations.[20] The differences in the *FLG* mutation landscape between China, Taiwan, Singapore and Japan also exist. The two mutations S2554X and S2889X are the most prevalent *FLG* mutations in Japan,[10,23] whereas mutations K4022X and 3321delA are the most common *FLG* mutations in AD cohort in China.[11,22] Hsu CK et al.[24] identified three *FLG* mutations, 3321delA, Q2417X, and E1795X, in Taiwanese ichthyosis vulgaris families. The 3321delA mutation was the most prevalent *FLG* mutation in Singapore.[21] Only 3321delA mutation was commonly detected Asian countries including China, Singapore, Japan, Korea and Taiwan.

Thus, eleven mutations R501X, 3321delA, S1695X, Q1701X, Q1745X, Y1767X, Q1790X, S2554X, S2889X, S3296X, and K4022X which were reported in Korean and other Asian population were selected for *FLG* mutation analysis in the present study. The first clear finding from this study is that we expanded the landscape of *FLG*-null mutations in Korean AD individuals. 3321delA was detected in 6 AD patients (9.1%) and K4022X was detected in 3 AD patients (4.5%). Two mutations, 3321delA and K4022X, appear to be the most common *FLG* mutations in Korean AD patients from this study. This prevalence is similar to China than Japan. Though S2554X which was the most common *FLG* mutations in Japan was not detected in this study, S2889X (n=1) and S3296X (n=2, 3.1%) which were commonly found in Japanese AD patients were detected in two Korean patients. One patient who had two mutations S2889X and S3296X showed hyperlinear palms and clinical features of IV and AD with scales, erythema and severe xerosis on the whole body. K4022X, S2889X and S3296X have never been reported in Korean populations before.

The frequency of *FLG* mutation was 31.4% and 26.0% in Chinese AD patients in previous reports.[11,22] A Japanese AD case–control study for the eight *FLG* mutations demonstrated that about 27% of the patients in Japanese AD case series carry at least one *FLG* mutation.[23] In our present *FLG* mutation study, the frequency (16.7%) of *FLG* mutations in Korean AD patients was higher than previous AD case-control study in which the frequency of *FLG* mutations (R501X, E2422X, and 3321delA) was much lower (2.6%) in Korean than other population.[14] And, this frequency was due to that we identified more mutations than previous study.

Palmar hyperlinearity which have been previously reported to be strong clinical markers of *FLG*-null mutations was shown in 72.7% of AD patients with *FLG* mutation.[4,25] The significant association between palmar hyperlinearity and *FLG* mutations was observed in the present study.

Strong association between *FLG* mutations and AD was shown in many literatures.[10,11,16,20-22] In this study, most patients (80.3%) had moderate to severe SCORAD index. Chen et al.[21] reported the significant association of the *FLG* mutations with AD severity. In present study, though percentage of severe AD was higher in patients with *FLG* mutations, there was no significant association was observed between *FLG* mutations and AD severity. Many previous reports did not identify association of *FLG* mutations with disease severity.[10,11,14,22] The lack of association with severity maybe due to the age at which SCORAD was determined and due to the fact that the SCORAD is a ‘‘snap shot’’ variable that does not reflect the overall disease activity.[26] Although *FLG* mutation is considered as major predisposing factor of AD, AD is multifactorial disease which is affected by many other candidate genes, environmental factors like humidity and infection.

It was shown that *FLG* mutations related to early onset and persistent AD with increased total IgE levels and allergic sensitization was also reported rather than SCORAD index.[26,27] H. Rupnik et al.[28] reported that 2282del4 mutation was associated with AD that developed during infancy or in had a much earlier age of onset than those not carrying any FLG mutations, indicating the effect of FLG mutations on the age of onset for AD. But, there was no significant association between onset age and *FLG* mutations in the present study. Meng et al.[29] also did not find the association between early-onset between early-onset AD and *FLG* mutation c.3321delA. There is still a controversy between early-onset AD and *FLG* mutation.

FLG mutations and allergic disease association was investigated. In our study, no statistical significance was observed for the association between associated allergic diseases and *FLG* mutations. However, it was shown in Japanese that there was a statistically significant association between the *FLG* mutations and asthma with AD.[23] *FLG* is not expressed in the respiratory epithelia and the mechanisms of this

relationship are as yet unclear. One possible mechanism is skin barrier defects caused by *FLG* mutations allow antigen transfer through a defective epidermal barrier, resulting in initiation of further immune response and leading to the development of systemic allergies, including atopic asthma.[30,31] If early intervention for the repair of the epidermal barrier is conducted in AD patients with *FLG* mutations for preventing the subsequent development of the 'atopic march', we may consider the screening for *FLG* mutations to be a noninvasive test to predict AD course in the clinical field.

Ⅴ. Conclusion

We performed *FLG* mutational analysis of 66 patients with atopic dermatitis. Eleven *FLG* mutations were screened. Four kinds of screened *FLG* null mutations (3321delA, S2889X, S3296X, and K4022X) were identified in total eleven patients. Mutations 3321delA and K4022X were two of the most common mutations in this AD cohort. S2889X, S3296X, and K4022X were newly identified in Korean AD populations from this study. Prevalence of *FLG* mutations in Korean AD population was 16.7%. We investigate the association of *FLG* mutations and clinical markers of AD. *FLG* mutations were significantly associated with allergic type of AD, palmar hyperlinearity, and a family history of allergic disease.

This study expanded the landscape FLG mutations in Korean AD population and showed the association of FLG mutations and clinical markers of AD.

References

1. Bieber T. Atopic dermatitis. N Engl J Med 2008;358:1483-94.
2. Williams H, Flohr C. How epidemiology has challenged 3 prevailing concepts about atopic dermatitis. J Allergy Clin Immunol 2006;118:209-13.
3. Kubo A, Nagao K, Amagai M. Epidermal barrier dysfunction and cutaneous sensitization in atopic diseases. J Clin Invest 2012;122:440-7.
4. Sandilands A, Sutherland C, Irvine AD, McLean WH. Filaggrin in the frontline: role in skin barrier function and disease. J Cell Sci 2009;122:1285-94.
5. Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. N Engl J Med 2011;365:1315-27.
6. Dale BA. Purification and characterization of a basic protein from the stratum corneum of mammalian epidermis. Biochim Biophys Acta 1977;491:193-204.
7. Steinert PM, Cantieri JS, Teller DC, Lonsdale-Eccles JD, Dale BA. Characterization of a class of cationic proteins that specifically interact with intermediate filaments. Proc Natl Acad Sci U S A 1981;78:4097-101.
8. Thyssen JP, Godoy-Gijon E, Elias PM. Ichthyosis vulgaris: the filaggrin mutation disease. Br J Dermatol 2013;168:1155-66.
9. Akiyama M. FLG mutations in ichthyosis vulgaris and atopic eczema: spectrum of mutations and population genetics. Br J Dermatol 2010;162:472-7.
10. Nomura T, Akiyama M, Sandilands A, Nemoto-Hasebe I, Sakai K, Nagasaki A, et al. Prevalent and rare mutations in the gene encoding filaggrin in Japanese patients with ichthyosis vulgaris and atopic dermatitis. J Invest Dermatol 2009;129:1302-5.
11. Li M, Liu Q, Liu J, Cheng R, Zhang H, Xue H, et al. Mutations analysis in filaggrin gene in northern China patients with atopic dermatitis. J Eur Acad Dermatol Venereol 2013;27:169-74.
12. Kim EJ, Jeong MS, Li K, Park MK, Lee MK, Yoon Y, et al. Genetic Polymorphism of FLG in Korean Ichthyosis Vulgaris Patients. Ann Dermatol 2011;23:170-6.
13. Ohguchi Y, Nomura T, Suzuki S, Mizuno O, Nomura Y, Nemoto-Hasebe I, et al. A new filaggrin gene mutation in a Korean patient with ichthyosis vulgaris. Eur J Dermatol 2014;24:491-3.
14. Yu HS, Kang MJ, Jung YH, Kim HY, Seo JH, Kim YJ, et al. Mutations in the Filaggrin are Predisposing Factor in Korean Children With Atopic Dermatitis. Allergy Asthma Immunol Res 2013;5:211-5.
15. Hannifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol 1980;92:44-7.

16. Nomura T, Sandilands A, Akiyama M, Liao H, Evans AT, Sakai K, et al. Unique mutations in the filaggrin gene in Japanese patients with ichthyosis vulgaris and atopic dermatitis. J Allergy Clin Immunol 2007;119:434-40.
17. Sandilands A, Terron-Kwiatkowski A, Hull PR, O'Regan GM, Clayton TH, Watson RM, et al. Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. Nat Genet 2007;39:650-4.
18. Nomura T, Akiyama M, Sandilands A, Nemoto-Hasebe I, Sakai K, Nagasaki A, et al. Specific filaggrin mutations cause ichthyosis vulgaris and are significantly associated with atopic dermatitis in Japan. J Invest Dermatol 2008;128:1436-41.
19. Smith FJ, Irvine AD, Terron-Kwiatkowski A, Sandilands A, Campbell LE, Zhao Y, et al. Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. Nat Genet 2006;38:337-42.
20. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet 2006;38:441-6.
21. Chen H, Common JE, Haines RL, Balakrishnan A, Brown SJ, Goh CS, et al. Wide spectrum of filaggrin-null mutations in atopic dermatitis highlights differences between Singaporean Chinese and European populations. Br J Dermatol 2011;165:106-14.
22. Zhang H, Guo Y, Wang W, Shi M, Chen X, Yao Z. Mutations in the filaggrin gene in Han Chinese patients with atopic dermatitis. Allergy 2011;66:420-7.
23. Osawa R, Konno S, Akiyama M, Nemoto-Hasebe I, Nomura T, Nomura Y, et al. Japanese-specific filaggrin gene mutations in Japanese patients suffering from atopic eczema and asthma. J Invest Dermatol 2010;130:2834-6.
24. Hsu CK, Akiyama M, Nemoto-Hasebe I, Nomura T, Sandilands A, Chao SC, et al. Analysis of Taiwanese ichthyosis vulgaris families further demonstrates differences in FLG mutations between European and Asian populations. Br J Dermatol 2009;161:448-51.
25. Novak N, Baurecht H, Schafer T, Rodriguez E, Wagenpfeil S, Klopp N, et al. Loss-of-function mutations in the filaggrin gene and allergic contact sensitization to nickel. J Invest Dermatol 2008;128:1430-5.
26. Weidinger S, Rodriguez E, Stahl C, Wagenpfeil S, Klopp N, Illig T, et al. Filaggrin mutations strongly predispose to early-onset and extrinsic atopic dermatitis. J Invest Dermatol 2007;127:724-6.
27. Margolis DJ, Apter AJ, Gupta J, Hoffstad O, Papadopoulos M, Campbell LE, et al. The persistence of atopic dermatitis and filaggrin (FLG) mutations in a US longitudinal cohort. J Allergy Clin Immunol

2012;130:912-7.
28. Rupnik H, Rijavec M, Korosec P. Filaggrin loss-of-function mutations are not associated with atopic dermatitis that develops in late childhood or adulthood. Br J Dermatol 2015;172:455-61.
29. Meng L, Wang L, Tang H, Tang X, Jiang X, Zhao J, et al. Filaggrin gene mutation c.3321delA is associated with various clinical features of atopic dermatitis in the Chinese Han population. PLoS One 2014;9:e98235.
30. Fallon PG, Sasaki T, Sandilands A, Campbell LE, Saunders SP, Mangan NE, et al. A homozygous frameshift mutation in the mouse Flg gene facilitates enhanced percutaneous allergen priming. Nat Genet 2009;41:602-8.
31. Elias PM, Schmuth M. Abnormal skin barrier in the etiopathogenesis of atopic dermatitis. Curr Opin Allergy Clin Immunol 2009;9:437-46.

ABSTRACT(IN KOREAN)

한국인 아토피 피부염 환자에서 필라그린 유전자 변이의 확인

<지도교수 김수찬>

연세대학교 대학원 의학과

온혜랑

아토피 피부염은 만성, 재발성 염증성 피부 질환으로 필라그린 유전자의 변이가 이러한 아토피 피부염의 주된 선행 인자로 생각된다. 호발하는 필라그린 변이의 종류와 빈도는 아시아와 유럽에서 각각 다르게 나타난다. 아시아에서도, 중국과 일본에서 각각 호발하는 변이가 다르게 나타난다. 아직까지 한국에서의 호발하는 필라그린 변이에 대해서는 많은 연구가 이루어 지지 않아 본 연구에서는 한국인에서 호발하는 필라그린 변이를 확인하고, 이러한 변이와 더불어 한국인 아토피 피부염 환자들의 임상 양상을 비교하고, 아시아의 다른 국가들과 변이 여부를 비교해보고자 하였다.

강남 세브란스 병원 피부과 외래에 내원하여 아토피 피부염으로 진단 받은 총 66명의 환자를 대상으로 하였고, 그 동안 한국인과 일본 및 중국에서 보고된 필라그린 변이를 확인하였다.

환자들의 평균 나이는 19.5살이었으며 71.2%가 남성이었다. 총 11명의 환자에서 4종류의 필라그린 변이(3321delA, S2889X, S3296X, K4022X)가 확인되었다. 한 명의 환자는 2종류의 필라그린 변이(S2889X

and S3296X)를 보였다. 필라그린 변이의 유무와 알레르기성 아토피 피부염, 손바닥의 많은 잔주름, 알레르기 질환의 가족력 간에 유의한 상관관계가 있었다. 그러나, 아토피 피부염의 발병 연령과 중증도는 필라그린 변이와의 유의한 상관관계가 없는 것으로 나타났다.

또한 본 연구에서 보고된 4종류의 변이 중에서 K4022X, S2889X, S3296X는 한국인에서는 처음으로 보고되었다. 본 연구를 통해 한국인에서 새로운 필라그린 변이를 확인하고 아토피 피부염의 특징적인 임상 양상과 필라그린 변이의 연관성을 확인하였다.

핵심되는 말 : 필라그린, 아토피 피부염, 한국인