

Increased compound heterozygous filaggrin mutations in severe atopic dermatitis in the United States

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Clinical Implications

- *Filaggrin* mutations are common in a US group of white patients with severe atopic dermatitis (48.5%).
- *Filaggrin* mutation analysis in patients with severe atopic dermatitis may be useful for the clinician because it provides a genetic basis to the severity of the disease process and predicts the atopic march as a loss of function mutations confer genetic risks to the development of peanut allergy, allergic rhinitis, and asthma in the presence of eczema.
- New therapies are being developed to augment filaggrin expression in atopic dermatitis skin and patients with *filaggrin* mutations may benefit the most from this information.

TO THE EDITOR:

Atopic dermatitis (AD) is a chronic inflammatory skin disorder with high prevalence rates worldwide, which affect 10% to 20% of children in the United States.¹ Mutations in the gene-encoding filaggrin protein (FLG), a filament-aggregating protein in the stratum corneum, have been highly replicated to be associated with AD.¹ In previous reports, it was found that fewer than a third of patients with AD carry a FLG-null mutation, whereas a mutation is found in 45.7% to 56.6% of patients with moderate-severe AD.² The majority of these studies were performed in Europe, with few studies that looked at the rates of FLG mutations in the United States. AD associated with FLG-null mutations characteristically is associated with early onset, severe persistent disease and has associated increased total IgE levels and allergic sensitization.³⁻⁵ Patients who are homozygous for the FLG mutation have significantly higher skin severity scores than those that carry 1 mutation or those with wild-type FLG.⁴ Mutations in FLG results in premature FLG protein truncation, and patients with homozygous-null mutations have a complete lack of filaggrin protein in the skin.⁶

The current study, therefore, was undertaken to determine how common FLG mutations are in patients with severe AD who were referred to a national eczema center in the United States, whether screening for 5 FLG mutations would result in the identification of a higher frequency of FLG mutations in severe AD, and whether patients with double FLG mutations (homozygous and compound heterozygotes) would have increased serum IgE compared with patients with heterozygous and wild-type mutations in the United States.

Patients from throughout the United States with severe AD, as judged by the criteria of Rajka and Langeland (range, 3-9 [>8 is severe]) and for whom outpatient therapy failed, referred to

TABLE I. Demographics and clinical features

Sex, no. (%)	
Male	60 (59.4)
Female	41 (40.5)
Median (range) age, y	8 (1-91)
Median (range) latitude, °N	39 (27-61)
Rajka Langeland Score, mean (range) *severe >8	8.9 (8-9)
Mean allele frequency, %	
R501X	13.3
2282del4	15.3
R2447X	3.5
S3247X	1.5
3702delG	0.0
Genotypes, no. (%)	
Wild type	52 (51.4)
Heterozygous	30 (29.7)
R501X/WT	12 (11.8)
2282del4/WT	12 (11.8)
R2447X/WT*	4 (3.9)
S3247X/WT*	2 (1.9)
3702delG/WT	0.0 (0.0)
Compound heterozygous/homozygous	19 (18.8)
R501X/R501X	2 (1.9)
2282del4/2282del4	3 (2.9)
R501X/2282del4	10 (9.9)
2282del4/R2447X*	3 (2.9)
R501X/S3247X*	1 (0.9)
Log10 serum IgE (KU/L), mean (25th-75th)	
Overall group	3.661 (2.846-4.075)
Homozygous/compound heterozygous	4.018 (3.635-4.139)
Heterozygous	3.736 (3.176-3.987)
Wild type	3.435 (2.438-4.021)

*Genotype was identified by screening for additional mutations.

National Jewish Health in Denver and genotyped for 5 FLG gene mutations (R501X, 2282del4, R2447X, S3247X, and 3702delG), were included in this study.⁷ Serum IgE levels were obtained from these patients. Nonwhite races were excluded. Clinical information was obtained from the electronic medical record. We compared log IgE among the 3 genotype groups by using an approximate *k*-sample permutation method.⁸ The study was approved by the National Jewish Health Institutional Review Board.

A total of 101 patients with severe AD (mean Rajka Langeland score, 8.9) were enrolled in the study, of whom 59% were male patients. Geometric mean age was 9.7 years (interquartile range, 4.0-24.5). Patients from 28 different states were represented, with 32% of the patients from Colorado. Baseline demographics and clinical characteristics are shown in Table I.

Forty-nine of 101 patients (48.5%) were found to have FLG mutations, of which there were 5 homozygous (5.0%) (2 R501X/R501X and 3 2282del4/2282del4), 14 compound heterozygous (13.8%) (10 R501X/2282del4, 3 2282del4/R2447X, and 1 R501X/S3247X), and 30 heterozygous mutations (29.7%)

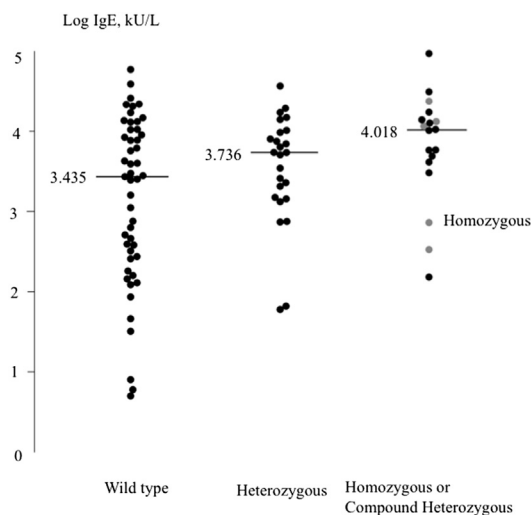


FIGURE 1. IgE levels in homozygous or compound heterozygous FLG mutation were higher than IgE levels in wild type ($P = .02$) but similar to IgE levels in heterozygous FLG mutation ($P = .22$). IgE levels in heterozygous FLG mutation were similar to IgE levels in the wild type ($P = .11$).

(12 R501X, 12 2282del4, 4 R2447X, 2 S2347X). Four of 14 compound heterozygous (28.5%), and 7 of 30 heterozygous mutations (23.3%) were identified by screening the 3 additional mutations (R2447X, S3247X, 3702delG). Serum IgE levels were higher in patients with homozygous FLG-null mutations when compared with heterozygous FLG mutations and wild-type FLG ($P = .03$) (Figure 1) in a stepwise manner.

This study demonstrated that FLG mutations are common in a US group of white patients with severe AD. Even more so, there was a high frequency of compound heterozygous and homozygous mutations in patients with severe AD (18.8%). Screening for 5 mutations identified heterozygous and compound heterozygous mutations that would otherwise have been missed by testing for only R501X and 2282del4 as previous studies have done.⁹ Those with homozygous or compound heterozygous mutations had significantly higher IgE levels than the wild-type genotype. Yet, more than half of the patients with severe AD in this group had wild-type genotypes, which indicated that additional genetic and/or environmental factors must play a role in severe AD.

Our study has several limitations. Our small sample size may make generalizations to all US children limited; however, our population represented 28 different states from various northern latitudes, with only 32% of the patients from Colorado. Second, the lack of racial diversity limits the findings to US whites, and patients with AD of different races have different FLG mutations that were not screened. Third, our study was retrospective, and our data relied on information in the electronic medical record. Not all patients with severe AD who were referred to our day program were genotyped, which may have led to a selection bias.

Future research aimed at answering whether early intervention in patients with FLG-deficient AD would diminish rates of allergy later in life or whether a proactive approach to skin barrier management in at-risk individuals would halt the atopic march will be of great interest. A number of FLG mutations in our

study were only identified because of sequencing additional mutations as opposed to the major 2 (R501X/2282del4), and, because therapeutics and prognosis may hinge on FLG status, it is important to know the true prevalence in our population and not mislabel heterozygotes as wild type or mislabeled homozygotes and/or compound heterozygotes as heterozygotes. FLG mutation analysis in patients with severe AD may be useful for the clinician because it provides a genetic basis to explain the disease process to patients, has familial genetic counseling implications, and predicts the atopic march because it confers genetic risks to the development of peanut allergy, allergic rhinitis, and asthma in the presence of eczema.¹ Patients with FLG mutations will benefit therapeutically from knowing their filaggrin status because recent advances in barrier restoration with filaggrin-replacing products may provide a more permanent solution than what is currently offered. More than half of the patients with severe AD studied were wild type for the mutations analyzed. Whether they have unidentified FLG mutations or mutations in other epidermal proteins remains to be seen.

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