Published in final edited form as:
J Allergy Clin Immunol. 2013 November ; 132(5): 1232–1234. doi:10.1016/j.jaci.2013.07.005.

Racial comparison of filaggrin null mutations in asthmatics in a U.S. population

Jackie P-D. Garrett, MD[1], **Ole Hoffstad, MA**[2], **Andrea J. Apter, MD, MSc, MA**[3], and **David J. Margolis, MD, PhD**[2,4]

[1]Division of Allergy and Immunology, Children's Hospital of Philadelphia Perelman School of Medicine at University of Pennsylvania

[2]Department of Epidemiology and Biostatistics, Perelman School of Medicine at University of Pennsylvania

[3]Hospital of the University of Pennsylvania, Section of Allergy and Immunology; Pulmonary, Allergy and Critical Care Division, Perelman School of Medicine at University of Pennsylvania

[4]Department of Dermatology, Hospital of University of Pennsylvania, Perelman School of Medicine at University of Pennsylvania

Capsule Summary

We examined the association of filaggrin loss-of-function mutations in U.S. atopic patients with asthma. We confirm that only Whites with the R501X mutation and AD have increased risk of asthma.

Keywords

Filaggrin; children; atopic dermatitis; asthma; mutation; race

To the editor:

Filaggrin (filament-aggregating protein), is encoded by the filaggrin (FLG) gene located within the epidermal differentiation complex along with 30 other genes on chromosome 1q21. Filaggrin is synthesized as a large precursor, profilaggrin, and is expressed in the upper layers of the epidermis. The discovery of the loss-of-function mutations in the gene *FLG* has improved our understanding of the pathophysiology of atopic dermatitis (AD) and associated atopic diseases[1, 2]. The presence of a filaggrin loss-of-function (*FLG* null) mutation has been estimated to increase the odds of having AD by more than 3-fold[3]. Furthermore, the presence of the *FLG* null mutations and AD, confers an increased risk for the development of asthma[4]. In a Scottish population, the R501X mutation of *FLG* was associated with asthma disease severity even in the absence of a history of eczema[5]. Prevalent *FLG* null mutations vary by the race/ethnicity of the population and by the country

Corresponding Author: Jackie P-D. Garrett, MD, 3550 Market Street, The Division of Allergy and Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA 19104, Telephone: 215-590-2549, Fax: 215-590-4529, garrettjp@email.chop.edu.

Conflicts of Interest: None

studied[1, 2, 6]. There are no studies of the racially diverse U.S. population examining the association of *FLG* null mutations and the diagnosis of asthma or symptoms of asthma among those with AD.

In a cross-sectional evaluation of children with AD and asthma, we evaluated the most common European *FLG* null mutations: R501X, 2282del4, R2447X, and S3247X. We studied the association of these mutations and the diagnosis of asthma or the frequency of wheezing in White and African-American children with AD. All of the children enrolled in our study were participants in the Pediatric Eczema Elective Registry (PEER; www.thepeerprogram.com)[7] PEER is an ongoing, prospective, 10-year observational registry that is part of a long-term post-marketing safety commitment by Valeant Pharmaceuticals International (formally the responsibility of Novartis) to the US Food and Drug Administration and the European Drug Agency. All children enrolled in this nationwide registry have physician-confirmed diagnosis of AD. At two points in time, PEER captured information on other atopic diagnoses, including asthma. The survey instruments used in PEER have been reported elsewhere[7].

The *FLG* null mutations were genotyped using custom-made TaqMan allelic discrimination assays (Applied Biosystems, Foster City, Calif) according to previously published protocols[7]. Ancestral race was inferred for all study subjects by using a panel of ancestral informative markers (AIMs) as previously described and revealed minimal differences between inferred race and self-reported race.[8,9]

To investigate the association between *FLG* null mutations and the diagnosis of asthma, we used a logistic regression model. To examine the association between the *FLG* null mutations and the frequency of wheezing, we used a proportional odds type of ordered logistic regression model. This is also called a proportional odds model. Wheezing was categorized as: no episodes, 1 to 3 episodes, 4 to12 episodes and greater than 12 episodes in the previous year. All effect estimates were presented with 95% CIs. All analyses were conducted with STATA 12.1 (StataCorp, College Station, Tex).

DNA was available from 857 PEER participants. The demographic and descriptive information have been previously published[9]. Briefly, 52.1% of the full cohort was female and 43.6% were self-described as African-American. The average age of enrollment was 7.2 years and the average age of disease onset was 2.1 years (sd 2.7, median <1 year). Table I contains a report of demographic information for those diagnosed with asthma. Table II displays the associations between the *FLG* null mutations, a diagnosis of asthma and the frequency of wheezing. Only the R501X mutation was associated with an increased likelihood of asthma as well as increased likelihood of more frequent wheezing. Few African-Americans had prevalent mutations. However, the magnitude of these effect estimates was generally similar to those in Whites.

The presence of a R501X *FLG* null mutation was associated with a diagnosis of asthma in our cohort of children with atopic dermatitis (OR 1.77; 95% CI 1.09–2.90; p = 0.021). This association has been previously described, but only in European populations. Unlike previous studies, we did not find an association with the combined genotype but we did find

an association with increased asthma related symptoms (i.e. wheezing). This has not been previously described in a US population. Like our study, a study by Palmer et al. found a greater association between R501X and increasing severity of asthma[5]. Like previous studies, the mutations were only statistically significant in the White population (See table II). However, we show that while the R501X mutation is rarely seen in African-Americans, those few with this mutation have a not a significant but elevated risk of asthma. Our findings validate previous studies that have described associations of R501X null mutations with asthma. Our findings add to previous findings by demonstrating that all those with the R501X mutations are more likely to frequently wheeze. Lastly, our findings expand upon the previous literature by comparing mutations interracially thus allowing for the description of significant mutations in the genetically diverse U.S. population, whereas previous studies have focused European populations.

Sincerely,

Jackie P-D. Garrett, MD; Children's Hospital of Philadelphia; Perelman School of Medicine at University of Pennsylvania; Philadelphia, PA

Ole Hoffstad, MA; Department of Epidemiology and Biostatistics, Perelman School of Medicine at University of Pennsylvania; Philadelphia, PA

Andrea J. Apter, MD, MSc, MA Hospital of the University of Pennsylvania, Section of Allergy and Immunology; Pulmonary, Allergy and Critical Care Division, Perelman School of Medicine at University of Pennsylvania; Philadelphia, PA

David J. Margolis, MD, Ph.D, Department of Dermatology, Hospital of University of Pennsylvania, Perelman School of Medicine at University of Pennsylvania; Department of Epidemiology and Biostatistics, Perelman School of Medicine at University of Pennsylvania; Philadelphia, PA

Acknowledgments

Dr. Margolis: NIH research grant: R01AR056755

Valeant Pharmaceuticals: Grant funding for PEER

Dr. Garrett: NIH Research Grant Supplement: 5R01AR056755-04

AAAAI Fellowship of Excellence training grant

Dr. Apter: NIH research grant: R01AR056755 (I think I am supported too)

Abbreviations

FLG	filaggrin
PEER	Pediatric eczema elective registry
AIM	ancestral informative marker

REFERENCES

1. Rodriguez E, Baurecht H, Herberich E, Wagenpfeil S, Brown SJ, Cordell HJ, et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease. J Allergy Clin Immunol. 2009; 123:1361 e7–1370 e7. [PubMed: 19501237]
2. Henderson J, Northstone K, Lee SP, Liao H, Zhao Y, Pembrey M, et al. The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study. J Allergy Clin Immunol. 2008; 121:872 e9–877 e9. [PubMed: 18325573]
3. Brown SJ, McLean WH. One remarkable molecule: filaggrin. J Invest Dermatol. 2012; 132:751–762. [PubMed: 22158554]
4. McLean WH, Palmer CN, Henderson J, Kabesch M, Weidinger S, Irvine AD. Filaggrin variants confer susceptibility to asthma. J Allergy Clin Immunol. 2008; 121:1294–1295. author reply 5–6. [PubMed: 18395783]
5. Palmer CN, Ismail T, Lee SP, Terron-Kwiatkowski A, Zhao Y, Liao H, et al. Filaggrin null mutations are associated with increased asthma severity in children and young adults. J Allergy Clin Immunol. 2007; 120:64–68. [PubMed: 17531295]
6. van den Oord RA, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. BMJ. 2009; 339:b2433. [PubMed: 19589816]
7. Kapoor R, Menon C, Hoffstad O, Bilker W, Leclerc P, Margolis DJ. The prevalence of atopic triad in children with physician-confirmed atopic dermatitis. J Am Acad Dermatol. 2008; 58:68–73. [PubMed: 17692428]
8. Stefflova K, Dulik MC, Barnholtz-Sloan JS, Pai AA, Walker AH, Rebbeck TR. Dissecting the within-Africa ancestry of populations of African descent in the Americas. PLoS One. 2011; 6:e14495. [PubMed: 21253579]
9. 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; 130:912–917. [PubMed: 22951058]

TABLE I

Basic demographic information of the study population

Variable	Full cohort	Any FLG null	R501X	2282del4	R2447X	S3247X
N (%)	447	106 (23.7)	44 (10.2)	30 (7.0)	11(2.5)	21 (4.7)
Female (%)	225 (50.3)	49 (21.8)	19 (8.4)	14 (6.2)	5 (2.2)	11(4.9)
Male (%)	217 (48.5)	57 (26.3)	25 (11.5)	16 (7.4)	6 (2.8)	10 (4.6)
White (%)	224 (50.1)	84 (37.5)	38 (17.0)	27 (12.1)	13 (5.8)	6 (2.7)
African-American (%)	201 (45.0)	21 (10.4)	8 (4.0)	2 (1.0)	6 (3.0)	5 (2.5)

TABLE II

Odds ratios (OR) and 95% CI for the association between *FLG* null mutations and the diagnosis of asthma and Proportional odds ratios (POR) and 95% CI for the association between *FLG* null mutations and the frequency of wheezing

Gene name	Unadjusted	Unadjusted White	Unadjusted Black	Adjusted for gender for entire population	Adjusted for gender among Whites	Adjusted for gender among African-Americans
Diagnosis of asthma						
R501X	OR 1.77 [1.09–2.90] *p =0.021	OR 1.81 [1.06–3.08] *p =0.029	OR 1.25 [0.47– 3.37] p = 0.654	OR 1.76 [1.08–2.88] *p =0.024	OR 1.79 [1.05–3.06] *p = 0.032	OR 1.25 [0.46–3.39] p = 0.659
2282del4	OR 1.04 [0.64–1.70] p =0.882	OR 0.99 [0.59–1.67] p =0.971	OR 1.30 [0.22–7.90] p=0.772	OR 1.04 [0.63–1.70] p =0.878	OR 0.99 [0.59–1.68] p =0.980	OR 1.24 [0.20–7.56] p=0.816
R2447X	OR 1.67 [0.61–4.57] p =0.314	OR 0.91 [0.29– 2.87] p =0.875	OR 1	OR 1.62 [0.59–4.42] p =0.351	OR 0.85 [0.27–2.68] p =0.776	OR – (not estimable)
S3247X	OR 1.12 [0.58–2.15] p =0.738	OR 1.23 [0.57–2.66] p =0.601	OR 2.14 [0.81–5.62] p=0.124	OR 1.13 [0.59–2.18] p =0.713	OR 0.1.25 [0.58–2.70] p =0.576	OR 2.13 [0.81–5.61] p=0.128
Frequency of wheezing						
R501X (Filaggrin)	POR 1.83 [1.18–2.85] *p =0.007	POR 1.92 [1.18–3.13] *p = 0.009	POR 1.36 [0.54–3.45] p = 0.513	POR 1.78 [1.15–2.76] *p = 0.010	POR 1.84 [1.12–3.00] *p = 0.015	POR 1.36 [0.54–3.43] p = 0.515
2282del4	POR 1.09 [0.68–1.76] p = 0.716	POR 1.09 [0.66–1.81] p = 0.739	POR 0.97 [0.19–4.72] p = 0.970	POR 1.08 [0.67–1.74] p = 0.763	POR 1.06 [−0.32 –0.71] p = 0.812	POR 0.91 [0.64–1.77] p = 0.905
R2447X	POR 1.36 [0.57–3.27] p = 0.485	POR 1.37 [0.66–2.84] p = 0.393	POR 4.61 [0.85–22.5] p = 0.059	POR 1.30 [0.54–3.11] p = 0.563	POR 0.73 [0.25 –2.13] p = 0.566	POR 4.92 [1.00–24.23] p = 0.050
S3247X	POR 1.36 [0.72–2.55] p = 0.347	POR 0.79 [0.27–2.30] p = 0.671	POR 2.17 [0.95–4.96] p = 0.067	POR 1.34 [0.71–2.52] p = 0.363	POR 1.35 [0.65–2.80] p = 0.422	POR 2.12 [0.92–4.84] p = 0.074

*denotes p value < 0.05