HHS Public Access

Author manuscript

JAMA Dermatol. Author manuscript; available in PMC 2015 November 25.

Published in final edited form as:

JAMA Dermatol. 2015 May ; 151(5): 557–559. doi:10.1001/jamadermatol.2014.4916.

Low filaggrin monomer repeats in African-American pediatric patients with moderate to severe atopic dermatitis

Ashley M. Quiggle, B.A., **Zane A. Goodwin, B.S.**, **Twinkal R. Marfatia, Ph.D.**, **Monique G. Kumar, M.D.**, **Heather Ciliberto, M.D.**, **Susan J. Bayliss, M.D.**, and **Cristina de Guzman Strong, Ph.D.**

Center for Pharmacogenomics, Center for the Study of Itch, Division of Dermatology, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri

The severity of atopic dermatitis (AD) and intragenic filaggrin (*FLG;* OMIM 135940) copy number variant (CNV) genotypes were assessed in African American pediatric patients, a health disparities group that is disproportionately affected with AD.[1]

METHODS

The study was approved by Washington University School of Medicine's institutional review board. Eligibility criteria for recruited pediatric patients were (1) age 3 months – 18 years, (2) United Kingdom Working Party's Diagnostic Criteria for Atopic Dermatitis,[2] (3) African American ethnicity (self-reported), (4) moderate to severe AD (SCORAD index, >25),[3] and (5) written informated assent or consent. Common European *FLG* R501X and 2282del4 mutations and intragenic *FLG* CNV (3 alleles of either 10, 11, or 12 *FLG* monomer repeats), upon high-quality DNA assessment, were genotyped[4] and correlated with AD severity.

Corresponding author: Cristina de Guzman Strong, Ph.D., Center for Pharmacogenomics, Center for the Study of Itch, Division of Dermatology, Department of Internal Medicine, Washington University School of Medicine, Campus Box 8123, St. Louis, MO 63110 (cstrong@dom.wustl.edu).

Author Contributions: Drs Bayliss and de Guzman Strong had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Marfatia, de Guzman Strong.
Acquisition, analysis, and interpretation of data: All authors.
Drafting of the manuscript: Quiggle, Bayliss, de Guzman Strong.
Critical revision of the manuscript for important intellectual content: Quiggle, Goodwin, Marfatia, Kumar, Ciliberto, Bayliss, de Guzman Strong.
Statistical analysis: Goodwin, de Guzman Strong.
Obtained funding: de Guzman Strong.
Administrative, technical, or material support: All authors.
Study supervision: Bayliss, de Guzman Strong.

Role of the Sponsor: The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of data, preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication.

Conflict of Interest Disclosures: None reported.

Additional Contributions: Emily Beck, M.D., Emily Gurnee, M.D, Kara J. Gulewicz, M.D., and Colleen Cotton, M.D. assisted with patient recruitment and were not compensated.

Previous Presentations: Presented in part at the 73rd Annual Meeting of the Society of Investigative Dermatology; May 8–9, 2014; Albuquerque, NM.

RESULTS

Thirty-nine pediatric African American AD patients were recruited with a mean (range) age of 6.7 (0.4–15) years (Table 1). Thirty-five patients reported a first-degree family member with atopy and 30 patients reported AD onset before age 2 years. Of the 31 patients who were 4 years or older at the time of visit, a history of asthma and allergic rhinitis and/or hay fever were reported in 24 (77%) and 16 (52%), respectively. Food allergies were reported as well (51% [n=20]), most commonly peanut (n=10) and fish and/or shellfish (n=10) that were not coincident. All but 1 were either being treated with or had been prescribed topical triamcinolone ointment, 0.1%.

The mean (range) SCORAD of the participants was 58.5 (28.0–94.1) (Table 1) with severe pruritus (mean, 7.8) and moderate sleep loss (mean 5.7, both scales 0–10). Twenty-four patients (62%) exhibited severe AD. The mean lesional body extent was 44% and mean lesional intensity was 10 (scale, 0–15; 15 = worst). Lichenification and dryness (both means, 2.2; scale 0–3, 3=worst) contributed the most to the lesional intensity (Figure, A).

We sought to explain the associated severe nonlesional skin dryness in our participants by genotyping a previously described European dose-dependent risk factor for AD, intragenic *FLG* repeats, or CNV.[4] Excluding 2 *FLG* R501X heterozygous patients (no *FLG* 2282del4 mutations identified), 16 cases (43%) were homozygous for the *FLG* CNV 10 allele, thus totaling 20 filaggrin monomers (Table 2). Of the total 74 *FLG* alleles in our cases (n = 37), the *FLG* CNV 10 allele made up 64% (Table 1). Patients with a total of either 20 or 21 *FLG* CNV exhibited higher SCORAD (mean, 63.7) and hence severe AD compared with those participants with 22, 23, and 24 *FLG* CNV (mean SCORAD, 48.5) (P=0.015) (Figure, B). Moreover, we found that individuals with 20 total filaggrin monomers are 1.9 times more likely to have severe AD (Table 2). However, this was not statistically significant (P=0.33).

DISCUSSION

Despite epidemiological data supporting a marked increase in AD in African American children,[1] to our knowledge, a quantitative measure of AD severity and an investigation of *FLG* CNV in this health disparities group have not been reported until now. We identify a significant difference between low *FLG* CNV (20 or 21) with severe AD versus *FLG* CNV (22, 23, or 24) with moderate AD (P=.01). Each *FLG* repeat encodes 1 posttranslationally modified active filaggrin monomer that is further degraded to metabolites such as urocanic acid that comprises part of the skin's natural moisturizing factor.[4] Addition of each *FLG* monomer decreases the odds ratio of disease risk of AD by 0.88.[4] A reduction of NMF metabolites was also observed in skin in South African patients with AD.[5] Although NMF metabolites were not assessed in this study, the parallels between our study and that of Brown *et al.*[4] with respect to low *FLG* CNV and AD suggest a reduction in filaggrin metabolites contributing to our patients' skin dryness. Observed low if not absent frequencies of *FLG* and/or *FLG-2* stop-gain mutations in African Americans[6–8] and Africans[5] suggest decreased likelihoods for these mutations in AD risk specific to this ancestry. Future case-control studies specific to this health disparities group are warranted to more fully understand the genetics of AD.

Acknowledgments

Funding/Support: This study was supported in parts by Dean's Faculty Diversity Scholar Award (Washington University School of Medicine, Dr de Guzman Strong) and from the National Institutes of Health grants T32 HG000045 (Mr Goodwin) and R00AR055948 (Dr de Guzman Strong). The Dean's Faculty Diversity Funds provided the materials for the study.

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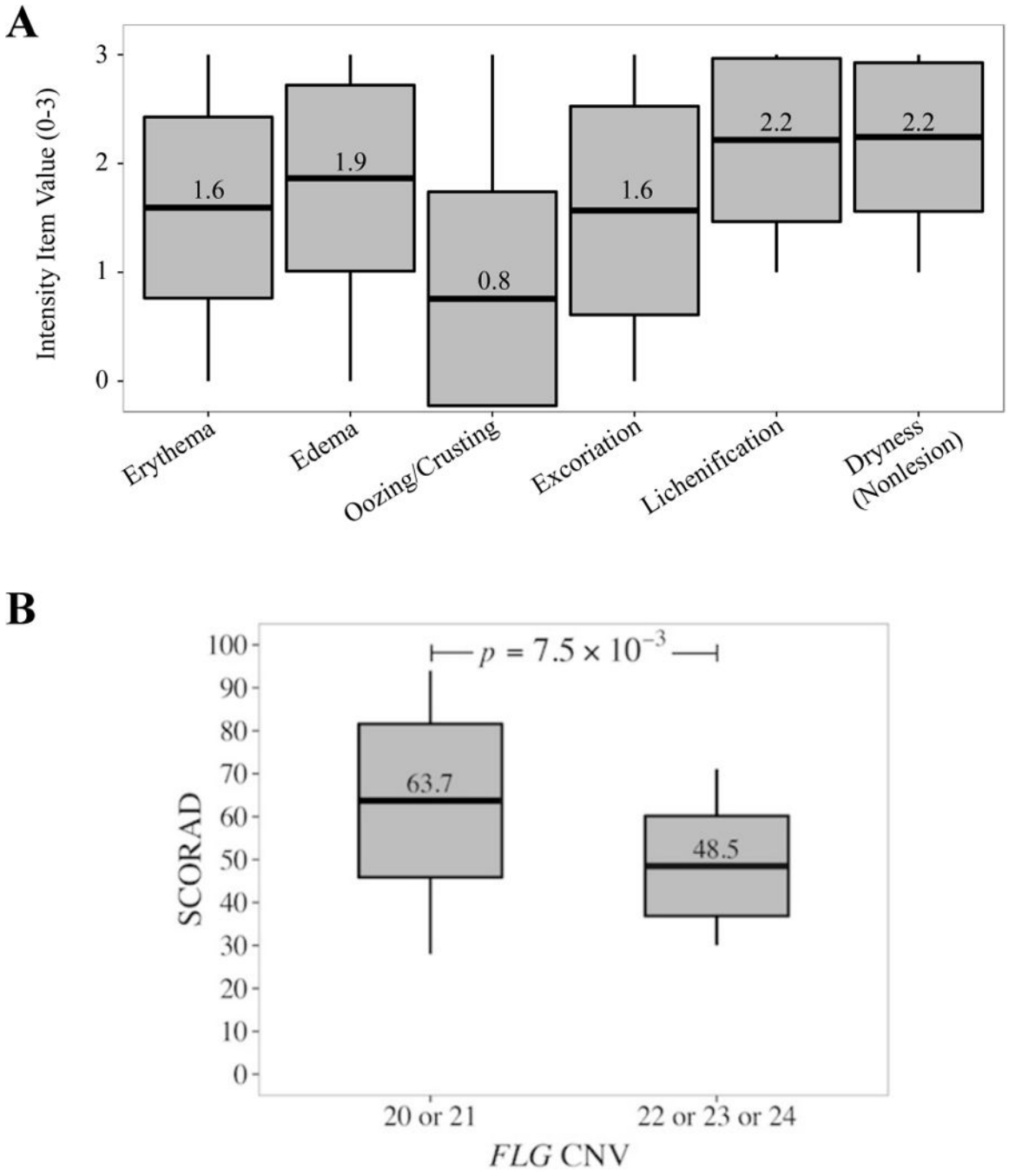

Figure.

A, Intensity item values that contribute to the collective intensity measure of a representative lesion. **B**, Distribution of total *FLG* repeats with respect to SCORAD, The horizontal line in the middle of each box indicates the mean, while the top and bottom borders of the box mark 1 standard deviation above and below the mean. The whiskers above and below the box mark the maximum and minimum values, respectively. Statistics, 2-sided Wilcoxon rank-sum test.

Table 1

Characteristics of 39 African American Pediatric Patients with Atopic Dermatitis (AD)

Variable	*Value*
Sex, No. (%)	
Female	18 (46)
Male	21 (54)
Age, mean (range), y	6.7 (0.4–15)
Atopy in immediate family, No. (%)	35 (90)
Onset age, No. (%), y	
<2	30 (77)
≥2	9 (23)
Asthma at age ≥4 y, No. (%)	24 (77)
Hay Fever at age ≥4 y, No. (%)	16 (52)
Allergy	
Food	20 (51)
Peanut	10 (26)
Fish or Shellfish	10 (26)
Quality of life disruption, mean (range)[a]	7.9 (1–10)
Triamcinolone ointment, 0.1%, treatment, No. (%)	38 (97)
SCORAD Index, mean (range)[b]	58.5 (28.0–94.1)
Moderate AD (SCORAD ≥ 25 – 49), No. (%)	15 (38)
Severe AD (SCORAD ≥ 50), No. (%)	24 (62)
FLG CNV Allele, R501X excluded, No. (%)	
10	47 (64)
11	13 (18)
12	14 (19)

Abbrevation: CNV, copy number variant.

[a] Scale of 0 to 10.

[b] Scale of 0 to 103.

Table 2

Total *FLG* Copy Number Variants (CNVs) and Unadjusted Odds Ratios (ORs)for participants with Severe Atopic Dermatitis (AD) (SCORAD Index >50), R501X excluded

Total *FLG* CNV	Patients, No. (%)	Severe AD (95% CI)	P value
20	16 (43)	1.91 (0.51–7.12)	0.33
21	8 (22)	1.12 (0.24–5.15)	0.88
22	8 (22)	1.12 (0.24–5.15)	0.88
23	3 (8)	0.38 (0.04–3.19)	0.35
24	2 (5)	Unable to estimate	