loss-of-function mutations in *FLG* leading to near-complete absence of profilaggrin in the homozygous or compound heterozygous state. Therefore it can be hypothesized that filaggrin deficiency contributes to the observed photosensitivity and/or reduced threshold to UVB-induced erythema in patients with AD. We have performed a detailed analysis of cutaneous photoresponse in clinically normal skin to avoid the confounding effects of atopic inflammation. Our findings have excluded a large effect of *FLG* genotype on photosensitivity (≥1.8-fold difference in MED) at any of the wavebands tested. In addition, the results of our monochromator phototesting did not indicate a differential erythemal sensitivity within the wavelengths representing UVB, as would be predicted from the known absorption spectrum of UCA.

One limitation of our study is that the healthy volunteers did not include any subjects with ichthyosis vulgaris, and therefore we have not excluded the possibility that *FLG* homozygous (or compound heterozygous) subjects might show greater erythemal sensitivity than wild-type subjects. However, *FLG*-null heterozygosity has a significant effect on filaggrin expression *in vivo*,[9,10] and therefore we would expect an effect to be observed in *FLG* heterozygotes if this was substantial.

The fact that observations of UVB-induced damage in murine and *in vitro* models have not been supported by clinical data suggest that different mechanisms lead to cutaneous erythema *in vivo* than the markers of UV damage studied *in vitro* and in mice. For example, apoptosis is known to occur within areas of skin damaged by UV exposure, and this is associated with cutaneous erythema, but the relationship is nonlinear. Furthermore, the photoprotective effect of the *FLG* wild-type genotype might be attributable to a mechanical filtering of UV radiation by the stratum corneum rather than by chemical photoimmunosuppression.

In conclusion, our *FLG* genotype–stratified analysis of responses to UV and visible radiation in clinically normal skin does not support the hypothesis that the breakdown products of filaggrin play a major role in the sensitivity of human skin to UV-induced erythema. This has relevance to the ongoing search for predictors of patient response in phototherapy for AD and for the development of personalized medicine.

We thank the patients and volunteers who participated in this study and Lynn Fullerton, who provided technical support in the photobiology investigations. We are very grateful to Professors James Ferguson and Peter Farr for their expert advice in the design and conduct of these studies.

*Deborah Forbes*[a]
*Leona Johnston, MSc*[b]
*June Gardner, RGN*[b]
*Stephanie F. MacCallum, MSc*[c]
*Linda E. Campbell, BSc*[c]
*Albena T. Dinkova-Kostova, PhD*[d]
*W. H. Irwin McLean, DSc*[c]
*Sally H. Ibbotson, MD*[b]
*Robert S. Dawe, MD*[b]
*Sara J. Brown, MD*[e]

From [a]Ninewells Hospital and Medical School, Dundee, United Kingdom; [b]the Photobiology Unit, Dermatology Department, and [d]the Division of Cancer Research, Medical Research Institute, Jacqui Wood Cancer Centre, University of Dundee, Ninewells Hospital and Medical School, Dundee, United Kingdom; [c]Dermatology and Genetic Medicine, Division of Molecular Medicine, College of Life Sciences and College of Medicine, Dentistry and Nursing, University of Dundee, Dundee, United Kingdom; and [e]Dermatology and Genetic Medicine, Medical Research Institute, College of Medicine, Dentistry and Nursing, Ninewells Hospital and Medical School, Dundee, United Kingdom. E-mail: s.j.brown@dundee.ac.uk.

D.F. was supported by the Muir Russell studentship. S.J.B. holds a Wellcome Trust Intermediate Fellowship (086398/Z/08/Z) and is supported by the Manknell Charitable Trust and the Tayside Dermatology Research Fund. The Centre for Dermatology and Genetic Medicine, University of Dundee, is funded by a Wellcome Trust Strategic Award (098439/Z/12/Z; to W.H.I.M.).

Disclosure of potential conflict of interest: D. Forbes has received research support in the form of a summer studentship from the Dundee Academic Clinical Track and has received travel support from DCAT Travel Bursary and the Tayside Dermatological Research Charity. W. H. I. McLean has received research support from the Wellcome Trust. S. J. Brown has received research support in the form of Fellowships from the Wellcome Trust and research grants from the Manknell Charitable Trust and the Tayside Dermatologyl Research Fund and has received speaker's honorarium from the American Academy of Allergy, Asthma & Immunology. The rest of the authors declare that they have no relevant conflicts of interest.

## REFERENCES

1. Sandilands A, Sutherland C, Irvine A, McLean W. Filaggrin in the frontline: role in skin barrier function and disease. J Cell Sci 2009;122:1285-94.
2. Barresi C, Stremnitzer C, Mlitz V, Kezic S, Kammeyer A, Ghannadan M, et al. Increased sensitivity of histidinemic mice to UVB radiation suggests a crucial role of endogenous urocanic acid in photoprotection. J Invest Dermatol 2011; 131:188-94.
3. Denecker G, Hoste E, Gilbert B, Hochepied T, Ovaere P, Lippens S, et al. Caspase-14 protects against epidermal UVB photodamage and water loss. Nat Cell Biol 2007;9:666-74.
4. Mildner M, Jin J, Eckhart L, Kezic S, Gruber F, Barresi C, et al. Knockdown of filaggrin impairs diffusion barrier function and increases UV sensitivity in a human skin model. J Invest Dermatol 2010;130:2286-94.
5. Sandilands A, Terron-Kwiatkowski A, Hull P, O'Regan G, Clayton T, Watson R, 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.
6. ten Berge O, van Weelden H, Bruijnzeel-Koomen CA, de Bruin-Weller MS, Sigurdsson V. Throwing a light on photosensitivity in atopic dermatitis: a retrospective study. Am J Clin Dermatol 2009;10:119-23.
7. Tajima T, Ibe M, Matsushita T, Kamide R. A variety of skin responses to ultraviolet irradiation in patients with atopic dermatitis. J Dermatol Sci 1998;17:101-7.
8. Dyer RK, Weinstock MA, Cohen TS, Rizzo AE, Bingham SF, Group VT. Predictors of basal cell carcinoma in high-risk patients in the VATTC (VA Topical Tretinoin Chemoprevention) trial. J Invest Dermatol 2012;132:2544-51.
9. Cole C, Kroboth K, Schurch NJ, Sandilands A, Sherstnev A, O'Regan GM, et al. Filaggrin-stratified transcriptomic analysis of pediatric skin identifies mechanistic pathways in patients with atopic dermatitis. J Allergy Clin Immunol 2014;134: 82-91.
10. Kezic S, O'Regan GM, Yau N, Sandilands A, Chen H, Campbell LE, et al. Levels of filaggrin degradation products are influenced by both filaggrin genotype and atopic dermatitis severity. Allergy 2011;66:934-40.

Available online January 29, 2016.
http://dx.doi.org/10.1016/j.jaci.2015.11.022

## Epidermal thymic stromal lymphopoietin predicts the development of atopic dermatitis during infancy

*To the Editor:*

To establish a primary prevention strategy for atopic dermatitis (AD), it is important to identify biomarkers that can predict the occurrence of AD. This study aimed to evaluate the expression level of epidermal proteins by using a tape stripping method to determine whether these proteins can be used as biomarkers predictive of AD development in infants.

In this prospective birth cohort study, we followed 75 infants in a risk group and 12 in a control group for 2 years (Fig 1). The control group consisted of infants with both parents who had neither allergy nor immediate skin test reactivity to 8 common inhalant allergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, tree pollen mixture I & II, weed pollen mixture, grass pollen mixture, cat, and cockroach). The risk group was defined

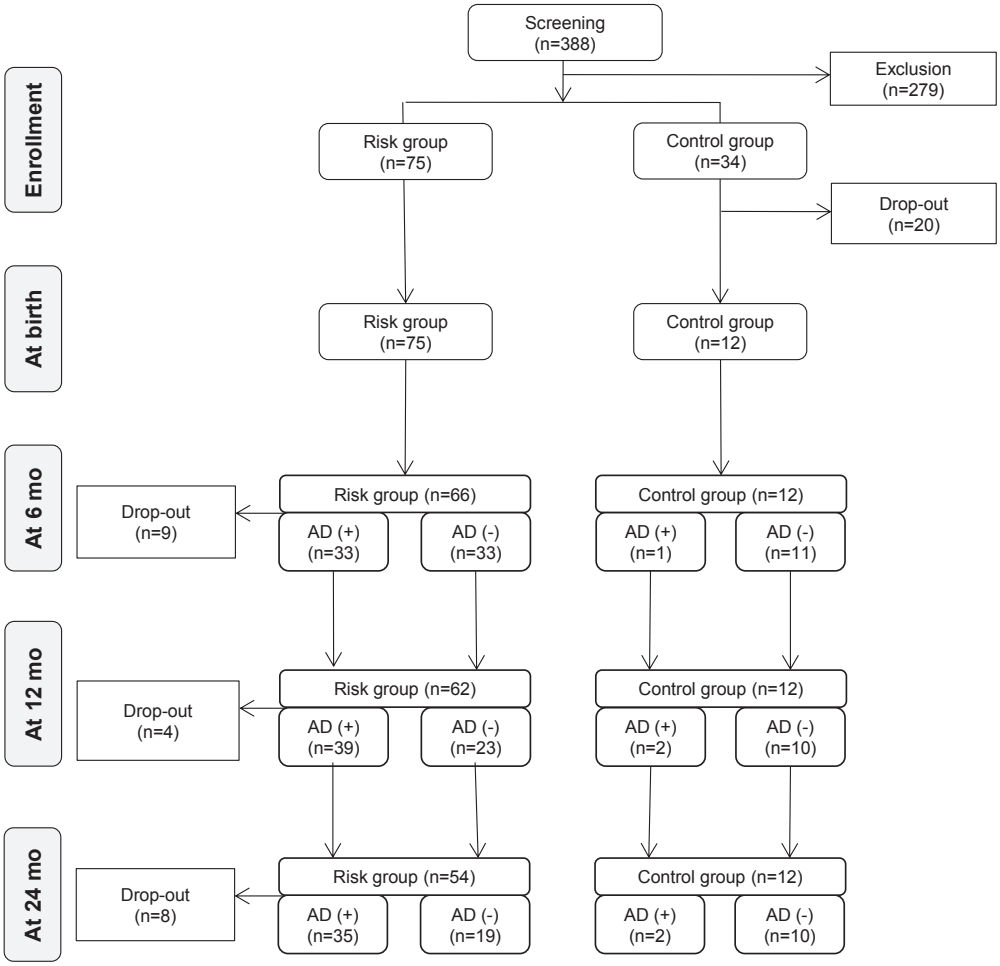


**FIG 1.** Flowchart of study population during the study period. The number of infants with AD indicates the cumulative number of patients who have developed AD at the time of evaluation. *mo,* Months.

when at least 1 parent had both positive skin test response and a history of asthma or allergic rhinitis, or when at least 1 family member had AD. The diagnosis of AD was based on the Hanifin and Rajka criteria, and the severity was assessed using the SCORing Atopic Dermatitis (SCORAD) method. Transepidermal water loss (TEWL) was measured on the volar surface of the forearm at age 2 months by using a Tewameter TM300 (Courage & Khazaka, Köln, Germany). Tape stripping was done on the volar surface of the forearm at 2 months, and epidermal protein levels were measured by mass spectrometry as previously described to evaluate the expression of filaggrin, alpha enolase, corneodesmosin, fatty acid– binding protein, serpin B3, transglutaminase 3, and thymic stromal lymphopoietin (TSLP).[1] Methods for mass spectrometry and statistics are described in this article's Online Repository at www.jacionline.org. This study was approved by the institutional review board (IRB) at Samsung Medical Center in Seoul (IRB no. 2011-11-072), and written informed consent was obtained from all the parents.

The cumulative incidence of AD was higher in the risk group than in the control group at 24 months (64.8% vs 16.7%; $P = .003$) (see Fig E1 in this article's Online Repository at www.jacionline.org). Eczema symptoms at age 12 months occurred mostly on the face (72.7%), but clinical AD did not appear on the forearm where tape stripping was conducted. The mean SCORAD score in affected infants was 13.3 ± 5.8 and 12.9 ± 5.4 at age 12 and 24 months, respectively. There was no difference between the risk group and the control group in sex, birth weight, intrauterine period, birth type, mother's age, family's monthly income, and maternal education levels (see Table E1 in this article's Online Repository at www.jacionline.org).

To estimate risk factors predicting AD development by the age of 24 months, a logistic regression model was used. A multivariable analysis was done by adjusting for TSLP and other variables with *P* value of less than .1 in a univariable analysis. When TSLP expression was dichotomized into low or high levels according to its median value, 0.83 pmol/mg skin (range, 0.32-1.60 pmol/mg skin), TSLP expression at 2 months was 5.3 times more likely to develop AD by age 24 months (95% CI, 1.3-21.4). When TSLP expression was added to family history, adjusted odds ratio (aOR) for AD development was higher in subjects with family history and high TSLP expression (aOR = 20.2; 95% CI, 1.5-272.3) than in those with family history alone (aOR = 12.6; 95% CI, 1.1-143.9; Fig 2). Male gender was also independently related to AD development (aOR = 5.5; 95% CI, 1.3-24.2). In contrast, other variables such as birth type, passive smoking, mold exposure during pregnancy, exclusive breast-feeding, TEWL on the nonlesional area of the forearm at 2 months, and