

Correspondence

Filaggrin variants confer susceptibility to asthma

To the Editor:

We read with interest the recent article by Rogers et al,¹ "Filaggrin mutations confer susceptibility to atopic dermatitis (AD) but not to asthma." Although this publication adds to the data on filaggrin (*FLG*) mutations in atopic disease, we have some concerns regarding the core conclusions asserted in this article's negative title. Data exist to support a role for *FLG* as a susceptibility gene for asthma; the data presented by Rogers et al¹ do not contradict this evidence.

Although filaggrin (*FLG*) mutations confer the strongest known genetic risk of atopic dermatitis (eczema), a widely replicated association,^{2,3} the association of *FLG* mutations with asthma ascertained *per se* (both with and without eczema) has been formally studied in only 2 publications to date.^{4,5} These studies were not *post hoc* with respect to asthma as asserted by Rogers et al.¹ Initially we examined 604 children from the Dundee BREATHE cohort, included because of a physician diagnosis of asthma, not a diagnosis of previous eczema.⁵ In this cohort we reported an overall odds ratio for all asthma of 1.8 (95% CI, 1.3-2.5; $P = .0002$).⁵ This risk was entirely limited to patients with previous eczema; the odds ratio for asthma plus eczema was 3.3 (95% CI, 2.0-5.6; $P = .000004$).

Marenholz et al⁴ studied 871 individuals ascertained from a longitudinal population-based cohort, the Multicenter Allergy Study, a detailed study that records all atopic manifestations and that was not limited to or directed toward eczema. Marenholz et al⁴ confirmed our initial findings of an association with the asthma plus eczema phenotype with a striking odds ratio of 6.21 (95% CI, 2.6-14.8; $P = 5.4 \times 10^{-8}$), and analysis of the combined asthma (with and without eczema) from the data presented in this study reveals an overall odds ratio for asthma of 3.611 (95% CI, 1.79-7.3; $P = .0005$; $n = 431$). In this study, the number of asthma cases was only 117, explaining the wider CIs. Consistent with the BREATHE study, the *FLG*-associated risk in MAS was for asthma with eczema, with no significant increased risk for asthma without eczema.

The reported findings of Rogers et al¹ are entirely consistent with the previous studies in that they demonstrate an association of *FLG* mutations with the asthma plus eczema phenotype and the absence of an association with asthma in the absence of eczema. When considering the effect of *FLG* mutations on asthma *sensu latu*, the authors have stated that their analysis has 60% power to detect an effect size for *FLG* mutations of 2.0 for asthma; however, the study is based on only 68 informative pairs in which a substantial distortion of transmission was observed (~52% increased transmission) for asthma overall (very similar to the discovery cohort odds ratio of 1.8). Indeed, this study has only 50% power to detect the primary effect size of 1.8. Therefore, the likelihood of this replicating the primary observation was as likely to fail as it was to succeed. This lack of power means that the study is not appropriate to determine robustly an absence of association of *FLG* mutations with asthma *per se*. This lack of sensitivity was exacerbated by their use of a transmission study as opposed to a more sensitive case-control association study. Notably the investigators chose to

present a case control analysis of AD with a noticeable increase in power using the same individuals ($P = 10^{-5}$ for association with AD; $P = .02$ for AD in the family-based transmission analysis). Association analysis was not possible because of the lack of an ethnically matched control group. This is important because the allele frequencies of R501X and 2284del4 are known to vary widely throughout the world.

Given the strong effect size of *FLG* mutations on eczema and the known association of eczema with asthma, it seems intuitive to hypothesize that a strong eczema risk factor might have a detectable effect on asthma on a population basis. Further confirmation of the association of *FLG* mutations with asthma has now been shown in 2 additional large, well ascertained, cross-sectional or longitudinal population-based studies, the Avon Longitudinal Study of Parents and Children (ALSPAC) and International Study of Asthma and Allergy in Childhood Phase II (ISAAC II) studies, both of which are free from the potential ascertainment bias that is a feature of all case series collected from hospital-based populations. Overall asthma risk associated with *FLG* mutations in the ALSPAC study was 1.80 (95% CI, 1.34-2.41; $P = .00019$),⁶ and in ISAAC II, the overall asthma risk was 1.79 (95% CI, 1.19-2.68; $P = .0048$).⁷ In each of these studies, this effect was limited to asthma occurring in association with eczema.

We fully agree with Rogers et al¹ that *FLG* is not expressed in the respiratory epithelium, and that risk of asthma is therefore not driven through local epithelial effects in the lung. However, this does not exclude *FLG* as an asthma susceptibility gene; it merely means that the mechanism of this risk is not yet fully understood. Indeed, the mechanisms through which eczema *per se* confers risk of asthma are unclear, although percutaneous priming⁸ or secondary immunologic effects from induction of T_H2 cytokines in epithelia⁹ are interesting hypotheses that merit further experimental exploration. Asthma is clearly not a single disease entity; evidence of a genetic susceptibility to the complex eczema plus asthma phenotype adds support to this coassociation as a distinct subtype of asthma, as previously suggested.¹⁰ The filaggrin data raise interesting and important questions regarding the mechanisms behind the association of a skin barrier gene with asthma; we suggest that this will be an interesting field for discovery.

W. H. Irwin McLean, PhD, DSc^a

Colin N. A. Palmer, PhD^b

John Henderson, MD^c

Michael Kabesch, MD^d

Stephan Weidinger, MD^{e,f}

Alan D. Irvine, MD^{g,h}

From ^athe Epithelial Genetics Group, Human Genetics Unit, Division of Pathology and Neuroscience, and ^bthe Population Pharmacogenetics Group, Biomedical Research Center, University of Dundee, Dundee, United Kingdom; ^cthe Departments of Community-Based Medicine, University of Bristol, Bristol, United Kingdom; ^dthe Children's Hospital, Ludwig-Maximilians-University, Munich, Germany; ^ethe Department of Dermatology and Allergy, Technical University Munich, Munich, Germany; ^fthe Division of Environmental Dermatology and Allergy, Helmholtz Zentrum Munich-German Research Center for Environmental Health and ZAUM-Center for Allergy and Environment, Technical University Munich, Munich, Germany; ^gthe Department of Pediatric Dermatology, Our Lady's Children's Hospital, Dublin, Ireland; and ^hthe Department of Clinical Medicine, Trinity College Dublin, Ireland. E-mail: irvinea@tcd.ie.

Disclosure of potential conflict of interest: A. D. Irvine has received research support from the Children's Medical and Research Foundation and has served as an expert witness in industrial dermatitis litigation. J. Henderson has received research support

from the Medical Research Council and Asthma UK. M. Kabesch has received research support from Gabriel, European Union, National Genome Research Network German Federal Ministry of Education and Research, and Sonderforschungsbereich TR22 Deutsche Forschungsgemeinschaft and has served as a member of the European Research Society. The rest of the authors have declared that they have no conflict of interest.

REFERENCES

1. Rogers AJ, Celedon JC, Lasky-Su JA, Weiss ST, Raby BA. Filaggrin mutations confer susceptibility to atopic dermatitis but not to asthma. *J Allergy Clin Immunol* 2007;120:1332-7.
2. Irvine AD. Fleshing out filaggrin phenotypes. *J Invest Dermatol* 2007;127:504-7.
3. Baurecht H, Irvine AD, Novak N, Illig T, Buhler B, Ring J, et al. Toward a major risk factor for atopic eczema: meta-analysis of filaggrin polymorphism data. *J Allergy Clin Immunol* 2007;120:1406-12.
4. Marenholz I, Nickel R, Ruschendorf F, Schulz F, Esparza-Gordillo J, Kerscher T, et al. Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march. *J Allergy Clin Immunol* 2006;118:866-71.
5. 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.
6. Henderson J, Northstone K, Lee SP, Liao H, Zhao Y, Pembrev M, et al. The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study. *J Allergy Clin Immunol* 2008;121:872-7.
7. Weidinger S, O'Sullivan M, Illig T, Baurecht H, Depner M, Rodriguez E, et al. Filaggrin mutations, atopic eczema, hay fever, and asthma in children. *J Allergy Clin Immunol* 2008. In press.
8. Hudson TJ. Skin barrier function and allergic risk. *Nat Genet* 2006;38:399-400.
9. Howell MD, Kim BE, Gao P, Grant AV, Boguniewicz M, De Benedetto A, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol* 2007;120:150-5.
10. Illi S, von Mutius E, Lau S, Nickel R, Gruber C, Niggemann B, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004;113:925-31.

Available online ■■■
doi:10.1016/j.jaci.2008.02.039