

Correspondence

Reply

To the Editor:

McLean et al¹ raise objection to our statement² that the filaggrin (*FLG*) mutations strongly associated with atopic dermatitis should not be classified as an asthma susceptibility variants. Elaborating on our brief review of the literature presented in the introduction of our manuscript, McLean et al¹ provide details from 2 studies that have indeed demonstrated significant association of *FLG* mutations with asthma. However, they correctly point out (as did we) that in both studies, the association is exclusive to patients who manifest atopic dermatitis: when analysis is limited to patients with asthma without atopic dermatitis, there is no association in any of the cohorts studied, including the CAMP cohort. Thus, while both McLean et al¹ and we have correctly cited the available literature, we reach distinctly divergent conclusions regarding the role of *FLG* mutations as asthma susceptibility factors. McLean et al¹ think these mutations should be classified as risk factors for both atopic dermatitis and asthma, whereas we would classify these mutations as risk factors only for atopic dermatitis.

Which interpretation is correct? Would a gene that promotes addiction to cigarette smoking be considered a lung cancer gene simply because cigarette smoke is a strong risk factor for lung cancer? Certainly not. When 2 traits like atopic dermatitis and asthma are highly correlated, it is important to clarify whether a genetic risk factor is causally involved in the codevelopment of both diseases through a shared molecular mechanism (ie, phenotypic pleiotropy), or whether the genetic variant directly causes only 1 of the 2 conditions, which in turn is a risk factor for the other. The fact that genetic risk for asthma is repeatedly observed for *FLG* mutations only among subjects who first manifest atopic dermatitis suggests the latter scenario is at play here. We do not contest that subjects with atopic dermatitis, regardless of *FLG* genotype status, are at increased risk of asthma (whether through percutaneous priming, epithelial T_H2-cytokine induction, or other mechanisms). Rather, we argue that without any evidence of association of *FLG* with asthma in the absence of atopic dermatitis, a more restrictive classification of *FLG* as an atopic dermatitis gene is most appropriate.

This distinction is not semantic. As we enter the era of personalized and molecular-based medicine, medical practitioners will base clinical decisions more frequently on genetic data. It is thus important that researchers clearly communicate findings of genetic association. As addressed in the discussion section of our article, 2 of the primary motivations for studies of complex genetic traits are to identify novel molecules for therapeutic targeting and to enable development of clinical diagnostic and prognostic tools. Using the classification by McLean et al¹ of *FLG* as an asthma susceptibility gene would imply that *FLG*-based therapies or clinical tools developed for the management

of atopic dermatitis would likely be efficacious in the management of asthma. The current scientific evidence would not support this likelihood. Thus, although we completely agree with McLean et al¹ that “*FLG* mutations confer the strongest known genetic risk of atopic dermatitis,” we maintain our position that *FLG* should not be considered an asthma gene.

A final word regarding statistical power. McLean et al¹ suggest that our study was underpowered to detect an association between *FLG* and asthma. We address this issue thoroughly in the Discussion section of our article discussion. Among the many points we make refuting this possibility as an explanation of our results, we highlight the fact that low statistical power affects the ability to claim statistically significant differences in allelic frequency or transmission, but does not in any way influence the absolute risk observed. In our study, transmission of *FLG* mutations from parent to offspring was balanced (17 transmissions vs 17 nontransmissions), following the expectation of random genetic transmission (akin to an odds ratio of 1.0) and implying no genetic relationship between *FLG* and asthma independent from atopic dermatitis. Increasing the sample size would not have changed this result, as evident from the studies of Palmer et al³ and Marenholz et al.⁴

Angela J. Rogers, MD^{a,b,c}

Juan C. Celedón, MD, DrPH^{a,b,c}

Jessica A. Lasky-Su, ScD^a

Scott T. Weiss, MD, MSC^{a,b,c}

Benjamin A. Raby, MDCM, MPH^{a,b,c}

From ^athe Channing Laboratory, Department of Medicine, and ^bthe Pulmonary Division, Brigham and Women's Hospital, Boston; and ^cHarvard Medical School, Boston, Mass. E-mail: rebar@channing.harvard.edu.

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