Published in final edited form as:

J Allergy Clin Immunol. 2008 October ; 122(4): 834–836. doi:10.1016/j.jaci.2008.07.027.

Filaggrin gene mutations are associated with asthma and eczema in later life

Neil E. Rice, MSc^a, Bipen D. Patel, MD, PhD^b, Iain A. Lang, PhD^a, Meena Kumari, PhD^c, Timothy M. Frayling, PhD^d, Anna Murray, PhD^{a,d}, and David Melzer, MB, PhD^a

Neil E. Rice: ; Bipen D. Patel: ; Iain A. Lang: ; Meena Kumari: ; Timothy M. Frayling: ; Anna Murray: ; David Melzer: david.melzer@pms.ac.uk

^aEpidemiology and Public Health, RD&E Wonford Site, Exeter, United Kingdom

^bThe Department of Respiratory Medicine, Royal Devon & Exeter Foundation Trust, Exeter, United Kingdom

^cThe Department of Epidemiology and Public Health, University College London, London, United Kingdom.

^dGenetics of Complex Traits, Peninsula Medical School, RD&E Wonford Site, Exeter, United Kingdom

To the Editor:

Atopic conditions are common in middle and later life. Although a genetic component in these conditions has long been suspected, only recently have mutations in the filaggrin gene (*FLG*) emerged as a major cause in children and young adults. Filaggrin is an epidermal protein involved in aggregating the keratin cytoskeleton¹ and is critical in forming the skin barrier. There are several mutations in the *FLG* locus associated with a loss of functional protein,² but 2 (R501X and 2282del4) are common in populations of European ancestry.³ In children and younger adults *FLG* mutations are strongly associated with eczema, and in those with eczema, *FLG* is also associated with asthma.⁴ It is hypothesized that the *FLG* mutation–compromised skin barrier allows percutaneous induction of T_H2 cytokines in epithelia and the development of a systemic atopic tendency.⁵

The effects of *FLG* mutations in middle-aged or older groups are not known. We aimed to estimate the effect of the 2 common *FLG* mutations on the prevalence of asthma and atopic conditions in persons aged 50 years and older in England using data from the English Longitudinal Study of Ageing (ELSA).

ELSA is a follow-up study of respondents to the Health Survey for England (HSE; <http://www.dh.gov.uk/>), an annual cross-sectional survey of the community-living population. All HSE respondents in 2001 were asked about allergic conditions, and most respondents donated a blood specimen for IgE measurement.

In 2002 and 2004, ELSA respondents were asked about diagnosed asthma, chronic bronchitis, or emphysema. In 2004, respondents were also asked to participate in a nurse-led physical

Correspondence to: David Melzer, david.melzer@pms.ac.uk.

Disclosure of potential conflict of interest: N. E. Rice has received research grants from the US National Institute on Aging and the BUPA Foundation. T. M. Frayling has received research grants from the Wellcome Trust, MRC UK, and Diabetic UK. A. Murray has received research support from the Wellcome Trust. D. Melzer has received research grants from the US National Institute on Aging and the BUPA Foundation. The rest of the authors have declared that they have no conflict of interest.

examination and to provide blood samples. The identification of asthma in elderly subjects is complex, with overlaps in presentation with chronic obstructive pulmonary disease and even cardiac failure. We therefore used several case definitions in our analysis: “any obstructive airways disease” (diagnosed asthma, emphysema, or chronic bronchitis), “diagnosed asthma,” “self-reported wheezing in the last 12 months,” and “symptomatic asthma.” We defined patients with symptomatic asthma as those with doctor-diagnosed asthma (in 2002 and 2004) and wheezing in the previous 12 months.

Of the 9432 respondents in ELSA 2004, 7156 underwent a nurse-led clinical visit, during which 6231 donated DNA specimens. Of these, genotyping was successfully completed on 5432 subjects for R501X and 5335 subjects for 2282del4 mutations. The combined *FLG* genotype was available for 5289 individuals, of whom 2051 had been asked about atopy in the HSE 2001. Genotyping was performed by The Geneservice Ltd (<http://www.geneservice.co.uk>) using Applied Biosystems TaqMan probes. The R501X and 2282del4 mutations were both in Hardy-Weinberg equilibrium, and there were no discrepancies between duplicate samples. The 2 variants were combined to produce the *FLG* genotype, according to the method of Palmer et al.⁶ Associations were tested in age- and sex-adjusted linear or logistic regression models, with IgE models additionally adjusted for smoking status and exposure by using Stata SE Version 9 (StataCorp, College Station, Tex).

In our sample 8.8% (n = 464) had at least 1 *FLG* mutation, and 0.25% (n = 13) were homozygous for either mutation or had copies of both, yielding a prevalence of 9% for *FLG* mutation presence. Although 11.7% reported doctor-diagnosed asthma and 17.7% reported attacks of wheezing in the previous 12 months, only 6.6% reported both diagnosed asthma and wheezing in the previous 12 months (ie, symptomatic asthma; Table I).

FLG mutations were not associated with “any obstructive lung disease” or “diagnosed asthma.” However, there was a borderline association with “wheezing in the previous 12 months” (odds ratio [OR], 1.26; *P* = .05) and a significant association with symptomatic asthma (OR, 1.45; *P* = .03; Table II).

Diagnoses of eczema were more common in those with mutations (OR, 1.69; *P* = .009; Table II), and a higher proportion of *FLG* carriers reported early ages of onset: 61% (n = 11/18 with data) of carriers compared with 26% of others (n = 36/138) had their skin conditions before the age of 20 years (OR, 4.93; 95% CI, 1.70–14.26; *P* = .003). *FLG* mutations were not associated with IgE levels. A history of dry skin in the past 12 months was also somewhat more common in those with mutations (OR, 1.47; *P* = .09; Table II), which is in line with recent findings by Novak et al.⁷

The R501X mutation was independently associated with both eczema (OR, 2.08; 95% CI, 1.29–3.36; *P* = .003) and symptomatic asthma (OR, 1.59; 95% CI, 1.05–2.40; *P* = .03). These associations for the 2282del4 mutation were not statistically significant, but trends were in the same direction.

In this first study of the effects of mutations in the *FLG* gene in middle and later life, there were strong associations between mutation status and eczema and symptomatic asthma. These associations showed a similar pattern to that found in children and young adults. We were unable to derive robust estimates of the risk of mutations resulting in both conditions together because of small numbers: in our data 41 individuals with symptomatic asthma also reported having eczema at baseline, of whom 8 had an *FLG* mutation. We found no association between mutation prevalence and age, providing no evidence of a significant loss of this genotype in the population because of increased mortality in those with *FLG* mutations.

In large population studies, such as ELSA, detailed clinical diagnosis of eczema and asthma is not possible for logistic reasons: carefully diagnosed comparisons of cases and control subjects are likely to provide even stronger estimates of the associations. The prevalence of asthma in the genotyped population was 5.6% (95% CI, 4.7% to 6.5%) in men and 7.5% (95% CI, 6.5% to 8.4%) in women, which is comparable with published prevalences in middle and later life.⁸ We also note that the prevalence of the studied mutations in our sample (9%) is very similar to that seen in children in England (8.8%). However, our observed prevalence of eczema (13.0%; 95% CI, 11.6% to 14.5%) is somewhat higher than that reported by Gupta et al⁹ (ie, 9% of ≥45-year-olds) for the United Kingdom: the reason for this is unclear.

Interestingly, only a minority of mutation carriers in our study actually had eczema or asthma (>80% of *FLG* mutation carriers had neither condition, which is consistent with the survival analysis by Henderson et al¹⁰), and work is needed to establish the factors that lead to either resilience or susceptibility in later life. More work is also needed on whether specific treatment approaches are possible for those with *FLG* mutations.

Acknowledgments

We thank the contributors, including the National Centre for Social Research, who collected samples used in this study, as well as the ELSA participants.

Supported by unrestricted research grants from US National Institute on Aging (NIA) (R01AG24233) and the BUPA Foundation. Samples were drawn from the English Longitudinal Study of Ageing DNA Repository, which receives support under a grant (R01AG1764406S1) awarded by the NIA. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

REFERENCES

1. Hudson TJ. Skin barrier function and allergic risk. *Nat Genet* 2006;38:399–400. [PubMed: 16570058]
2. Weidinger S, O'Sullivan M, Illig T, Hr Baurecht, Depner M, Rodriguez E, et al. Filaggrin mutations, atopic eczema, hay fever, and asthma in children. *J Allergy Clin Immunol* 2008;121:1203–1209. [PubMed: 18396323]
3. Sandilands A, Terron-Kwiatkowski A, Hull PR, O'Regan GM, Clayton TH, Watson RM, et al. Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. *Nat Genet* 2007;39:650–654. [PubMed: 17417636]
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. [PubMed: 18395783]
5. 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;118:866–871. [PubMed: 17030239]
6. Palmer CNA, 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]
7. Novak N, Baurecht H, Schafer T, Rodriguez E, Wagenpfeil S, Klopp N, et al. Loss-of-function mutations in the filaggrin gene and allergic contact sensitization to nickel. *J Invest Dermatol* 2007;128:1430–1435. [PubMed: 18049447]
8. Gupta R, Sheikh A, Strachan DP, Anderson HR. Burden of allergic disease in the UK: secondary analyses of national databases. *Clin Exp Allergy* 2004;34:520–526. [PubMed: 15080802]
9. Gupta R, Sheikh A, Strachan DP, Anderson HR. Burden of allergic disease in the UK: secondary analyses of national databases. *Clin Exp Allergy* 2004;34:520–526. [PubMed: 15080802]
10. 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;121:872–877. [PubMed: 18325573]

TABLE I

Sample characteristics of those genotyped for *FLG*

	Proportion with or mean value of characteristic (95% CI)
Full sample (n = 5289)	
Female sex	54.2% (52.9% to 55.6%)
Mean age (y)	66.0 (65.8 to 66.3)
Smoking status	
Smoker	14.2% (13.2% to 15.1%)
Former smoker	49.4% (48.0% to 50.7%)
Never smoked	36.4% (35.1% to 37.7%)
<i>FLG</i> genotype	
AA	91.0% (90.2% to 91.8%)
Aa	8.8% (8.0% to 9.5%)
aa	0.25% (0.1% to 0.4%)
Reported conditions at ELSA 2004	
Diagnosed asthma	11.7% (10.8% to 12.6%)
Symptoms of wheezing in past 12 mo	17.7% (16.7% to 18.8%)
Asthma and wheezing in past 12 mo ("symptomatic asthma")	6.6% (5.9% to 7.3%)
Baseline individuals with atopy data (n = 2057)	
Sex (female)	54.3% (52.1% to 56.5%)
Mean age (y)	62.9 (62.5 to 63.3)
Smoking status	
Smoker	15.7% (14.1% to 17.2%)
Former smoker	45.5% (43.4% to 47.7%)
Never smoked	38.8% (36.7% to 40.9%)
<i>FLG</i> genotype	
AA	90.8% (89.5% to 92.0%)
Aa	9.0% (7.8% to 10.3%)
aa	0.2% (0.004% to 0.39%)
Reported conditions	
Diagnosed asthma	13.0% (11.6% to 14.5%)
Eczema	13.0% (11.6% to 14.5%)
Itchy skin	37.1% (35.1% to 39.2%)
Generally dry skin in past 12 mo	9.6% (8.3% to 10.8%)
Total IgE concentration, geometric mean *	29.32 (27.4 to 31.3)
House dust mite IgE concentration (% >0.4 kU/L) *	12.0% (10.5% to 13.5%)

* From a subgroup of 1786 individuals who had IgE levels measured at baseline.

TABLE II

Association of *FLG* mutations with asthma and atopy

	Common	<i>FLG</i> , n (%) Mutation	Age- and sex-adjusted OR (95% CI)	P value
Full sample				
Any obstructive lung disease	735 (15.3%)	81 (17.0%)	1.13 (0.88–1.45)	.34
Reporting any asthma diagnosis only	554 (11.5%)	64 (13.4%)	1.19 (0.90–1.57)	.23
Reporting wheezing in the past 12 mo	837 (17.4%)	100 (21.0%)	1.26 (1.00–1.59)	.05
Symptomatic asthma: diagnosed asthma plus wheezing in past 12 mo	306 (6.4%)	43 (9.0%)	1.45 (1.04–2.03)	.03
Association with atopic conditions				
Eczema	231 (12.4%)	36 (19.2%)	1.69 (1.14–2.49)	.009
Itchy skin condition	685 (36.7%)	79 (41.6%)	1.24 (0.92–1.68)	.16
Dry skin in past 12 mo	172 (9.2%)	25 (13.2%)	1.47 (0.94–2.31)	.09
Association with baseline IGE levels, logistic regression adjusting for age, sex, smoking status, and pack years				
Total IgE (% ≥ 200 kU/L)	165 (10.2%)	14 (8.5%)	0.86 (0.48–1.53)	.61
House dust mite IgE (% ≥ 0.4 kU/L)	191 (11.8%)	24 (14.6%)	1.31 (0.82–2.07)	.26