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A familial study of filaggrin mutation in atopic dermatitis

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Filaggrin is an epidermal structural protein critical for the development of a functional skin barrier. People who have null mutations in the *FLG* gene are at increased susceptibility of atopic dermatitis (AD), peanut allergy, and asthma associated with AD.[1–4] AD has a high familial occurrence evidenced by concordance rates of 0.72 to 0.77 in monozygotic and 0.15 to 0.23 in dizygotic twin pairs.[5] These studies were primarily carried out in Northern Europe, particularly in large cohorts in Ireland, where there is a high prevalence of *FLG* mutations in AD.

The identification of a genetic defect as a key event in the pathophysiology of AD and allergic sensitization has brought up many clinical questions among sufferers. On reading "Filaggrin Mutations Associated with Skin and Allergic Diseases" by Irvine, McLean, and Leung, published in 2011 *The New England Journal of Medicine*, a 91-year-old physician who suffered from lifelong atopic disease contacted the authors to determine whether *FLG* mutation could predict which of his 4 generations of family members were prone to AD or asthma and whether any environmental factors increased or decreased the risk of developing disease. Only early life cat exposure and exposure to other children have shown an additional interactive risk of AD in patients with *FLG* mutation.[6–8] These studies were birth cohort studies, and no family pedigree study has been used to study gene–environment interactions for *FLG* mutation.

The patient is a 91-year-old man with a history of early-onset, severe, persistent AD, asthma, food allergy, and skin cancer. He was of Scottish–Irish decent, and lived in Colorado his entire life. Members of the family regardless of atopic status were genotyped for 5 *FLG* gene mutations (R501X, 2282del4, R2447X, S3247X, and 3702delG). Additionally, members of the family who enrolled in this study were genotyped and filled out a questionnaire assessing for history of asthma, allergic rhinitis, AD, food allergy, history of skin cancer, pet exposure, mold exposure, and dust mite exposure (eFig 1). The study was approved by the

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Supplementary Data

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National Jewish Health Institutional Review Board with consent and assent obtained from each subject before enrollment. We assessed the relationship between *FLG* mutation and AD using Fisher's exact test.

The family pedigree is shown in Figure 1. Demographics and clinical data are shown in eTable 1. Twenty-two family members across 4 generations were genotyped and completed questionnaires. All 22 family members were Caucasian, mainly of Scottish/Irish decent. Sixteen members of this family had an *FLG* mutation, 11 males and 5 females. Four females and 2 males had wild-type (WT) genotype. There were 15 heterozygous and 1 compound heterozygous mutations (11 R501X/WT, 4 2282del4/WT, 1 R501X/2282del4). Carrying an *FLG* mutation was significantly associated with having AD ($P = .02$), but did not increase the risk of developing other atopic disease (asthma, allergic rhinitis, food allergy) ($P = .14$). Of the 16 family members who had an *FLG* mutation, 9 developed AD in early childhood, whereas 7 had no history of AD. Of those that had AD, all reported early-onset disease, and only 1 family member outgrew their disease whereas 8 others reported persistent AD into adulthood. If someone had an FLG mutation, their odds ratio of developing AD was 6 (95% confidence interval 0.78–46.1) times higher than someone without an FLG mutation ($P = .09$). Four family members with heterozygous mutations had no atopic disease at all. Four family members, all heterozygous for mutation, had skin cancer (2 with squamous cell carcinoma [SCC] and basal cell carcinoma [BCC], 1 with SCC, and 1 with BCC). Two family members, both heterozygous for mutation, reported keratosis pilaris, and 13 family members, 8 heterozygous for mutation and 5 without mutation, reported warts. Only 2 family members, both heterozygous for mutation, reported superficial staphylococcus infection, and no one reported eczema herpeticum. No differences in exposures to animal dander, dust mite, and swamp cooler were reported among the family members with or without disease.

Previously, family pedigree studies have looked for the prevalence of *FLG* mutations in patients with ichthyosis vulgaris or AD. These studies were instrumental in establishing the semidominant inheritance pattern with variable penetrance of filaggrin, the development and severity of eczema, and the associations with other atopic conditions.[2] Large birth cohort studies have been used to look at gene–environment interactions in patients with AD, showing that early exposure to cat resulted in early-life atopic dermatitis.[6,7] No family pedigree has been used to study the effects of gene–environment interactions in patients with *FLG* mutation. Our study has the advantage of having multiple family members with and without disease and mutation, many of whom shared the same environment.

In our current study, knowing the *FLG* status in this family was helpful in predicting who was at risk of developing AD Twelve of the 16 family members that had a mutation had atopic disease, with more than half of them having a diagnosis of AD. The epidermal innate immunity enhances the physical, chemical, microbial, and immunologic barriers.[9] We were unable to identify whether certain exposures (pets, mold, dust mite) increased the risk or were protective for developing atopic disease if they had *FLG* mutation.

Limitations in this small familial study include recall bias, because patients were not all directly evaluated, but filled out questionnaires (eFig 1). Although early life exposures

were assessed by the questionnaire, these were not corroborated with house dust samples or evidence of allergic sensitization in the family members. Family-based studies have the advantage, to some extent, of controlling for genetic background and environmental exposures in closely related members.

Further studies are needed to understand the gene–environment interplay in *FLG* and potential skin cancer risks, and larger familial studies may be helpful in answering these questions. Following a family longitudinally, although challenging, with documented exposures collected from house dust samples may shed light on specific environmental effects in patients with *FLG* mutation and may allow those patients to diminish risks with environmental control. A motivated family such as that described here would be ideal for this type of study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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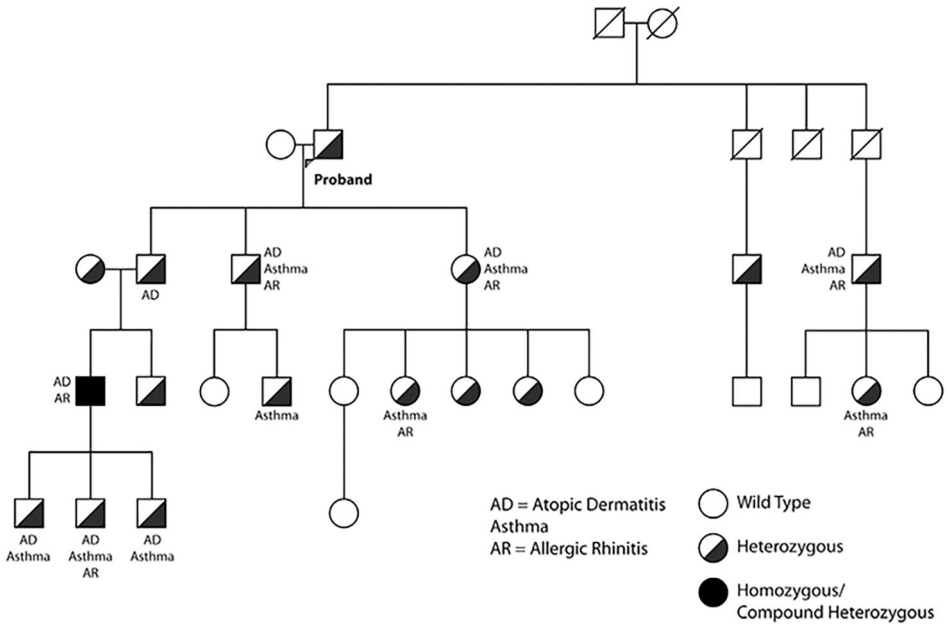

Figure 1.

Family pedigree showing filaggrin genotype (wild type, heterozygous, compound heterozygous mutation) and allergic diseases in each individual.