

with any severity of egg allergy and that these patients can be vaccinated safely with a single dose of IIV, without requiring administration by an allergist, which otherwise poses an unnecessary barrier to immunization and is not justified based on available safety data.

- Two new influenza vaccines not grown in eggs have been approved for patients 18 years and older; Flucelvax,⁶ prepared from virus propagated in cell culture, and Flublok,⁷ recombinant hemagglutinin proteins produced in an insect cell line.

Based on this additional information, the following are recommended:

- As per the 2012 update, all patients with egg allergy of any severity, including anaphylaxis, should receive IIV annually, using any age-approved brand of IIV in an age-appropriate dose. Such patients can receive the vaccine as a single dose without prior vaccine skin testing.
- For egg-allergic patients 18 years of age and older, either egg-based or egg-free IIV can be used.
- Special precautions regarding medical setting and waiting periods after administration of IIV to egg-allergic recipients beyond those recommended for any vaccine are not warranted. As per ACIP General Recommendations on Immunization,⁸ providers should be aware that “Although anaphylactic reactions are rare after vaccination, their immediate onset and life-threatening nature require that all personnel and facilities providing vaccinations have procedures in place for anaphylaxis management.” For IIV, language that describes egg-allergic recipients as being at increased risk compared with non-egg-allergic recipients or requiring special precautions should be removed from guidelines and product labeling.

John M. Kelso, MD*

Matthew J. Greenhawt, MD, MBA†

James T. Li, MD, PhD‡

The Joint Task Force on Practice Parameters (JTFFP)

*Division of Allergy, Asthma and Immunology

Scripps Clinic

San Diego, California

†University of Michigan Food Allergy Center

Division of Allergy and Clinical Immunology

University of Michigan Medical School

Ann Arbor, Michigan

‡Division of Allergic Diseases

Mayo Clinic

Rochester, Minnesota

kelso.john@scrippshealth.org

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A familial study of filaggrin mutation in atopic dermatitis

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 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

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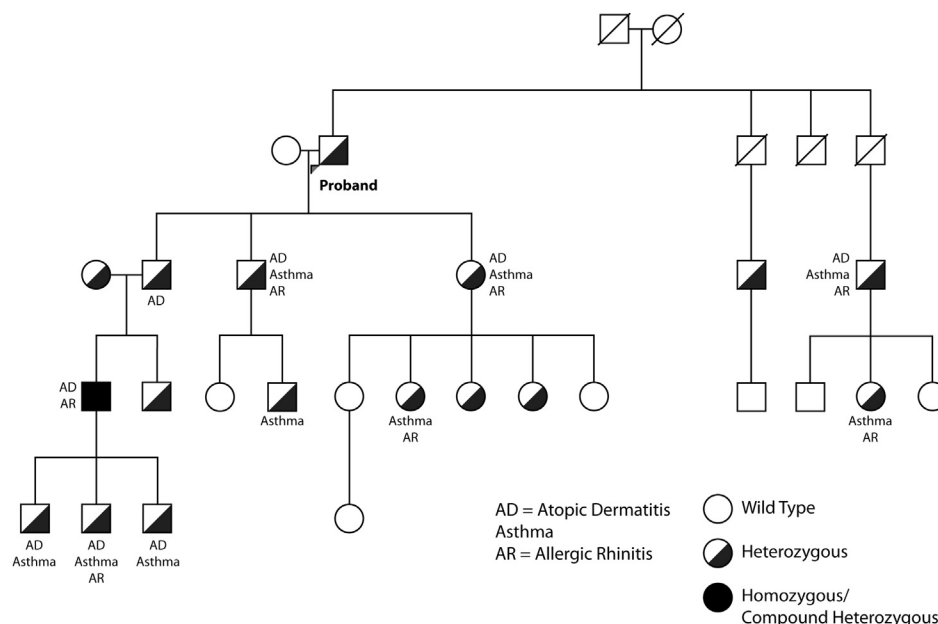


Figure 1. Family pedigree showing filaggrin genotype (wild type, heterozygous, compound heterozygous mutation) and allergic diseases in each individual.

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.

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Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2013.08.001>.

Maaz S. Mohiuddin, MD*
Douglas Curran-Everett, PhD†,‡
Donald Y.M. Leung, MD, PhD*

*Department of Pediatrics
Division of Allergy-Immunology
National Jewish Health
Denver, Colorado

†Division of Biostatistics and Informatics
National Jewish Health
Denver, Colorado

‡Department of Biostatistics and Informatics
Colorado School of Public Health
University of Colorado Denver
Denver, Colorado
leungd@njhealth.org

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Food and aeroallergen sensitization in adult eosinophilic esophagitis

Eosinophilic esophagitis (EoE) is a disorder that has increased in prevalence and causes significant morbidity in children and adults.¹ The diagnosis of EoE requires endoscopic demonstration of greater than 15 eosinophils per high-power field in at least 1 esophageal biopsy specimen.

Although numerous studies have been published describing the clinicopathologic features of pediatric patients with EoE, fewer have reported findings in adult EoE patients. The objective of this study is to report the baseline clinical characteristics, endoscopic evaluation, and sensitization profile of adult patients with EoE.

Patients were retrospectively selected based on the following study criteria: (1) Demonstration of a clinical history suggestive of EoE, (2) presence of 15 or more eosinophils/high-power field on esophageal biopsy, (3) age 18 years or older. All patients had been evaluated by a gastroenterologist and referred to the Allergy department with a diagnosis of EoE. Sixty-six eligible patients evaluated between January 2008 and December 2012 were included. Not all patients had baseline proton-pump inhibitor treatment data available. The protocol was approved by the Institutional Review Board of the Ohio State University Medical Center.

Allergy evaluation included atopic and diet histories. Food allergy was defined by a clinical history of IgE-mediated symptoms (e.g., hives, angioedema, anaphylaxis) and positive allergy testing. No oral food challenges were performed. Immediate hypersensitivity was evaluated by skin prick testing (SPT) to a panel of food and environmental allergens using a Greer pick with commercially available extracts (Greer Laboratories, Inc, Lenoir, North Carolina). The standard food panel included egg, milk, wheat, soy, peanuts, tree nuts, fish, and shellfish. In select patients, when guided by clinical history, other foods were tested to include other legumes, grains, meats, vegetables, and fruits. A standard panel of environmental allergens included pollens, molds, dust mite, cat, and dog. Skin prick responses with wheal sizes 3 mm or larger than the negative control were considered positive.

Fisher's exact method was used to test differences in categorical variables, and the Wilcoxon rank-sum procedure was used in continuous variables. Exact logistic regression was used to estimate odds ratios.

The median duration of symptoms before endoscopy was 2 months (range, 0–62). The most frequently reported atopic diseases were allergic rhinitis (92%), asthma (38%), and food allergy (21%). Dysphagia was the most common symptom reported (92%), followed by oral symptoms (17%). Reported disease complications included food impaction (48%) and the need for esophageal dilation (27%). Common endoscopic findings included esophageal rings (36%), Schatzki's ring (23%), and longitudinal furrows (30%).

Most of the patients had positive SPT to aeroallergens (89%). Younger patients (age <40 years) had a higher likelihood of having

positive SPT to both food allergens and environmental allergens ($P = .015$ and $.001$, respectively; Table 1). Patients younger than age 40 years were more likely to have sensitivity to soy ($P = .04$), milk ($P = .04$), shellfish ($P = .04$), dust mite ($P = .01$), and animal dander ($P = .04$) as compared with those who were 40 years of age or older.

Eighteen patients (27%) had a total of 66 esophageal dilations. Although we found no significant associations with age, the proportion of patients having dilation increased among those in their third and fourth decades of life and peaked in the fifth decade.

This study highlights some of the differences between our adult population and pediatric EoE populations. In our group of adult patients, the most commonly identified food sensitizations were to tree nut, peanut, and other legumes. These data contrast reported findings in the pediatric population, where milk, egg, and wheat are the most commonly identified sensitizing foods.^{2,3} When divided by age, our adult patients younger than 40 years were most commonly positive to milk, soy, and shellfish, which more closely resembles pediatric sensitivities. Although milk and soy may be more frequently implicated in pediatric EoE data, the increased milk sensitivity observed in children has been identified through serum-specific immunoglobulin E (IgE) testing in pediatric studies, whereas it was identified by skin prick testing in our adult population.⁴ Additionally, some centers have found that milk protein allergy can be relevant in pediatric patients even in the face of negative serum milk-specific IgE testing, which adds confounding features to this observation.⁵

Complications of EoE, including food impaction and need for esophageal dilation, have been widely described.¹ The rate of food impaction in our group (48%) was higher than that reported in children (7%–36%). The rate of esophageal dilations in studies looking only at adult EoE patients has been reported to be as high as 28% to 30%, which is consistent with the 27% found in our study.^{6–8} This contrasts with studies that have followed pediatric EoE cohorts into adulthood, which have found rates to be closer to 15%.^{9,10} We found that the peak age of esophageal dilation was in the age group of 41 to 50 years, with a decline as the patient age increased. This trend may suggest that the risk of esophageal dilations may peak in middle-aged adults with EoE, perhaps signifying a need for more aggressive management and monitoring in this group of patients.

A major limitation is that this study is a retrospective review; therefore, aside from the standard 8 foods, the remainder of the food skin prick tests performed varied by ordering provider, and specific IgE testing and total IgE levels were not performed on all patients. This study does not address the effect of dietary interventions. Additionally, we could not determine whether food sensitization was clinically relevant, because post-food avoidance endoscopy was not standardly performed. Although the updated 2011

Subject Questionnaire

1. What allergic conditions have you been diagnosed with and when? (eczema, asthma, environmental allergies, food allergies)
2. If you had or have eczema, were you born with it? Did you outgrow it?
3. Have you ever had wheezing or asthma?
4. Do you still have wheezing or asthma?
5. Do you use any controller medications for your asthma?
6. Have you ever lived with pets? (specify which ones and when)
7. What cities have you lived in?
8. Have you ever had warts?
9. Have you ever had molluscum?
10. Have you ever had skin cancer?
11. Have you ever had herpes skin infection?
12. Have you ever had zoster?
13. Have you ever had staph or strep skin infections (impetigo)?
14. Have you ever had skin testing? Results?
15. Do you have a swamp cooler?

eFigure 1. Questionnaire sent to family members that were genotyped.

eTable 1

Demographics and clinical data

Demographics, clinical characteristics	Number
Number	22
Sex	
Male	13 (59%)
Female	9 (41%)
Mean age (range)	42 (1–91)
History/symptoms of asthma	
Yes	10 (45%)
No	12 (55%)
History/symptoms of allergic rhinitis	
Yes	9 (41%)
No	13 (59%)
History/symptoms of atopic dermatitis	
Yes	9 (41%)
No	13 (59%)
History of food allergy	
Yes	5 (23%)
No	17 (77%)
Exposures	
Dog	17 (77%)
Cat	7 (32%)
Swamp cooler	5 (23%)
Dust mite	15 (68%)
Skin cancer	
Squamous cell carcinoma	3 (14%)
Basal cell carcinoma	3 (14%)
Filaggrin	
Wild type	6 (27%)
Heterozygous	15 (68%)
Homozygous/Compound heterozygous	1 (5%)