

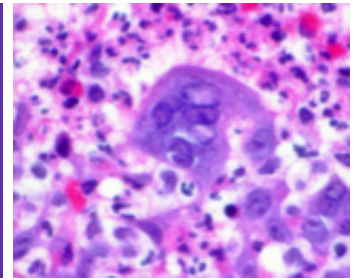


eLITERATURE REVIEW

eMedicalDermatology Review

Presented by
The Johns Hopkins University
School of Medicine & The Institute
for Johns Hopkins Nursing

Supported by an Educational Grant
from Centocor, Inc.



HOME CME/CNE INFORMATION PROGRAM DIRECTORS NEWSLETTER ARCHIVE EDIT PROFILE RECOMMEND TO A COLLEAGUE

December 2008: VOLUME 1, NUMBER 11

Atopic Dermatitis - A Disease Caused by a Barrier Defect?



In this Issue...

Although atopic dermatitis (AD) is a common and often chronic condition, its treatment remains a frustration to both clinicians and patients alike. Much of our understanding of the disease has focused on characterization of the inflammation observed within lesions. From this work, we have recognized the importance of allergen-reactive T-helper cells that release the cytokines interleukin (IL)-4, and IL-13, or the so-called Th2 cells. These cytokines are responsible for the eosinophilia and elevated immunoglobulin (Ig)E levels observed in the circulation and tissues of individuals with AD. Recent studies have begun to better characterize the cutaneous barrier defects observed in this disease. Several stratum corneum proteins have been implicated (eg, filaggrin, loricrin, and involucrin), as well as proteases and antiproteases that may be important in posttranslational modifications of these proteins.

In this issue, we review the evidence that patients with AD have a barrier defect that is apparent in both their lesional and nonlesional (ie, clinically normal-appearing) skin; examine the data suggesting that several of these epidermal proteins are AD candidate genes; and discuss how this notion of defective skin barrier function might affect the susceptibility of individuals with AD to allergens, irritants, and pollutants.

Program Information

- [CE Info](#)
- [Accreditation](#)
- [Credit Designations](#)
- [Intended Audience](#)
- [Learning Objectives](#)
- [Internet CME/CNE Policy](#)
- [Faculty Disclosure](#)
- [Disclaimer Statement](#)

Length of Activity

- 1 hours Physicians
- 1 contact hour Nurses

Release Date

December 18, 2008

Expiration Date

December 17, 2010

Next Issue

February 4, 2009

COMPLETE THE POST-TEST

Step 1.
Click on the appropriate link below. This will take you to the post-test.

Step 2.
If you have participated in a Johns Hopkins on-line course, login. Otherwise, please register.

Step 3.
Complete the post-test and course evaluation.

Step 4.
Print out your certificate.

PHYSICIAN
POST-TEST

NURSE
POST-TEST

THIS ISSUE

- [COMMENTARY from our Guest Authors](#)
- [FILAGGRIN MUTATIONS ASSOCIATED WITH ATOPIC DERMATITIS AND ICHTHYOSIS VULGARIS](#)
- [REDUCED FILAGGRIN EXPRESSION CAN BE AN ACQUIRED DEFECT](#)
- [TH2 CYTOKINE MODULATION OF OTHER STRATUM CORNEUM PROTEINS](#)
- [TRANSEPIDERMAL WATER LOSS \(TEWL\) IS NOT HIGHER AMONG ATOPIC DERMATITIS PATIENTS WITH FLG MUTATIONS VS THOSE WITHOUT SUCH MUTATIONS](#)

Program Directors

Bernard A. Cohen, MD

Professor of Pediatrics and Dermatology and Director of Pediatric Dermatology,
Johns Hopkins Children's Center
Baltimore, MD

Susan Matra Rabizadeh, MD, MBA

Private Practice
Los Angeles, CA

Mark Lebwohl, MD

Professor and Chairman
Department of Dermatology
The Mount Sinai School of Medicine
New York, NY

Elizabeth Sloand, PhD, CRNP

Assistant Professor of Pediatric Nursing
The Johns Hopkins University
School of Nursing
Baltimore, MD

■ **GENETIC DEFECTS IN STRATUM CORNEUM GENES (SPINK5, KLK7, AND FLG) AND RISK FOR ATOPIC DERMATITIS**

■ **BARRIER DEFECTS IN NONLESIONAL SKIN OF PATIENTS WITH ATOPIC DERMATITIS**

GUEST AUTHORS OF THE MONTH



Commentary & Reviews:

Lisa A. Beck, MD

Associate Professor of Dermatology and Medicine
Director of Translational Research
University of Rochester Medical Center
Rochester, New York



Commentary & Reviews:

Kemp Bundy, MD

Fellow in Allergy/Immunology
University of Rochester Medical Center
Rochester, New York

Guest Faculty Disclosures

Dr. Beck has served as a consultant for Merck, Glyco-mimetics, Anacor, Novartis and CombinatorRx, and is an investigator for Lucid, Anacor and Centocor.

Dr. Bundy has disclosed no relationships with commercial supporters.

Dr. Rabizadeh has disclosed no relationships with commercial supporters.

Unlabeled/Unapproved Uses

The authors have indicated that there will be no reference to unlabeled or unapproved uses of drugs or products in this presentation.

[Program Directors' Disclosures](#)

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Explain how both inherited and acquired defects in filaggrin and other stratum corneum proteins may impact barrier function in patients with atopic dermatitis (AD)
- Describe the clinical observations that support the notion that individuals with AD have a barrier defect
- Identify 3 different genes linked to AD and explain the strength of the association of each with the disease

DECEMBER PODCAST



A podcast by Lisa Beck, MD and Susan Rabizadeh, MD, eMedDerm Program Director

eMedicalDermatology Review is proud to continue our accredited PODCASTS for 2008.

[Listen here.](#)

The *eMedicalDermatology Review* podcast is a clinical discussion between our December author, Lisa Beck, MD, Susan Rabizadeh, eMedDerm Program Director and Robert Busker, eMedicalDermatology Review's Medical Editor. The topic is *Atopic Dermatitis - A Disease Caused by a Barrier Defect?*

Participants can now receive 0.5 credits per podcast after completing an online post-test via the links provided on this page.

To learn more about podcasting and how to access this exciting new feature of *eMedicalDermatology Review*, please [visit this page](#).

Podcasts

Please remember that you don't need this



to listen to our podcasts. You can listen directly from your computer.

[back to top](#)

COMMENTARY

Atopic dermatitis (AD) is a chronic pruritic eczematous dermatitis that affects up to 20% of children in the United States. The majority of persons with AD exhibit hypersensitivity, as defined by allergen-specific immunoglobulin (Ig)E to numerous environmental allergens that collectively result in elevated total serum IgE levels. This group is also at greatest risk for developing other atopic diseases and are thought to have the greatest epidermal barrier defect.¹ Much of this barrier function resides within the cells that comprise the outer layer of the epidermis, called the stratum corneum (SC). The SC has been likened to a brick wall, consisting of terminally differentiated keratinocytes or corneocytes (bricks), which are surrounded by a matrix of specialized lipids (mortar). AD barrier dysfunction was first suspected as having a genetic basis when genome-wide studies identified linkage to the epidermal differentiation complex (EDC) on chromosome 1q21 (ATOD2).² In a landmark paper by Palmer and colleagues published in 2006, two null mutations in an EDC gene - namely, filaggrin (*FLG*) - were identified and shown to be strongly linked to the phenotype of AD and asthma-associated AD, whereas no associations were observed with psoriasis, another inflammatory skin disease with EDC (1q21-PSORS4) linkage.³ As addressed in this newsletter, Sandilands and associates demonstrated the robustness of these findings by confirming this association in several primarily European populations.

The articles by Nemoto-Hasebe and coworkers and Jakasa and colleagues, reviewed in this issue, help to validate the AD barrier defect theory. Kim and associates and Weidinger et al. highlight the fact that additional epithelial genes may play a role in this barrier abnormality. Howell and colleagues demonstrate that some of these barrier proteins are regulated on a genetic as well as on an environmental basis.

References

1. Cork MJ, Robinson DA, Vasilopoulos Y, et al. [New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions.](#) *J Allergy Clin Immunol.* 2006;118(1):3-21

 LISTEN TO OUR PODCAST

 RECOMMEND TO A COLLEAGUE

 NEWSLETTER ARCHIVE

 LISTEN TO OUR PODCAST

2. Cookson WO, Ubhi B, Lawrence R, et al. [Genetic linkage of childhood atopic dermatitis to psoriasis susceptibility loci](#). *Nat Genet.* 2001;27(4):372-373.
3. Palmer CNA, Irvine AD, Terron-Kwiatowski, et al. [Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis](#). *J Am Acad Dermatol.* 2006;38(4):441-446.

FILAGGRIN MUTATIONS ASSOCIATED WITH ATOPIC DERMATITIS AND ICHTHYOSIS VULGARIS

Sandilands A, Terron-Kwiatowski A, Hull PR, 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.

(For non-journal subscribers, an additional fee may apply for full text articles.)



[View journal abstract](#)



[View full article](#)

Filament aggregation protein (filaggrin) is a critical protein thought to play an important role in the barrier function of the stratum corneum. Two publications in 2006 identified 2 relatively common filaggrin (*FLG*) null mutations strongly associated with AD or with the most common genetic ichthyotic disorder, ichthyosis vulgaris (IV), in Northern European populations.^{1, 2} Since that time, these results have been replicated in multiple European AD populations, and different *FLG* mutations have been found among Asian AD populations. The goal of Sandilands' 2007 study was to comprehensively evaluate additional ethnic populations (Dutch, Austrian, and Irish) with IV and/or AD for both known and unique mutations in *FLG*. The large, repetitive *FLG* exon 3 was targeted for sequencing using a combination of long-range polymerase chain reaction (PCR) and numerous primer pairs, because of significant base polymorphism in the 10 to 12 full-tandem *FLG* repeats located within this exon.

This approach identified 3 novel but rare null mutations, several nonsense or frameshift mutations, as well as confirmed the 2 originally described null mutations (R501X and 2282del4). Five of these *FLG* mutations were observed even in a population of Irish controls (n=736), with a combined minor allele frequency (MAF) of 0.039. The MAF is the frequency of the less common (eg, *FLG* null mutations) allele in a polymorphic locus and can range from 0 to 0.5. In contrast, Irish children with dermatologist-diagnosed moderate to severe AD had a significant increase in their combined MAF to 0.287. Analysis of the combined allele frequency between Irish controls and AD cohorts yielded a chi-squared (χ^2) test with a P value of 2.12×10^{-51} . In general, the more 3' mutations were not a significant as those observed for the mutations in exon 1 (eg. R501X and 2282del4).

In summary, this study has highlighted the importance of gene sequencing in identifying both common and rare *FLG* gene variants, many of which might not have been identified by single nucleotide polymorphisms. This investigation brings the number of known *FLG* mutations associated with AD to 15. An unanswered question is why the frequency of some of the null mutations is so high, even among control (ie, clinically unaffected) populations. The authors speculate that these mutations may have developed because they provide an evolutionary advantage to the host, allowing for a "natural vaccination" to microbial antigens through a leaky epithelium. It is important to note that little is known about the role that these *FLG* mutations play in populations of African descent and in European Americans. Interestingly, a recent publication reports the complete lack of association between the 2 most common null mutations (R501X and 2282del4) in an Italian AD population, providing additional support for the polymorphic nature of this gene among different racial and ethnic groups.³

References

1. Palmer CN, Irvine AD, Terron-Kwiatowski A, et al. [Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis](#). *Nat Genet.* 2006 Apr;38(4):441-446.

 RECOMMEND TO A COLLEAGUE

 NEWSLETTER ARCHIVE

 LISTEN TO OUR PODCAST

