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JOURNAL SCAN

SUMMARY OF KEY ARTICLES

Exploring the Role of Genetics in Atopic Dermatitis

INTRODUCTION BY LAWRENCE F. EICHENFIELD, MD

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Journal of Allergy and Clinical Immunology	O'Regan GM, Sandilands A, McLean WH, Irvine AD. Filaggrin in atopic dermatitis. *J Allergy Clin Immunol.* 2008;122:689–693.
Journal of Allergy and Clinical Immunology	Henderson J, Northstone K, Lee SP, 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.
The Fall Clinical Dermatology Conference	Sugarman JL, Parish LJ. A topical physiologic, lipid-based, barrier repair formulation (EpiCeram® Emulsion) is highly effective monotherapy for moderate pediatric atopic dermatitis. Presented at: The Fall Clinical Dermatology Conference; October 16-19, 2008; Las Vegas, NV.
Journal of Investigative Dermatology	Nomura T, Akiyama M, Sandilands A, et al. Specific filaggrin mutations cause ichthyosis vulgaris and are significantly associated with atopic dermatitis in Japan. *J Invest Dermatol.* 2008;128:1436–1441.
Journal of Allergy and Clinical Immunology	Weidinger S, Baurecht H, Wagenpfeil S, et al. Analysis of individual and aggregate genetic contributions of previously identified serine peptidase inhibitor Kazal type 5 (SPINK5), kallikrein-related peptidase 7 (KLK7), and filaggrin (FLG) polymorphisms to eczema risk. *J Allergy Clin Immunol.* 2008;122:560–568.
Journal of Investigative Dermatology	Morar N, Cookson WO, Harper JI, Moffatt MF. Filaggrin mutations in children with severe atopic dermatitis. *J Invest Dermatol.* 2007;127:1667–1672.

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INTRODUCTION

Exploring the Role of Genetics in Atopic Dermatitis

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New research insights concerning genetic mutations associated with atopic dermatitis are improving our understanding of cutaneous barrier dysfunction and fueling new approaches to therapy in the pathophysiology of atopic dermatitis. Recent scientific investigations have identified filaggrin mutations as one predisposing risk factor for patients with atopic dermatitis, and suggest that there are other genetic mutations that are risk factors for atopic dermatitis, as well, and others that are not. Several mutations track to a complex of genes involved in the formation of essential components of the epidermis. These findings support the theory that a dysfunctional skin barrier is a factor in the pathophysiology of atopic dermatitis. Traditional therapy—topical steroids and immunodulators—are used effectively as anti-inflammatory agents, but have cutaneous and systemic effects or risks that create concerns amongst patients and prescribing physicians. A novel treatment option has been introduced that specifically addresses the cutaneous barrier dysfunction of atopic dermatitis.

Basic research has demonstrated that atopic dermatitis evolves in large part from structural and functional defects in the skin's permeability barrier, or stratum corneum. Once considered a biologically inert layer of dead skin cells, the stratum corneum has been shown to be a metabolically and biochemically active structure.

Recognition that atopic dermatitis has a strong genetic component has stimulated research aimed at identifying variants that might underlie the barrier dysfunction that characterizes atopic dermatitis. In particular, many investigators have begun to focus on chromosome 1q21, a region that comprises genes involved in the formation of essential components of the epidermis.[1]

Loss-of-function mutations in the structural protein filaggrin have been identified as a major risk factor for atopic dermatitis.[2] The discovery followed insights gained into the genetics of ichthyosis vulgaris, the most common of the ichthyotic disorders.

Indirect evidence had implicated the filaggrin gene (*FLG*) variants in ichthyosis for more than 20 years. Ultimately, the loss-of-function *FLG* mutations R501X and 2282del4 were identified in studies that revealed a semidominant pattern of inheritance and incomplete penetrance.[3] Subsequently, multiple other mutations have been identified, and population-specific patterns of mutations have emerged in different populations throughout the world. However, R501X and 2282del4 remain the most common variants identified to date.

Better understanding of the mechanisms of atopic dermatitis has given rise to investigation of new approaches to treatment that address more specifically the underlying barrier dysfunction. Research focusing on atopic barrier dysfunction, conducted at University of California, San Francisco, produced EpiCeram® Emulsion, a multi-lipid, ceramide-dominant emulsion designed to address the barrier abnormality associated with atopic dermatitis.

In a clinical trial, the multi-lipid, ceramide-dominant emulsion demonstrated comparable efficacy to a mid-potent topical steroid in patients with mild to moderate atopic dermatitis at day 28 of treatment.[4] The results suggest that a proper treatment strategy based on correction of barrier dysfunction could replace the use of glucocorticoids and immunomodulators in mild to moderate atopic patients.

The R501X and 2282del4 variants in the *FLG* gene account for 18% to 48% of atopic dermatitis cases.[5] Clearly, other mutations, environmental factors, or as-yet unidentified triggers contribute to the worldwide burden of atopic dermatitis. This *Journal Scan* supplement to SKIN & ALLERGY NEWS summarizes some of the recent studies that have continued the exploration of potential genetic causes of atopic dermatitis. The review includes a summary of recent clinical investigation into a therapy that has evolved from improved understanding of the role of skin barrier dysfunction in atopic dermatitis. ■

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Filaggrin Variants and Susceptibility to Atopic Dermatitis

The structural protein filaggrin plays a major role in the formation and maintenance of the skin's cornified envelope, or barrier. In response to deficiency, injury, or environmental insults, the barrier's protective proteins, including filaggrin, might be upregulated to maintain barrier integrity.

Recently, loss-of-function mutations in filaggrin have been identified as a major risk factor for atopic dermatitis. The discovery has provided much-needed insight into the underlying mechanisms of atopic dermatitis, the etiology and pathogenesis of which previously had been viewed primarily as a consequence of immunologic dysfunction.

O'Regan et al have summarized developments in understanding the contributions of filaggrin genetics in the pathogenesis of atopic dermatitis.

Table 1. Putative Filaggrin Function

- Hydration through hygroscopic amino acids
- Possible contribution to acid mantle through amino acid degradation
- Filament binding and barrier integrity
- Profilaggrin: nonfunctional pro-protein

Source: Adapted from O'Regan GM, Sandilands A, McLean WH, Irvine AD. Filaggrin in atopic dermatitis. *J Allergy Clin Immunol*. 2008;122:689-693.

Filaggrin Expression and Function

During formation of the cornified cell envelope, the inactive precursor profilaggrin is dephosphorylated and cleaved to release copies of the functional *FLG* repeat peptide units. Subsequently, within the stratum corneum, the filaggrin peptide is enzymatically degraded into hydrophilic amino acids, their metabolites, and ions that constitute natural moisturizing factor (NMF), which helps maintain hydration in the stratum corneum.

Expression of *FLG* and activation of hydrolysis of filaggrin peptides into NMF also are influenced by the stratum corneum microenvironment, including local pH, external humidity, and transepidermal water loss.

FLG Mutations and Atopic Dermatitis

As O'Regan and colleagues noted, the role of *FLG* mutations in susceptibility to atopic dermatitis evolved from evidence implicating similar mutations in ichthyosis vulgaris, the most common of the ichthyotic disorders. In particular, identification of two loss-of-function mutations (R501X and 2282del4) revealed a semidominant pattern of inheritance.

Over the past 2 years, dozens of *FLG* mutations have been identified, each predicting nonsense or out-of-frame deletion/insertion mutations. Population-specific patterns have emerged worldwide. Among European populations, for example, 20 mutations have been identified, six of which are prevalent. An additional 17 mutations have been revealed in Asian populations, including eight prevalent mutations.

Table 2. Molecular Control of Filaggrin Homeostasis

- Dephosphorylation in the presence of increasing calcium concentrations
- Proteolytic cleavage by matriptase and CAP1/prss
- Filaggrin B domain location to the nucleus as part of terminal differentiation
- Free filaggrin protein cross-linked to keratin filaments by transglutaminases
- Posttranslational modification by caspase 14

Source: Adapted from O'Regan GM, Sandilands A, McLean WH, Irvine AD. Filaggrin in atopic dermatitis. *J Allergy Clin Immunol*. 2008;122:689-693.

The contributions of *FLG* mutations to atopic dermatitis have been confirmed in recent studies. One study involving 3,000 German children showed that the presence of FLG variants tripled the relative risk of atopic dermatitis, as compared with children who did not have the variants.

FLG Mutations and Atopic Dermatitis Mechanisms

O'Regan et al pointed out that the mechanistic pathways from *FLG* mutations to inflammatory atopic dermatitis have yet to be completely elucidated. *FLG* deficiency leads to reduced levels of NMF. Triggers for the inflammatory response remain unclear, however. About 40% of all carriers of *FLG*-null alleles develop no signs of atopic dermatitis.

Speculation about the mechanisms of atopic dermatitis includes modification of pH-related commensal bacteria expression; altered immunity that predisposes the skin to bacterial colonization and infection; and reduced activity of key lipid-processing enzymes, leading to disruption of the permeability barrier.

Conclusions

O'Regan et al concluded that *FLG* mutations have a predisposing effect on the early inflammatory activity associated with atopic dermatitis. Identification of these mutations has raised the possibility of targeted intervention and therapy. Environmental and genetic factors that interact with *FLG*-null alleles to initiate pathogenesis offer a promising area for investigations aimed at identifying specific triggers of atopic dermatitis. ■

Based on O'Regan GM, Sandilands A, McLean WH, Irvine AD. Filaggrin in atopic dermatitis. *J Allergy Clin Immunol.* 2008;122:689–693.

Impact of Prevalent FLG Mutations on Atopic Dermatitis Risk

The recognition that mutations in the filaggrin gene (*FLG*) greatly increase susceptibility to atopic dermatitis created a vast potential for research to characterize with greater certainty the mechanistic pathways involved in the disease.

Dozens of population-specific *FLG* mutations have been linked to atopic dermatitis and to asthma. However, the R501X and 2282del4 variants are the two most common null alleles associated with atopic dermatitis. Henderson and colleagues recently reported findings from an investigation designed to characterize and quantify the impact of these two variants in a population of 7,000 children born in England during 1990 to 1991.

Methods

The study comprised offspring of women recruited into the Avon Longitudinal Study of Parents and Children. The mothers were asked to complete and return mailed questionnaires about the children's health status at 6, 18, 30, 42, 54, 69, and 81 months after birth. The questionnaires included items about skin rashes on joints or creases of the body and about symptoms suggestive of asthma.

Table 1. Association of FLG Genotype with Eczema and Early Wheeze

	AA	Aa	aa*
Eczema, no early wheeze	629/2,809	94/231	3/3
Odds Ratio	1.00	2.38	∞
Eczema plus early wheeze	602/2,782	114/254	3/3
Odds Ratio	1.00	3.01	∞
Early wheeze, no eczema	1,385/3,565	108/245	0/0
Odds Ratio	1.00	1.24	

* AA=wild type; Aa=heterozygote; aa=homozygote

Source: Adapted from Henderson J, Northstone K, Lee SP, 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.

From ages 7 to 11 years, the children had annual clinic visits that included assessments for the presence of flexural dermatitis. Trained observers noted lesions >3 cm in diameter in specific locations: around the eyes and the sides or front of the neck; in front of the elbows; behind the knees; or in front of the ankles.

The children's atopic status was determined by skin prick tests at 7 to 8 years of age. Atopy was defined as a wheal >1 mm. The children were genotyped for the *FLG* variants R501X and 2282del4.

Results

Henderson and colleagues reported that the *FLG* null alleles were associated with flexural dermatitis at all questionnaire time points and at all observed time points. The alleles had strong associations with atopic and nonatopic dermatitis, but the association was stronger for atopic dermatitis (P=0.0023).

Table 2. Population-Attributable Risk (PAR) of Eczema and Asthma Phenotypes

(Combined genotype AA, Aa; prevalence=0.088)

	PAR
Atopic eczema	15.1%
Nonatopic eczema	6.9%
Atopic asthma	9.6%
Nonatopic asthma	3.3%
Eczema plus asthma	15.5%
Eczema plus early wheeze	16.6%

Source: Adapted from Henderson J, Northstone K, Lee SP, 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.

The R501X and 2282del4 alleles also correlated with disease trajectory and persistence. In a subgroup of children with disease persistence beyond 42 months, those with FLG mutations had an average persistence of 76.7 months versus 65.6 months among children without the mutations.

A survival analysis based on follow-up until disease clearance yielded a hazard ratio of 0.67 for children with the mutations compared with those who did not have the mutations. The result provided strong evidence that children with the *FLG* mutations are much less likely to "grow out of" atopic dermatitis.

The *FLG* null alleles also predisposed the children to asthma (odds ratio, 1.80; P=0.00019), and the association was stronger for atopic versus nonatopic asthma. Notably, the association with asthma existed only in children who had coexisting atopic dermatitis (odds ratio, 3.16). The null alleles did not predispose to asthma alone (odds ratio, 0.80). The *FLG* variants also increased the likelihood of early wheeze.

The null alleles had a strong association with sensitization to grass, house dust mites, and cat dander, and to multiple allergens (odds ratio, 2.12).

Conclusions

Henderson and colleagues concluded that *FLG* mutations constitute strong genetic determinants of atopic dermatitis, early wheeze, asthma in the context of atopic dermatitis, and atopic sensitization. The null alleles confer risk of a disease trajectory that includes increased duration of disease and increased risk of asthma and multiple allergic sensitizations. *FLG* mutations help define a risk profile for children with atopic dermatitis, as well as the "atopic dermatitis plus early wheeze" and "atopic dermatitis plus asthma" phenotypes. ■

Based on Henderson J, Northstone K, Lee SP, 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.

EpiCeram® Emulsion, A Multi-Lipid, Ceramide-Dominant Emulsion, Demonstrates Comparable Efficacy To A Mid-Potent Topical Steroid for Atopic Dermatitis Control

Current therapy for atopic dermatitis includes use of topical steroids and immunomodulators, which may be associated with potentially unacceptable long-term side effects. The limitations of existing therapies have created a need for other therapeutic options. EpiCeram® Emulsion, a multi-lipid, ceramide-dominant emulsion, is a new product with potential to fill the therapeutic void.

It is theorized that atopic dermatitis evolves from inherited defects in the structure and function of the permeability barrier (an outside-in pathophysiology). The defects are characterized by abnormalities in the lipid content of the barrier, specifically ceramides, cholesterol, and free fatty acids. The multi-lipid, ceramide-dominant emulsion delivers an optimal 3:1:1 ratio of ceramides, cholesterol, and free fatty acids that helps to restore normal barrier function and control the signs and symptoms of atopic dermatitis.

Recently, Sugarman and Parish reported results of a randomized clinical trial that compared the multi-lipid, ceramide-dominant emulsion (EpiCeram® Emulsion) with fluticasone cream (Cutivate Cream) in patients with atopic dermatitis.

Methods

The study involved patients ages 6 months to 18 years, who had mild to moderate atopic dermatitis. The patients were randomized to 4 weeks of twice daily treatment with the multi-lipid, ceramide-dominant emulsion or fluticasone cream 0.05%. The primary outcome measures were the change from baseline to week 4 in disease severity (measured by the Scoring Atopic Dermatitis [SCORAD] index), pruritus, and sleep habits. Investigators were blinded to treatment assignment.

Results

Investigators randomized 121 patients ages 6.5 months to 18 years, however, 23 patients were ≤2 years, and all but eight patients completed the trial. Baseline SCORAD severity was 36.6 among patients assigned to the multi-lipid, ceramide-dominant emulsion group and 33.4 among those treated with fluticasone cream. Outcomes were assessed at 14 and 28 days.

Table 1. Statistical Comparisons of Responses to EpiCeram® and Fluticasone

	Mean Reduction from Baseline	
SCORAD	**EpiCeram (%)**	**Fluticasone (%)**
Day 14	15.42 (41.5)	19.39 (61.2)
	Anova P=0.0051[1]; Rank sum P=0.1227[2]	
Day 28	20.75 (56.4)	22.64 (68.8)
	Anova P=0.0679[2]; Rank sum P=0.5000[2]	

[1]Significant difference between treatments; [2]No significant differences between treatments

Pruritus	**EpiCeram**	**Fluticasone**
Day 14	2.5[1]	3.1[1]
Day 28	3.5[2]	3.7[2]

[1]Rank sum P=0.30; [2]Rank sum P>0.50; No significant differences

Sleep Habits	**EpiCeram**	**Fluticasone**
Day 14	1.9[1]	2.4[1]
Day 28	2.6[2]	2.8[2]

[1]Rank sum P=0.39; [2]Rank sum P>0.50; No significant differences

SCORAD (%>75% improvement)	**EpiCeram**	**Fluticasone**
Day 14	4[1]	20[1]
Day 28	21[2]	26[2]

[1]Chi-Squared P<0.0005; [2]No significant differences

Source: Adapted from Sugarman JL, Parish LJ. A topical physiologic, lipid-based, barrier repair formulation (EpiCeram® Emulsion) is highly effective monotherapy for moderate pediatric atopic dermatitis. Presented at: The Fall Clinical Dermatology Conference; October 16-19, 2008; Las Vegas, NV.

By the end of the study, the two treatments had achieved similar reduction in SCORAD: 56.4% with the lipid-based emulsion versus 68.8% with the topical steroid (P=0.0679), and there was no difference in the proportion of patients in each group who had >75% improvement in the SCORAD index (P>0.500). At the 14-day assessment, SCORAD scores had improved by an average of 41.5% with the lipid-based emulsion and by 61.2% with fluticasone cream (P=0.0051). The treatment groups had similar improvement in pruritus and sleep habits at both assessments.

Conclusions

The authors concluded that the multi-lipid, ceramide-dominant emulsion (EpiCeram® Emulsion) offers effective monotherapy for mild to moderate atopic dermatitis. As such, the results suggest a new therapeutic paradigm based on use of targeted lipid-replacement therapy, which could reduce requirements for topical steroids or immunomodulators. ■

Based on Sugarman JL, Parish LJ. A topical physiologic, lipid-based, barrier repair formulation (EpiCeram® Emulsion) is highly effective monotherapy for moderate pediatric atopic dermatitis. Presented at: The Fall Clinical Dermatology Conference; October 16-19, 2008; Las Vegas, NV.

Exploring Population-Specific Genetics of Atopic Dermatitis

Multiple studies have established that mutations in the gene encoding filaggrin (*FLG*) cause ichthyosis vulgaris and predispose individuals to atopic dermatitis. Most of the studies to date have been carried out in European populations. As a result, the extent to which *FLG* mutations contribute worldwide to atopic dermatitis has remained unclear.

Nomura et al examined the role of *FLG* mutations in a Japanese population. However, the investigation focused on individuals with ichthyosis vulgaris.

This study followed previous work by the same group that led to identification of two Oriental-specific *FLG* mutations in Japanese families with ichthyosis vulgaris. Nomura et al concentrated on patients with ichthyosis vulgaris, in whom potential carriers of *FLG* mutations could be readily identified. After identifying the mutations, rapid genotyping tests were developed to study population-wide incidence and associations with atopic dermatitis.

Methods

Investigators examined blood samples from 23 Japanese patients representing seven families with ichthyosis vulgaris. Additionally, samples from 102 unrelated patients with atopic dermatitis were evaluated. Genotyping was performed in patients and family members.

Results

Genotyping revealed the two previously identified Oriental-specific *FLG* mutations in five of the seven families. Probands for the remaining two families were of the wild type for both mutations.

Nomura and colleagues conducted comprehensive sequencing of *FLG*, using recently developed polymerase chain reaction technology. The work led to identification of a new paternal *FLG* mutation in the proband of one of the two families originally identified as having the wild-type mutation. Additionally, sequencing identified another mutation.

The 102 patients with atopic dermatitis were screened for the two previously identified Oriental-specific *FLG* mutations and for the two new mutations identified in the patients with ichthyosis vulgaris. All four mutations were found in families of the atopic dermatitis cohort.

Table 1. Case-Control Association Analysis for *FLG* Null Variants S2554X and S2889X

	S2554X		S2889X	
Genotypes	**Controls**	**Cases**	**Controls**	**Cases**
AA	132	96	131	92
Aa	1	6	2	10
aa	0	0	0	0
Totals	133	102	133	102
X^2	$P=0.022$		$P=0.004$	

Source: Adapted from Nomura T, Akiyama M, Sandilands A, et al. Specific filaggrin mutations cause ichthyosis vulgaris and are significantly associated with atopic dermatitis in Japan. *J Invest Dermatol.* 2008;128:1436-1441

Table 2. Case-Control Association Analysis for *FLG* Null Variants S3296X and 3321delA

	S3296X		S3321delA	
Genotypes	**Controls**	**Cases**	**Controls**	**Cases**
AA	133	99	132	98
Aa	0	3	1	4
aa	0	0	0	0
Totals	133	102	133	102
X^2	$P=0.022$		$P=0.004$	

Source: Adapted from Nomura T, Akiyama M, Sandilands A, et al. Specific filaggrin mutations cause ichthyosis vulgaris and are significantly associated with atopic dermatitis in Japan. *J Invest Dermatol.* 2008;128:1436-1441

More than 20% of the patients with atopic dermatitis carried one or more of the *FLG* mutations. In contrast, evaluation of a control population without atopic dermatitis revealed a 3% prevalence of the mutations. The investigators found a highly significant association between the four mutations and atopic dermatitis ($P=8.4 \times 10\text{-}6$).

Conclusions

Nomura and colleagues identified two *FLG* mutations specific to the Japanese population. The results increased the number of known prevalent mutations among Japanese to four.

The authors further concluded that *FLG* null variants likely play a predisposing role in the development of atopic dermatitis in various populations worldwide. They suggested that future studies should focus on the overall contribution of the *FLG* gene to atopy and the associated global health care burden. ■

Based on Nomura T, Akiyama M, Sandilands A, et al. Specific filaggrin mutations cause ichthyosis vulgaris and are significantly associated with atopic dermatitis in Japan. *J Invest Dermatol.* 2008;128:1436–1441.

Genetics of Atopic Dermatitis: Beyond Filaggrin Variants

Filaggrin has a central role in maintaining skin barrier integrity and function. Mutations in the filaggrin gene (*FLG*), including two prevalent variants and several rare ones, confer a strong risk for atopic dermatitis and allergen sensitization.

Evidence linking *FLG* mutations to atopic dermatitis suggest that the breakdown of the epidermal skin barrier is a primary event in the development of the disease. A weakness in the barrier might allow greater penetration of antigens, allergens, and environmental irritants, potentially predisposing an individual to allergic sensitization and abnormal responses to infection.

Despite a strong association with atopic dermatitis, *FLG* mutations provide only a partial accounting for pathogenesis. Weidinger et al recently examined the potential contributions of variants in two genes involved in the conversion of profilaggrin to filaggrin: serine peptidase inhibitor Kazal type 5 gene (*SPINK5*) and the kallikrein-related peptidase 7 gene (*KLK7*).

SPINK5 encodes a serine protease inhibitor that might be involved in regulating stratum corneum chymotryptic enzyme (SCCE), a protease implicated in profilaggrin processing. KLK7 encodes SCCE and previously has been implicated in the etiology and pathogenesis of atopic dermatitis.

Table 1. Associations Between Polymorphisms and Eczema

	Gene	Polymorphism	OR
German	*FLG*	Combined genotype (het vs wt)	4.15
Cases: 773		Combined genotype (hom vs wt)	23.11
Control subjects: 3992	*SPINK5*	rs2303067 (het vs wt)	1.14
Total: 4765		rs2303067 (hom vs wt)	1.22
	KLK7	AACC ins (het vs wt)	1.11
		AACC ins (hom vs wt)	0.95
Irish/English	*FLG*	Combined genotype (het vs wt)	4.34
Cases: 418		Combined genotype (hom vs wt)	2.6×10^{56}
Control subjects: 552	*SPINK5*	rs2303067 (het vs wt)	0.78
Total: 970		rs2303067 (hom vs wt)	1.15
	KLK7	(het vs wt)	1.29
		(hom vs wt)	0.91
ALSPAC	*FLG*	Combined genotype (het vs wt)	2.17
Cases: 1583		Combined genotype (hom vs wt)	3.3 x 106
Control subjects: 6063	*SPINK5*	rs2303067 (het vs wt)	0.96
Total: 7646		rs2303067 (hom vs wt)	1.14
Pooled	*FLG*	Combined genotype (het vs wt)	3.04
Cases: 2774		Combined genotype (hom vs wt)	49.38
Control subjects: 10,607	*SPINK5*	rs2303067 (het vs wt)	0.97
Total: 13.381		rs2303067 (hom vs wt)	1.13

Source: Adapted from Weidinger S, Baurecht H, Wagenpfeil S, et al. Analysis of individual and aggregate genetic contributions of previously identified serine peptidase inhibitor Kazal type 5 (*SPINK5*), kallikrein-related peptidase 7 (*KLK7*), and filaggrin (*FLG*) polymorphisms to eczema risk. *J Allergy Clin Immunol.* 2008;122:560-568.

Methods

Variants of *SPINK5*, *KLK7*, and *FLG* were typed in several cohorts: 486 unrelated patients from a German family-based study; an additional 287 German patients with atopic dermatitis; and 418 unrelated Irish and English patients with atopic dermatitis. Additionally, the investigators examined the *SPINK5* 420LysSer polymorphism and the R501X and 2282del4 *FLG* mutations in 1,583 patients with atopic dermatitis in a longitudinal English study.

Results

The authors found no associations with atopic dermatitis for *SPINK5* or *KLK7* in a case-control analysis. They found a weak association for the *SPINK5* variant with maternal transmission in the family-based study. They found no interactions among polymorphisms in *KLK7*, *SPINK5*, and *FLG*.

Table 2. Summary of Key Findings

- The *SPINK5* Lys420Ser polymorphism confers a risk of eczema when maternally inherited, but is not a major genetic contributor to eczema risk.
- A previously reported association of a *KLK7* insertion and eczema could not be confirmed.
- There is no evidence for epistatic effects between *KLK7* or SPINK5 variants and *FLG* mutations.

Source: Adapted from Weidinger S, Baurecht H, Wagenpfeil S, et al. Analysis of individual and aggregate genetic contributions of previously identified serine peptidase inhibitor Kazal type 5 (*SPINK5*), kallikrein-related peptidase 7 (*KLK7*), and filaggrin (*FLG*) polymorphisms to eczema risk. *J Allergy Clin Immunol.* 2008;122:560-568.

Conclusions

The *SPINK5* 420LysSer variant confers a risk of atopic dermatitis limited to maternal inheritance, making the mutation a minor risk factor. The authors found no evidence to confirm the previously reported association between a *KLK7* insertion variant and atopic dermatitis. The analyses revealed no interactions among *SPINK5*, *KLK7*, and the *FLG* mutations.

Weidinger and colleagues called for functional studies to explore the roles of individual gene products within the filaggrin pathway and their interactions. Large-scale studies with adequate statistical power are needed to elucidate relationships between polymorphism combinations and atopic dermatitis susceptibility. ■

Based on Weidinger S, Baurecht H, Wagenpfeil S, et al. Analysis of individual and aggregate genetic contributions of previously identified serine peptidase inhibitor Kazal type 5 (*SPINK5*), kallikrein-related peptidase 7 (*KLK7*), and filaggrin (FLG) polymorphisms to eczema risk. *J Allergy Clin Immunol.* 2008;122:560–568.

Common FLG Variants Provide Incomplete Explanation of Atopic Dermatitis Genetics

Studies have demonstrated a strong genetic component to atopic dermatitis. The linkage tracks to chromosome 1q21, which contains the epidermal differentiation complex. The complex consists of genes involved in the formation of essential components of the epidermis, including the filaggrin gene (*FLG*).

The R501X and 2282del4 variants of *FLG* increase susceptibility to atopic dermatitis and coexisting asthma. Morar et al examined the impact of the *FLG* mutants in families of children with and without atopic dermatitis. The study population provided an opportunity to characterize the effects of *FLG* mutations in children sharing common genetic and environmental backgrounds.

Table 1. Association Between FLG Mutations (Compound Genotype) and Atopic Dermatitis

	P-value	OR
FLG501X	0.001	2.55
FLG2282del4	0.004	1.93
Compound genotype	<0.001	2.03

Source: Adapted from Morar N, Cookson WO, Harper JI, Moffatt MF. Filaggrin mutations in children with severe atopic dermatitis. *J Invest Dermatol.* 2007;127:1667-1672.

Methods

Investigators recruited panels of families who have children with atopic dermatitis. The children received care at a tertiary referral center and represented the most severe end of the disease spectrum. The authors noted that such patients often prove resistant to therapy, and approximately 60% have coexisting asthma.

Affected and unaffected children came from the same families, allowing investigation of potential factors that predispose some children to atopic dermatitis and asthma; whereas, siblings have no such predisposition.

Results

The study population comprised a total of 426 families and 990 children with and without atopic dermatitis. Investigators genotyped all of the families.

Genotyping revealed *FLG* mutations in 26.7% of children with atopic dermatitis, but also in 14.4% of children without the disease. The R501X and 2282del4 mutations had significant association with atopic dermatitis ($P=0.0001$), asthma ($P=0.006$), and atopy ($P=0.002$). The mutations had only a weak association with disease severity.

Table 2. Association Between FLG Mutations and Atopic Dermatitis

	P-value	OR
Atopic children	<0.001	2.28
Non-atopic children	0.45	1.29

Source: Adapted from Morar N, Cookson WO, Harper JI, Moffatt MF. Filaggrin mutations in children with severe atopic dermatitis. *J Invest Dermatol.* 2007;127:1667-1672.

The overall logarithmetic odds (LOD) score for genetic linkage of markers to the 1q21 region was 3.57. However, the LOD score decreased to 2.03 after accounting for *FLG* mutations, indicating the presence of other genetic variants that influence atopic dermatitis susceptibility at the locus.

Conclusions

Morar and colleagues concluded that their findings confirmed the importance of *FLG* mutations in the pathogenesis of atopic dermatitis. However, the results also demonstrated the need to investigate other genes within the epidermal differentiation complex as potential contributors to the development of atopic dermatitis. ■

Based on Morar N, Cookson WO, Harper JI, Moffatt MF. Filaggrin mutations in children with severe atopic dermatitis. *J Invest Dermatol.* 2007;127:1667–1672.