New Insights into Atopic Dermatitis
Skin Barrier Abnormalities and Implications for an Atopic March

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Eczema Prevalence in the United States


Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three

Atopic March and beyond: The prevalence of atopic triad in children with physician-confirmed atopic dermatitis

- In the largest cross-sectional study of a cohort of 2270 children with diagnosis of AD confirmed by physician and treated for a minimum of 6 wks with topical prescription product for their AD:
  - nearly 66% had symptoms of asthma or allergic rhinitis and 38% had both associated with their AD
  - nearly 80% reported some additional allergic illness (asthma, allergic rhinitis, seasonal allergy, food allergy, animal allergy, or drug allergy) by the third year of life
- Results differ from previous studies in that prevalence rates of asthma and allergic rhinitis are higher and the onset is earlier i.e., if an additional illness is to be noted, it will be by the age of 3 years


Complex immune response to environment


... getting even more complex and exciting

![Diagram of immune response](J Allergy Clin Immunol 2006;118)
Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for AD

- Filaggrin (filament-aggregating protein) is a key protein that facilitates terminal differentiation of the epidermis and formation of the skin barrier
- FLG gene located on chromosome 1q21 in the EDC
- 2 loss-of-function genetic variants (R510X and 2282del4) in FLG shown to be very strong predisposing factors for AD
- These variants also show highly significant association with asthma occurring in the context of AD
- This data suggests a key role for impaired skin barrier function in development of atopic disease


Filaggrin in atopic dermatitis


Skin barrier function and allergic risk

Hudson TJ. Nature Genetics 2006;38:399
The burden of disease associated with filaggrin mutations: a population based, longitudinal birth cohort study

- To determine the natural history and burden of atopic disease conferred by the 2 most common FLG mutations in a large, population-based birth cohort study
- Analyzed the effect of the most common null alleles (R501X and 2282del4) on several atopic phenotypes in a cohort of approximately 7000 English children born in 1990-1991
- FLG null alleles associated strongly with eczema: eczema associated with these mutations presents in early life and is more persistent (hazard ratio for eczema resolution for those with FLG mutations to FLG wild type, 0.67; 95% CI, 0.58-0.77; P = 5 x 10^-8)


Persistence of eczema: time from first report of rash to first negative report of rash that was not followed by a positive report*

- AA/wild type for 2 mutations
- Aa/heterozygote for either mutation
- aa/homozygote for individual mutations (ie, R501X/R501X or 2282del4/2282del4) or compound heterozygote for each mutation (ie, 2282del4/R501X)
- *hazard ratio, 0.670; 95% CI, 0.58-0.77; P = 5 x 10^-8


- FLG mutations conferred a population asthma risk of 1.80 (95% CI, 1.34-2.41; P = .00019); asthma risk was especially high in the context of eczema (odds ratio, 3.16; 95% CI, 2.25-4.43; P = 1.4 x 10^-11)
- Strong associations were identified with sensitization to grass, house dust mite, and cat dander and sensitization to multiple allergens (odds ratio, 2.12; 95% CI, 1.03-4.37; P = 5.42 x 10^-27)
- FLG mutations confer risk of a particular trajectory for eczema, with increased duration of disease and greater risk of asthma and multiple allergic sensitizations
- FLG alleles help define the risk profile of children with eczema and help define the “eczema plus early wheeze” and “eczema plus asthma” phenotypes

Filaggrin gene variants and atopic diseases in early childhood assessed longitudinally from birth

- High-risk cohort of 411 European Caucasian children assessed in a prospective clinical study from birth to school-age
- FLG variants R501X and Del4 determined in 382 pts
- FLG variants increased risk of developing recurrent wheeze, asthma and asthma exacerbations (hazard ratio 1.82 [1.06-3.12], \( p = 0.03 \)), expressed within the first 1.5 yr of life
- Children with FLG variants had marked and persistent increase in acute severe asthma exacerbations from 1 yr of age (incidence ratio 2.40 [1.19–4.81], \( p = 0.01 \)) and increased risk of asthma by age 5 (odds ratio 2.62 [1.12–6.11], \( p = 0.03 \))


- FLG variants increased the risk of eczema, manifesting fully in the first year of life (point prevalence ratio for age 0–5 was 1.75 [1.29–2.37]; \( p = 0.0003 \)) contrasting the increased risk of specific sensitization by age 4 (odds ratio 3.52 [1.72–7.25], \( p = 0.0007 \)) but not age 1.5 yr
- This study describes a FLG-associated pattern of atopic diseases characterized by the early onset of asthma symptoms and eczema and later development of sensitization
- The association of filaggrin variants with asthma suggests skin barrier dysfunction as a novel, and potentially modifiable, mechanism driving early childhood asthma

Asthma related phenotype

Acute severe asthma exacerbations

Asthma point prevalence

Sensitization point prevalence
Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease

• FLG mutations significantly increase risk of
  – AD, odds ratio 3.12; 95% CI 2.57-3.79
  – Asthma, odds ratio 3.29; 95% CI 2.84-3.82
• Associated with more severe AD


Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis

• 24 studies
• Odds of developing allergic sensitization was 1.91 (95% CI 1.44 to 2.54) in family studies and 1.57 (1.20 to 2.07) in case-control studies

Filaggrin is a robust biomarker for allergic conditions


A homozygous frameshift mutation in the mouse Flg gene facilitates enhanced percutaneous allergen priming

• 1-bp deletion mutation 5303delA analogous to common human FLG mutations, within the murine Flg gene in the spontaneous mouse mutant flaky tail (ft)
• Topical application of allergen to mice homozygous for this mutation results in cutaneous inflammatory infiltrates and enhanced cutaneous allergen priming with development of allergen-specific antibody responses
• Supports hypothesis that antigen transfer through defective epidermal barrier is a key mechanism underlying elevated IgE sensitization and initiation of cutaneous inflammation in humans with FLG mutations

Allergen exposure exacerbates skin inflammation in ft/ft mice but not wt/wt or wt/ft mice


Eczematous skin lesions and serum IgE and IgG1 levels in ft/ft mice


**FLG**

- FLG null alleles occur in up to 50% of patients with moderate-severe AD suggesting a fundamental role for barrier homeostasis in this disease…
- While not the whole story, FLG mutations are the strongest and most widely replicated genetic risk factors for AD identified to date

Raman profiles* of the stratum corneum define 3 filaggrin genotype-determined atopic dermatitis endophenotypes

*Raman spectroscopy is capable of measuring in vivo information regarding the molecular composition of the skin, including quantitative analysis of amino acids and water content based on inelastic light (Raman) scattering of monochromatic light when the frequency of photons, usually from a laser source, changes on interaction with a sample, giving rise to characteristic Raman spectra and providing noninvasive real-time signatures of biological samples at a molecular level.

...getting even more complex and exciting

Buccal swab to ADx

Boguniewicz M, et al. In Pediatric Allergy 2010; 566
Cytokine modulation of atopic dermatitis filaggrin skin expression

Filaggrin deficiency in AD skin


Decreased filaggrin staining in AD skin


TH2 cytokines downregulate filaggrin gene expression

Different effects of pimecrolimus and betamethasone on the skin barrier in patients with atopic dermatitis

- 15 AD pts randomized to pimecrolimus (P) to one upper limb and betamethasone (B) to other 2x/day for 3 wks
- Stratum corneum (SC) hydration and TEWL improved and dye penetration reduced with both treatments
- EM evaluation of barrier structure showed prevalently ordered SC lipid layers and regular lamellar body extrusion in P-treated skin but inconsistent extracellular lipid bilayers and only partially filled lamellar bodies with B treatment
- Both drugs normalized epidermal differentiation and reduced epidermal hyperproliferation
- Decreased filaggrin restored with both treatments
- B was superior in reducing clinical symptoms and epidermal proliferation; however, it led to epidermal thinning


Recent insights into atopic dermatitis and implications for management of infectious complications

Increased susceptibility to infections or colonization with microbial organisms: Staphylococcus aureus, Herpes simplex


FLG mutations and Th2 polarization (Genetic variants in thymic stromal lymphopoietin are associated with AD & EH)

- A critical link between barrier defect in AD patients with FLG mutations and Th2 polarization could be explained in part by enhanced allergen penetration through the damaged epidermis accompanied by increased production of TSLP* by keratinocytes leading to a Th2-type milieu
- Significant associations for TSLP and IL7R tagging SNPs and AD and ADEH in European Americans with replication of associations between TSLP and IL7R SNPs in an independent African American sample

ADRN S. aureus related research

Research area 2: Susceptibility to staphylococcal colonization and infections, including MRSA

• Clinical Mechanistic Studies:
  – Identification of genetic determinants for bacterial dissemination in ethnically diverse patients with AD
  – Identification of epidermal barrier defects that predispose AD subjects to colonization with S. aureus
  – Exploratory studies on PBMC immunoprofiles in AD subjects with and without bacterial colonization

• Clinical Trial:
  – AD, innate immunity and vitamin D

• Animal Mechanistic Study:
  – S. aureus, innate immunity and vitamin D in mouse models

Research area 3: Susceptibility to colonization and/or infection with other commensal organisms

• Clinical Mechanistic Study of the skin microbiome in AD patients to understand the susceptibility to colonization and/or infection with other commensal organisms

Registry & Repository of Biological Specimens

• S. aureus repository

Proactive therapy of atopic dermatitis - an emerging concept

• Proactive therapy is an attempt to control residual disease with minimal use of anti-inflammatory drugs and not the application of an active drug to non-involved skin

• The choice of a proactive therapy regimen is favored by immunological data, clinical efficacy data, quality of life data and pharmacoeconomic data in the case of the more severely affected patients

Boguniewicz M, et al. In Pediatric Allergy 2010; 566

Wollenberg A, Bieber T. Allergy 2009;64:276
Intermittent topical fluticasone propionate

- After stabilization of AD with daily therapy, FP applied to areas of previous involvement that appeared visually normal as maintenance therapy 2x/week in adult and pediatric patients, suggesting better disease control with less need for topical steroids vs reactive therapy for flares

Intermittent therapy for flare prevention and long-term disease control in stabilized atopic dermatitis: A randomized comparison of 3-times-weekly applications of tacrolimus ointment versus vehicle

Kaplan-Meier plot of probability of remaining free from relapse

Interruption therapy for flare prevention and long-term disease control in stabilized atopic dermatitis: A randomized comparison of 3-times-weekly applications of tacrolimus ointment versus vehicle


Number of disease relapses


Boguniewicz M, et al. In Pediatric Allergy 2010; 566