The Role of Skin Barrier Function in the Atopic March

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Disclosures

Work presented today was funded by the NIH

Outline

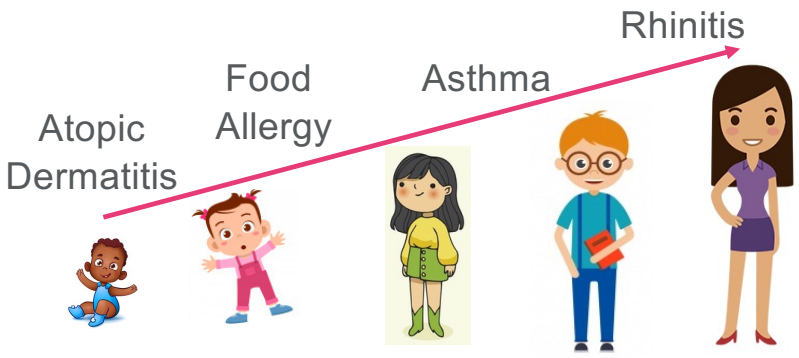
- Background
- MPAACH cohort
- Identify longitudinal phenotypes and endotypes of AD in Black and White children.
- Novel mechanisms that are critical for barrier homeostasis.
- New longitudinal data and insights into microbiome.

Atopic Dermatitis (AD)

- AD is a chronic relapsing inflammatory skin disease
- Affects 15-30% of children, 2-10% of adults
  - Mostly begins in the first year of life
- Up to 70%: spontaneous remission before adolescence

NEJM 2008;358:1483-94

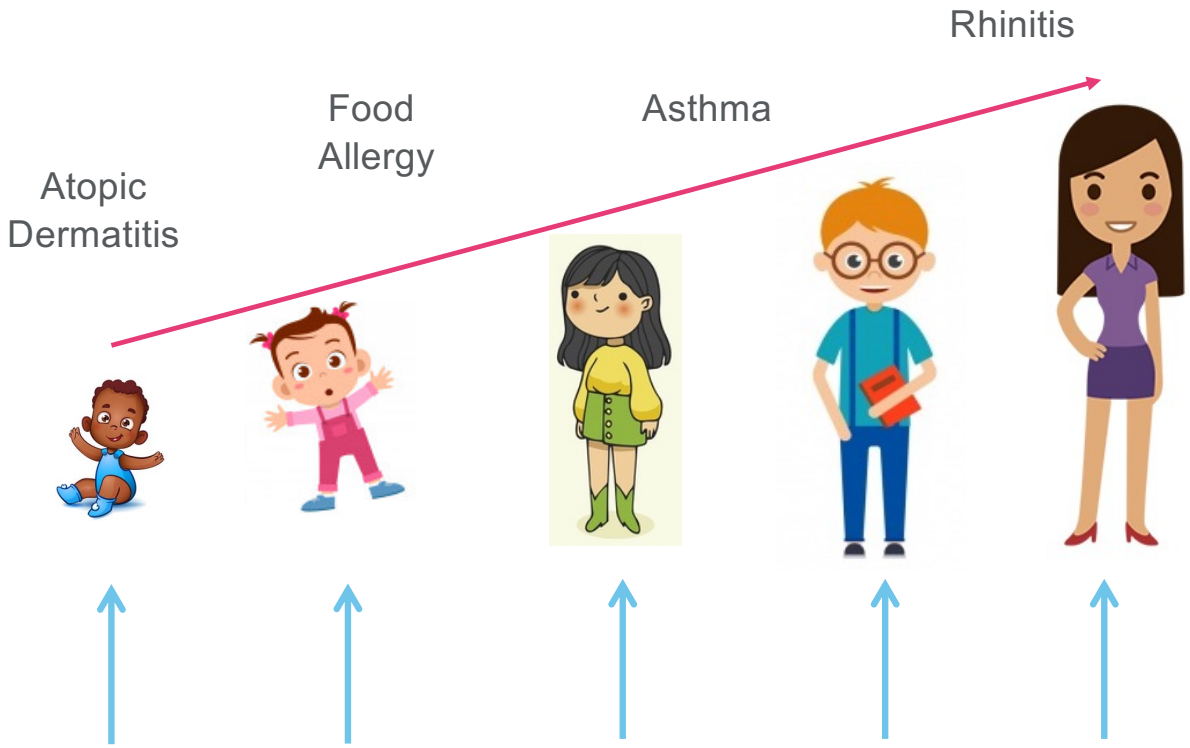
The “Atopic March”



- Early-life AD is a major risk factor for the development of other allergic diseases.
  - One-half to one-third of children with AD will go on to develop asthma.
- Black children have a higher prevalence of asthma and increased rates of asthma morbidity and mortality than White children, which has been documented for decades; this disparity persists as the child ages, even when controlling for socioeconomic status.
- Despite these disparities, studies focused on understanding the trajectories of allergic disorders have been conducted almost exclusively in White populations, so our current paradigms of the atopic march are biased toward White children.
- NIAID workshop convened to evaluate mechanisms underlying progression of AD to other allergic diseases.

Only about 3% of children follow the traditional march.

Development of Allergic Co-morbidity



Compromised barrier function

NIAID Workshop Summary

- Recommended a new, large, prospective cohort study.
- Study should incorporate evaluations of skin, gut, airway, and peripheral blood.
- Multiparametric approaches are required to better define phenotypic/endotypic subgroups of AD and to predict AD outcomes and development of allergic comorbidities.

MPAACH: Mechanisms of the Progression of Atopic Dermatitis to Asthma in Children

- We designed MPAACH to meet this need.
- Early life prospective cohort → exclusively enroll children with AD.
- Objectives:
  - Carefully define AD phenotypes and endotypes
  - Dissect the mechanisms that contribute to the progression of AD to other allergic disorders
- Funded by U19 AADCRC

M-PAACH

Mechanisms of Progression of Atopic Dermatitis to Asthma in Children

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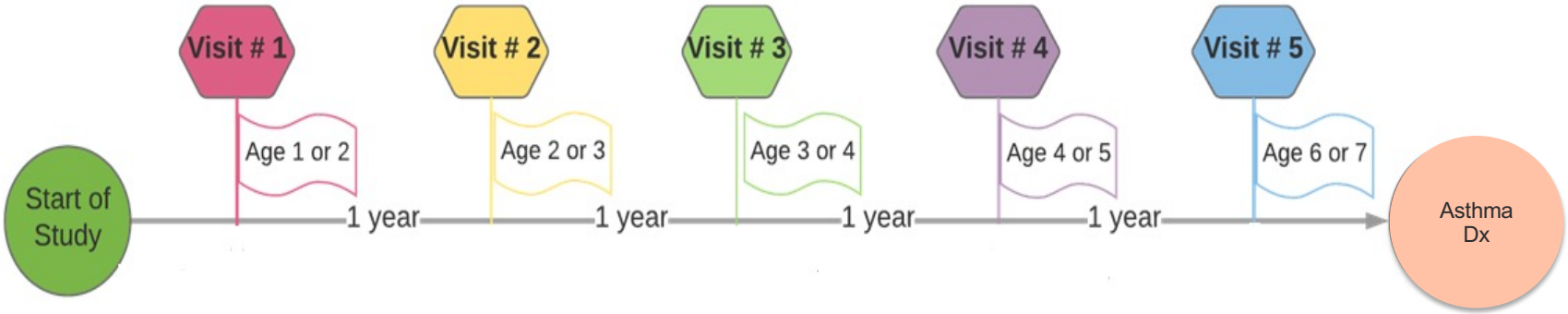
MPAACH

- Inclusion criteria:
  - Children aged 0-2 at enrollment
  - Have either:
    - physician diagnosed AD
    - positive response to all 3 questions on the Children's Eczema Questionnaire
  - ≥36 weeks gestation

- Exclusion criteria:
  - Co-morbid lung condition
  - Immunosuppression or oral steroids for condition other than asthma
  - Condition that precludes sample collection or spirometry
  - Bleeding diathesis



- Annual visits:
  - Questionnaires
  - Physicial examination
    - PFTs
    - Food challenges
  - Biospecimen collection
- Renewed
  - Will continue visits for 5 more years

MPAACH Biospecimens

Genome wide genotyping DNA methylation

Saliva -DNA

Immunophenotype CyTOF, flow

Cytokines/Chemokines Vitamin D, Specific and Total IgE

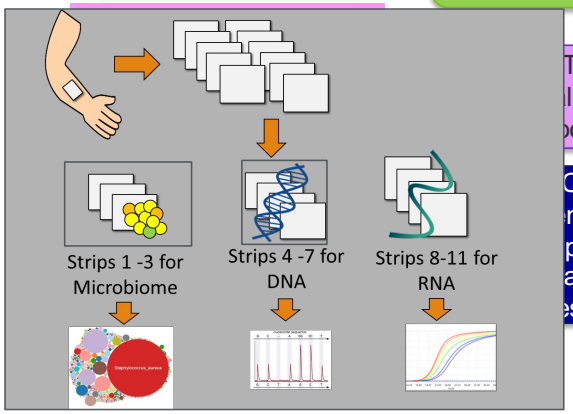
Whole blood RNA/DNA

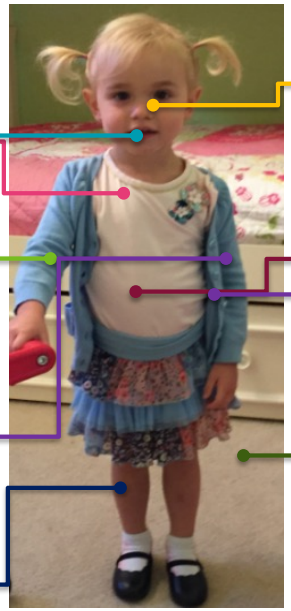
Skin Assessment -SCORAD -TEWL (lesional and non-lesional)

Blood -PBMCs -Serum

Test llergens ods

Cells ntial tape ps al and esional)





Nasal Samples -HydraFlock 6" sterile standard nasal swab -Epithelial cells

Next Gen Shotgun Sequencing – Biome

Cells- DNA methylation Trancriptome

Gut Biome -stool

Skin Biome -3 tapes -Contact agar plates (lesional and non-lesional)

Assess *S. aureus* colonization

Home Dust -bedroom -primary activity room

Dust Biome MARIA ERMI

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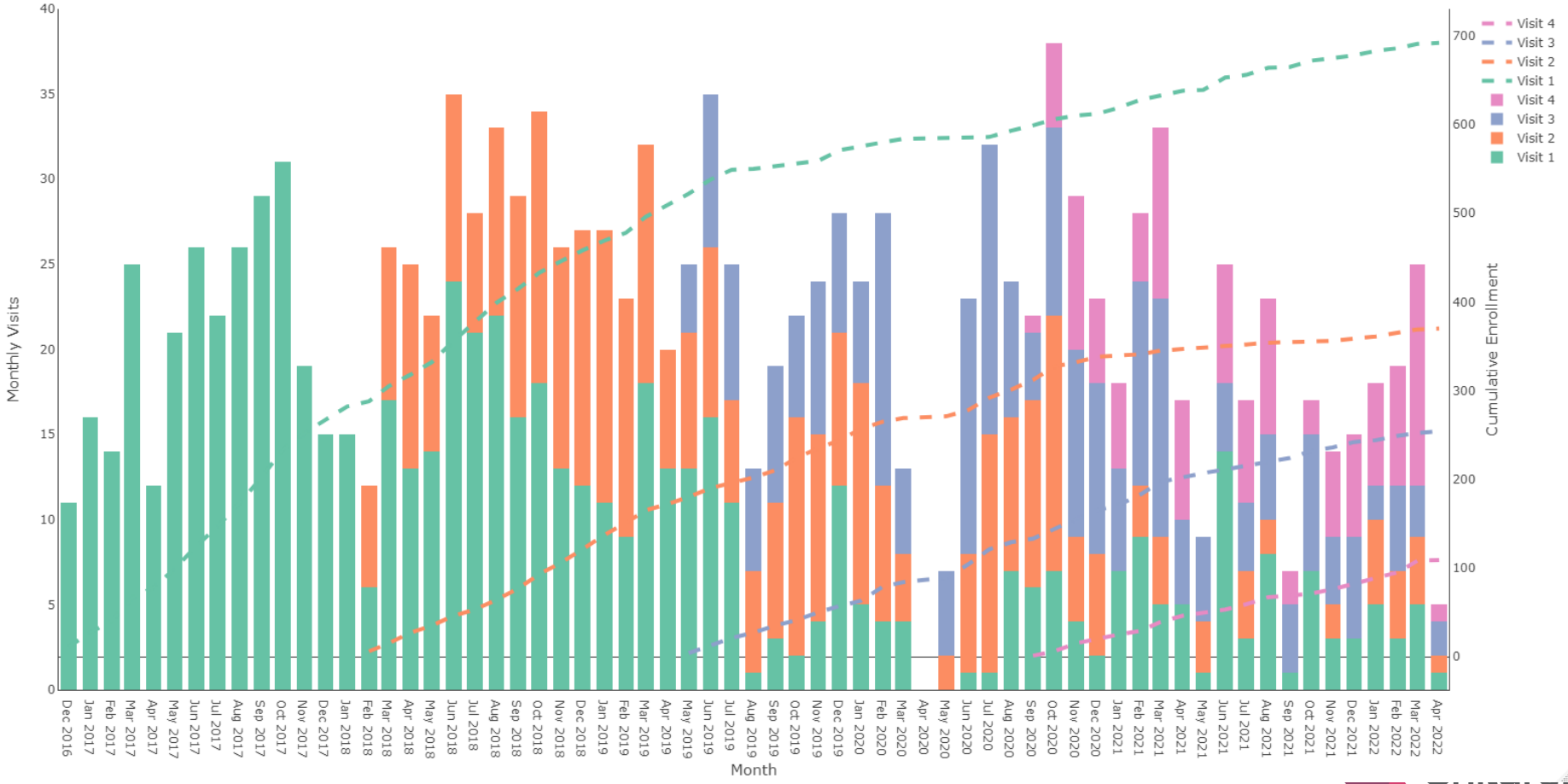
Recruitment summary



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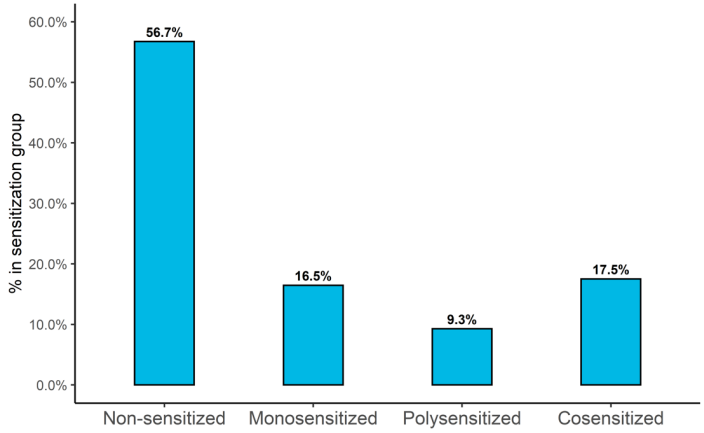
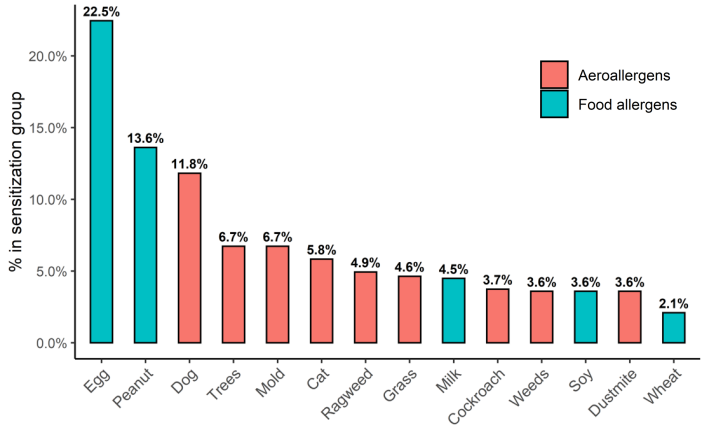
Characteristics of the MPAACH cohort

	N = 672
Demographic	
Age (y)	1.9 (1.2-2.4)
Male sex	356 (53)
Black race	444 (66)
Public insurance	457 (68)
AD Severity	
SCORAD (score)	19.6 (12.3-30.6)
Severity group	
Mild (SCORAD < 25)	422 (63)
Moderate (25 ≤ SCORAD < 50)	205 (30)
Severe (SCORAD ≥ 50)	38 (6)
PARS (score)	6 (4-9)
Skin barrier function	
Lesional skin	
TEWL (g/m^2/h)	12.4 (8.6-19.9)
Keratinocyte *FLG* expression	1.01 (0.27-2.74)
Non-lesional skin	
TEWL (g/m^2/h)	9.7 (7.4-13.4)
Keratinocyte *FLG* expression	1.76 (0.56-4.23)
Sensitization	
Total serum IgE	30 (10-111)
Sensitization group	
Nonsensitized	386 (57)
Monosensitized	
Food	55 (8)
Aero	54 (8)
Polysensitized	
Food	43 (7)
Aero	14 (2)
Cosensitized	120 (18)
Comorbid conditions	
Food allergy	91 (14)
Wheezing in the past 12 mo	241 (36)
Allergies or allergic rhinitis	102 (15)

Data are presented in median (IQR) or *n* (%). FLG expression were multiplied by 1000 for the ease of interpretation.





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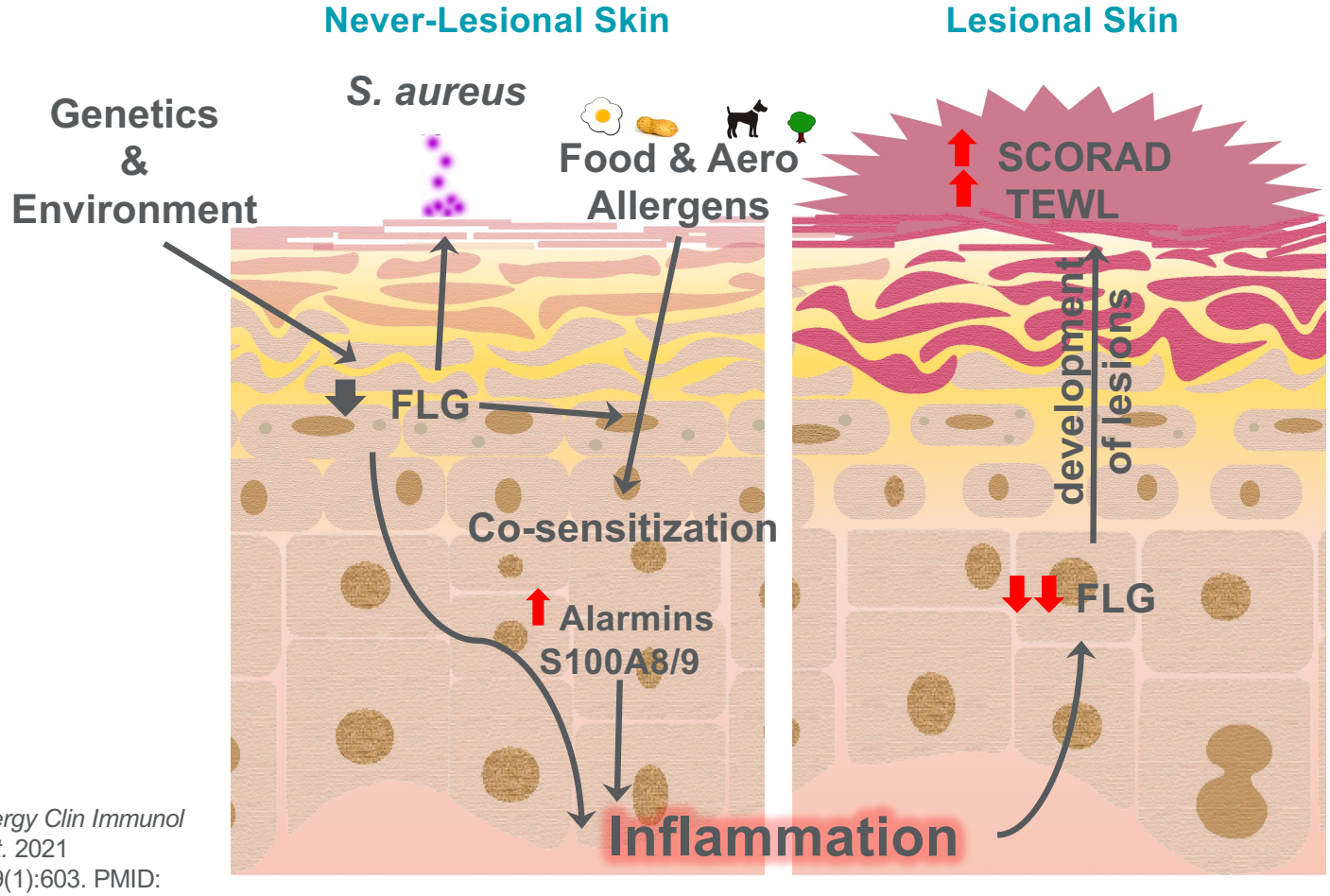
Events in Normal Skin Promote Early-Life Atopic Dermatitis (N=400)



- In patients with known AD, barrier dysfunction is global beyond actively inflamed areas.
- Events in the nonlesional skin are integral to the development of atopic disorders.
- The expression level of FLG in never lesional (but not lesional) skin was associated with co-sensitization and the development of moderate to severe AD.

J Allergy Clin Immunol Pract. 2021 Jan;9(1):603. PMID: 32302785; PMCID: PMC7338239

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Research Question

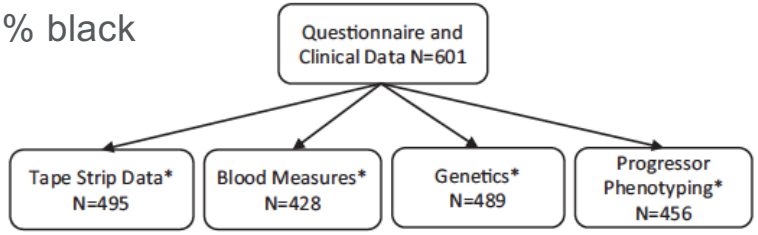
- What are the longitudinal phenotypes and endotypes of AD in MPAACH?
- How do they differ between black and non-black children?
- What factors underlie observed differences in atopic trajectories by race?
- Data from the first 601 participants at V1 and 456 from V2 were available.

Biagini et al. Longitudinal atopic dermatitis endotypes: An atopic march paradigm that includes Black children. J Allergy Clin Immunol. 2022 May;149(5):1702-1710.e4. doi: 10.1016/j.jaci.2021.09.036. Epub 2021 Oct 18. PMID: 34673050; PMCID: PMC9275099.

TABLE I. Demographics and AD onset and severity in 601 Black and White MPAACH children

Characteristic	Black (n = 410)	White (n = 191)	*P* value
Demographics			
Male sex	52.4%	52.9%	.920
Age at enrollment (years), median (IQR)	2.06 (1.29-2.39)	2.12 (1.57-2.44)	.012
Public insurance	93.1%	30.8%	<.0001
Early AD onset (0-3 months)	44.5%	44.0%	.9050
AD severity			
SCORAD (score) median (IQR)	19.7 (12.3-30.7)	18.9 (11.6-27.7)	.295
SCORAD (severity group)			
Mild (SCORAD <25)	62.9%	67.5%	.469
Moderate (SCORAD ≥25)	32.2%	27.2%	
Severe (SCORAD ≥50)	4.9%	5.2%	

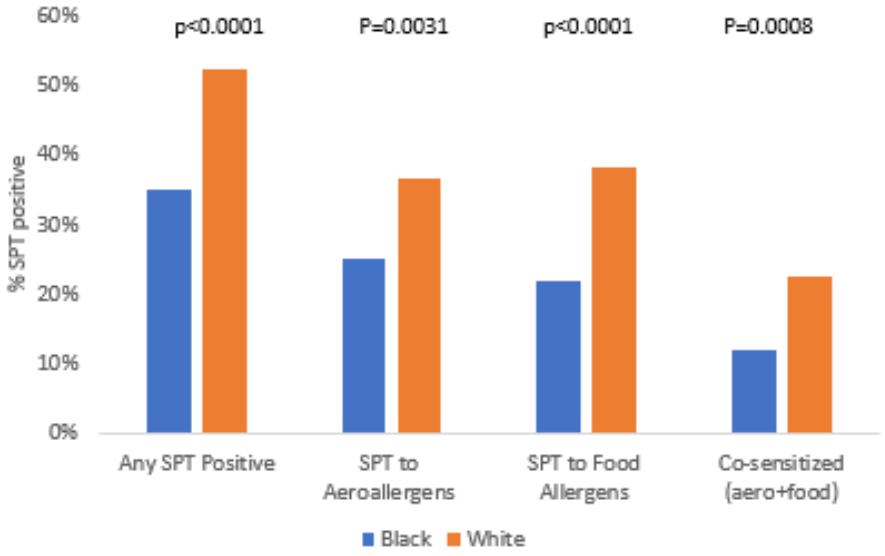
68% black



Genetic data were available for 489 of the MPAACH subjects, so we compared parent reported race to percentage African ancestry →
*strong correlation between %African ancestry and reported race (Spearman coefficient 0.81, P < .0001) →
*present the analyses with parent-reported race to maximize sample size.

J Allergy Clin Immunol. 2022 May;149(5):1702-1710.e4.
doi: 10.1016/j.jaci.2021.09.036.

Development of Sensitization and Co-morbidity



White children were much more likely to be sensitized to food and/or aeroallergens, and have food allergy and allergic rhinitis.

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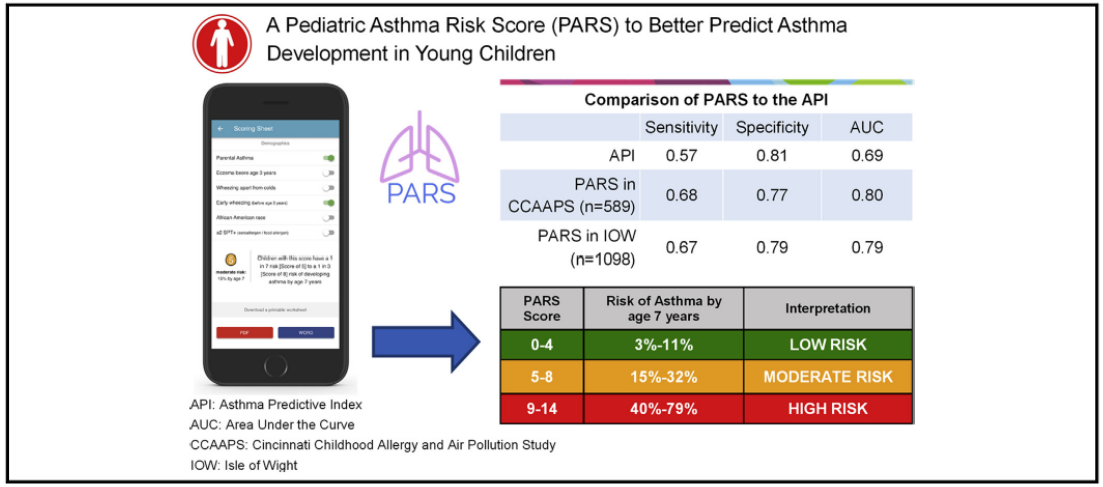
A Pediatric Asthma Risk Score to better predict asthma development in young children

Check for updates

Jocelyn M. Biagini Myers, PhD,[a,e] Eric Schauberger, DO, PhD,[a,b] Hua He, MS,[c] Lisa J. Martin, PhD,[c,e] John Kroner, MS,[a] Gregory M. Hill, BS,[a] Patrick H. Ryan, PhD,[d,e] Grace K. LeMasters, PhD, MSN,[f] David I. Bernstein, MD, MS,[f,g] James E. Lockey, MD,[f] S. Hasan Arshad, DM, FRCP,[h] Ramesh Kurukulaaratchy, DM,[h] and Gurjit K. Khurana Hershey, MD, PhD[a,e]

Cincinnati, Ohio, and Isle of Wight, United Kingdom

GRAPHICAL ABSTRACT



Pediatric Asthma Risk Score (PARS) Sheet

	Possible Scores		
	No	Yes	Child's Score
1. Parental Asthma	0	2	
2. Eczema before age 3 years	0	2	
3. Wheezing apart from colds	0	3	
4. Wheezing before age 3 years	0	3	
5. African-American Race	0	2	
6. SPT positive to ≥ 2 aero and/or food allergens	0	2	
Child's PARS (add lines 1-6 above):			

Patient Score Interpretation

Score	Risk of Asthma by age 7 years	Interpretation	
0	3%	LOW RISK	Children with these scores have a 1 in 33 [score of 0] to a 1 in 9 [score of 4] risk of developing asthma by age 7 years
2	6%		
3	8%		
4	11%		
5	15%	MODERATE RISK	Children with these scores have a 1 in 7 risk [Score of 5] to a 1 in 3 [Score of 8] risk of developing asthma by age 7 years
6	19%		
7	25%		
8	32%		
9	40%	HIGH RISK	Children with these scores have a 2 in 5 [Score of 9] to a 4 in 5 [Score of 14] risk of developing asthma by age 7 years
10	49%		
11	58%		
12	66%		
14	79%		

J Allergy Clin Immunol. 2019 May;143(5):1803-1810.e2. doi: 10.1016/j.jaci.2018.09.037. PMID: 30554722; PMCID: PMC6504569.
Expert Rev Clin Immunol. 2019 Nov;15(11):1115-1118. doi: 10.1080/1744666X.2020.1682552. PMID: 31647698; PMCID: PMC6837242.
Ann Allergy Asthma Immunol. 2020 Jun;124(6):629-631.e2. doi: 10.1016/j.anai.2020.03.010. PMID: 32201305; PMCID: PMC7309532.

Progressor Phenotypes

- Phenotypes were defined across V1 and V2 for 456 subjects with both time points.

- Subjects were defined by the presence of:
  - food allergy (FA),
  - allergic rhinitis (AR)
  - asthma risk (PARS ≥9)

Biagini et al. Longitudinal atopic dermatitis endotypes: An atopic march paradigm that includes Black children. J Allergy Clin Immunol. 2022 May;149(5):1702-1710.e4. doi: 10.1016/j.jaci.2021.09.036. Epub 2021 Oct 18. PMID: 34673050; PMCID: PMC9275099.

Progressor Phenotypes

A

Allergic co- and multi morbidity progressor phenotypes in Black and White MPAACH Children.

Total N=456	Black n=306	White n=150
Asthma risk only	36.3%	6.0%
Asthma + AR	11.8%	6.7%
Asthma + FA	3.6%	4.7%
Asthma risk + AR + FA	4.3%	5.3%
AR only	9.5%	16.7%
FA only	4.3%	18.0%
AR + FA	1.3%	14.7%
Non-progressor*	29.1%	28.0%

- Black children were more likely to progress to asthma risk with or without AR/FA
- White children were more likely to progress to AR/FA

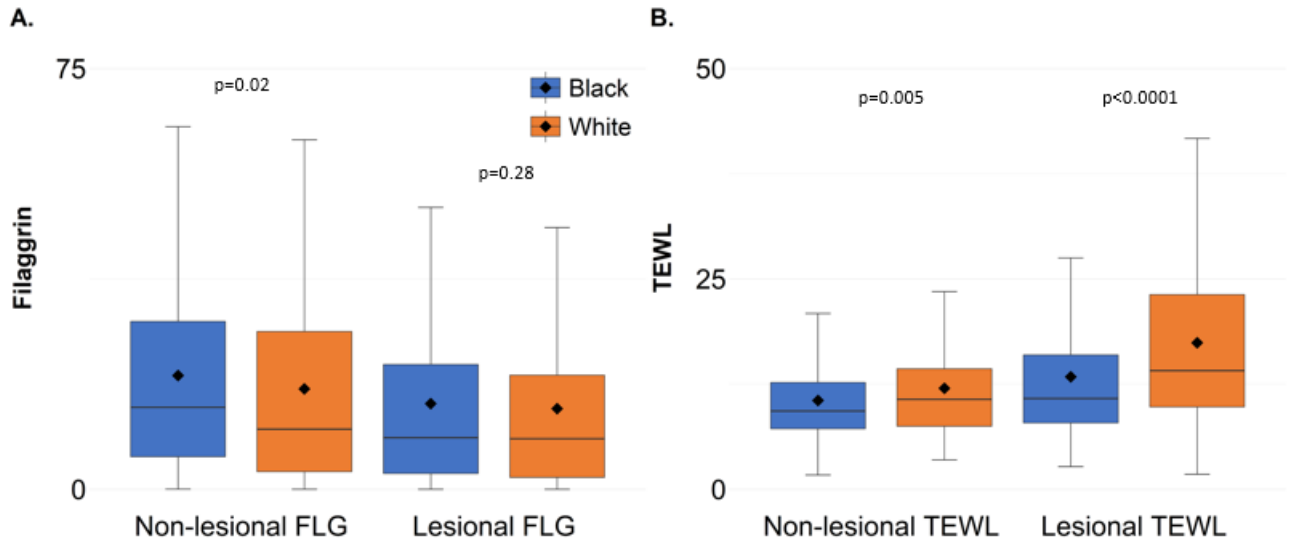
Biagini et al. Longitudinal atopic dermatitis endotypes: An atopic march paradigm that includes Black children. J Allergy Clin Immunol. 2022 May;149(5):1702-1710.e4. doi: 10.1016/j.jaci.2021.09.036. Epub 2021 Oct 18. PMID: 34673050; PMCID: PMC9275099.

Longitudinal phenotypes differ by race

- Black and White children do not differ in AD severity but White children have increased sensitization.
- White children have increased FA and AR while Black children have increased respiratory symptom scores and PARS.
- Black children progress to asthma risk with or without AR/FA while White children progress to AR/FA.

- What mechanisms may be contributing to these differences?
  - Barrier integrity
  - Heritability
  - Environmental exposures

Racial Differences in Skin FLG expression and skin permeability (TEWL)



- White children had decreased non-lesional FLG and increased TEWL.

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Does Genetic Heritability Differ by Race?

- Children receiv…ck race, but we observed a 3-p…sus White.
  - This suggests …RS score is not due to Black race a…
- To assess gene…
  - evaluated pare… race.
  - estimated sing…ased heritability of PARS by race.

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5	15%	MODERATE RISK	Children with these scores have a 1 in 7 risk [Score of 5] to a 1 in 3 [Score of 8] risk of developing asthma by age 7 years
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10	49%		
11	58%		
12	66%		
14	79%		

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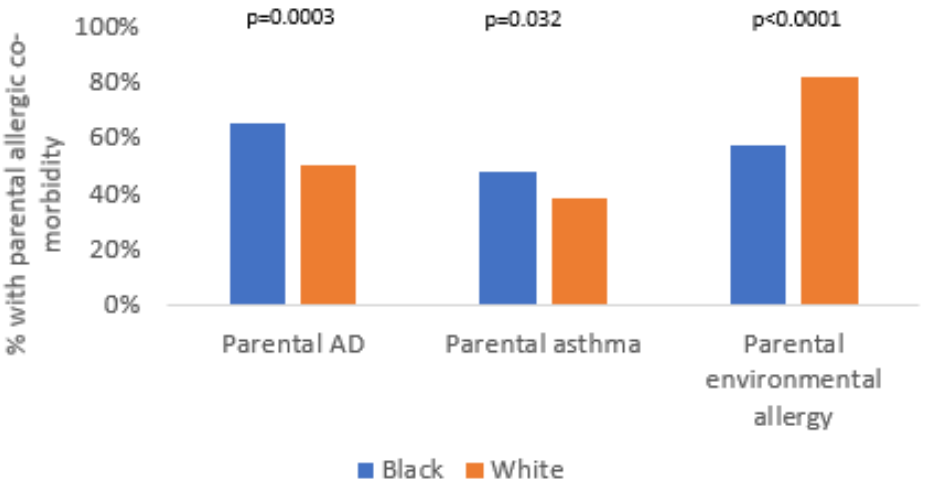
Parental History Differs by Race



- Black children had increased parental AD and asthma.
- White children had increased parental environmental allergies.

Biagini et al. Longitudinal atopic dermatitis endotypes: An atopic march paradigm that includes Black children. *J Allergy Clin Immunol.* 2021 Oct 18:S0091-6749(21)01555-4. doi: 10.1016/j.jaci.2021.09.036. Epub ahead of print. PMID: 34673050.

SNP-based Estimate of Heritability differs by race

- We used a likelihood ratio test to compare 2 models (with and without genetic data) separately by Black and White.
  - In Black children, there was a significant genetic contribution to PARS (heritability estimate ± SD, 0.66 ± 0.37, P = 0.019).
  - The genetic contribution to PARS was not significant in White children (heritability estimate ± SD, 0.43 ± 0.52, P = 0.10).

- This data in conjunction with the higher parental history of allergic disease in Black children supports that Black children have a higher genetic contribution to their asthma risk compared to White children.

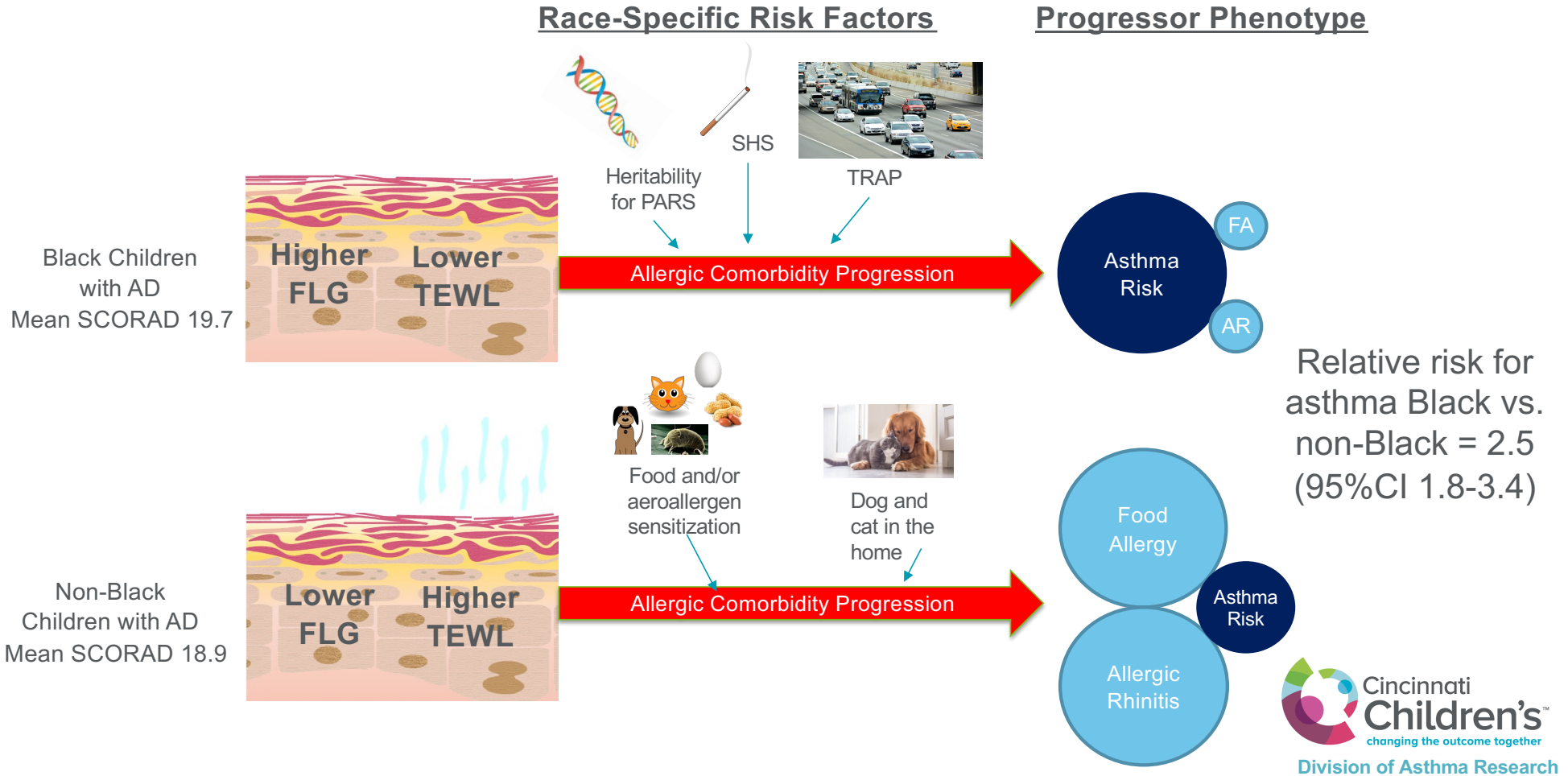
Do Environmental Exposures Differ by Race?

TABLE II. Environmental exposures in 601 Black and White MPAACH children at V1

Characteristic	Black (n = 410)	White (n = 191)	*P* value
Owned a dog in the first year of life	21.5%	55.5%	<.0001
Currently live with a dog	12.2%	48.2%	<.0001
Owned a cat in the first year of life	5.1%	22.5%	<.0001
Currently live with a cat	3.4%	20.9%	<.0001
Parent-reported SHS exposure (cigarettes/cigars)	56.8%	33.5%	<.0001
Serum cotinine (ng/mL), median (IQR)	0.33 (0.0-1.46)	0.17 (0.0-0.91)	.108
TRAP ($\mu g/m^3$), median (IQR)	0.4 (0.3-0.5)	0.3 (0.3-0.4)	<.0001

- White children were more likely to have a dog or a cat.
- Black children were more likely to be exposed to secondhand smoke and higher air pollution estimates.

Atopic March Progression in Children Participating in the Mechanisms of Progression of Atopic Dermatitis to Asthma in Children (MPAACH) Longitudinal Cohort (n=601) Differs by Race



Relative risk for asthma Black vs. non-Black = 2.5 (95%CI 1.8-3.4)

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nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-17895-x OPEN

Disease-associated *KIF3A* variants alter gene methylation and expression impacting skin barrier and atopic dermatitis risk

Mariana L. Stevens[1], Zhonghua Zhang[1], Elisabet Johansson[1], Samriddha Ray[1], Amrita Jagpal[1], Brandy P. Ruff[1], Arjun Kothari[1], Hua He[2], Lisa J. Martin[2,3], Hong Ji[1,3], Kathryn Wikenheiser-Brokamp[3,4,5], Matthew T. Weirauch[3,6,7,8], Dorothy M. Supp[9,10], Jocelyn M. Biagini Myers[1,3] & Gurjit K. Khurana Hershey[1,3]✉

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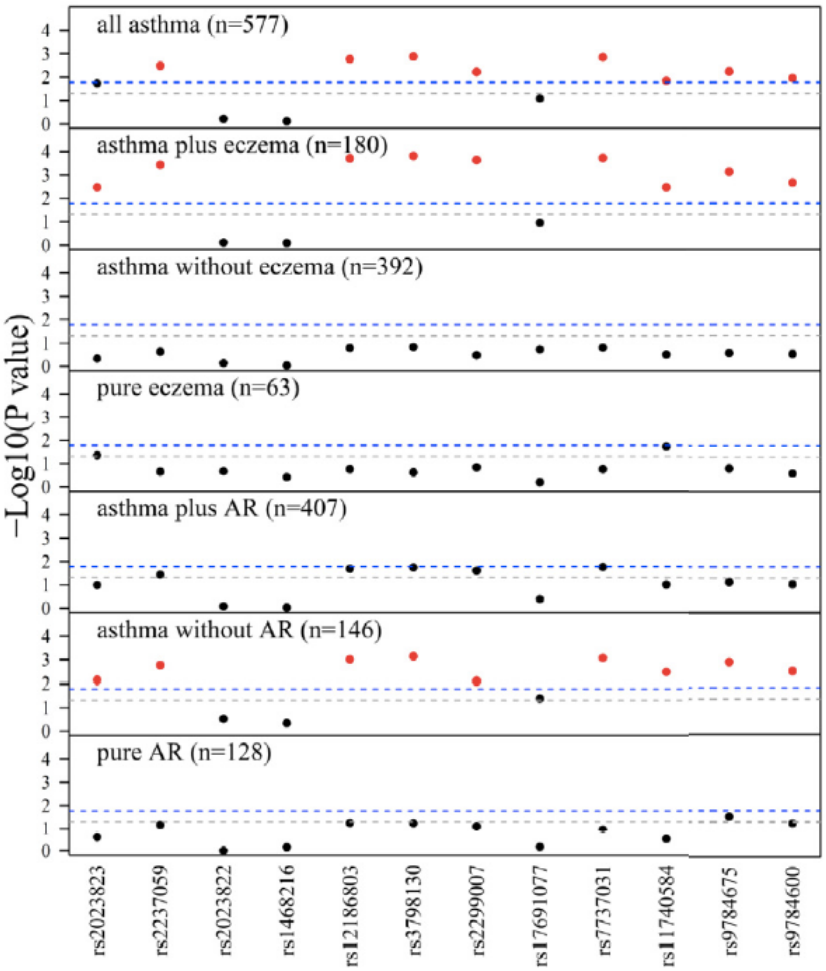
The gene f) has been identified as a susceptil ma by our group and others (Bu 2011; Michel et al., 2010; Paternoste re et a , 2013).

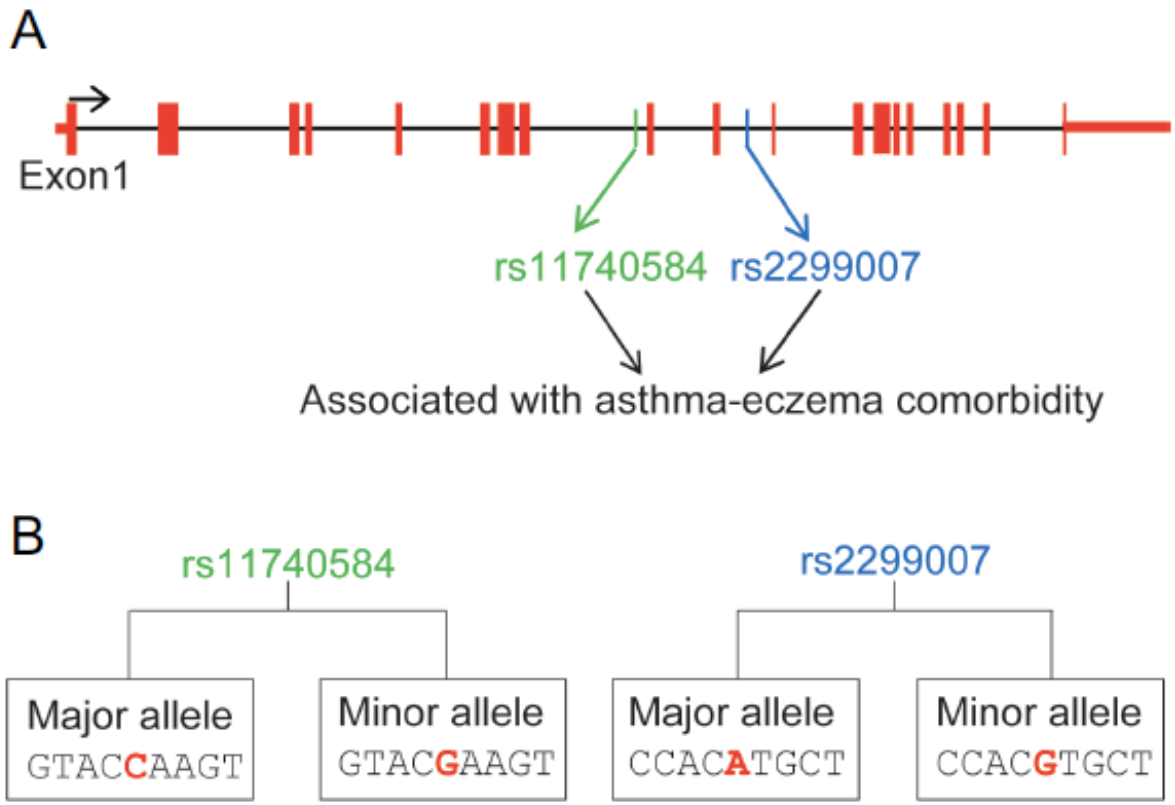


Association of KIF3A is with the asthma + eczema phenotype -suggests that KIF3A may play a role in disease progression

KIF3A has ssociated with disease progressio z et al., 2015).

Clin Exp Allergy. 2019 Jun;49(6):829-837. doi: 10.1111/cea.13379. Epub 2019 Mar 27.PMID: 30830718

SNPs Create New CpG Sites



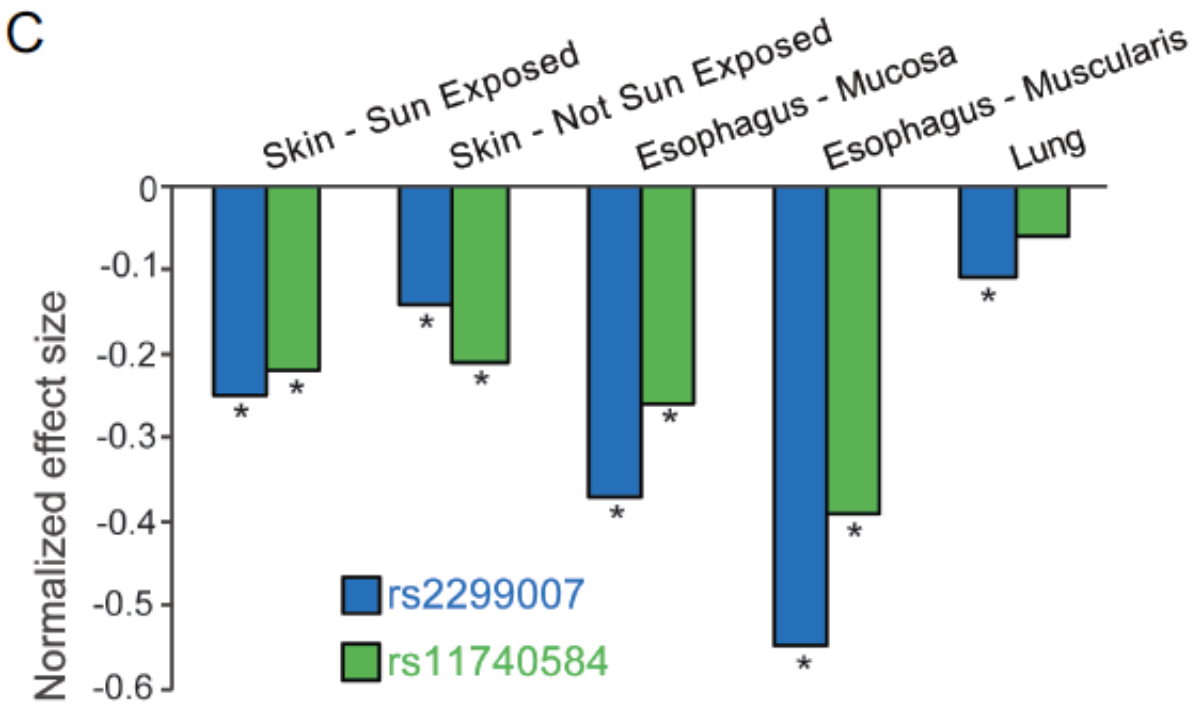
Stevens, M et al, Nature Communications

GOAL: Determine how KIF3A SNPs contribute to phenotype.

Elucidate relationship between *KIF3A* CpG-SNPs, *KIF3A* gene methylation, and *KIF3A* expression.

- Are SNPs eQTL?
- Is there allele-specific methylation of KIF3A?
- Elucidate whether these epigenetic marks are correlated with barrier function?

KIF3A SNPs are eQTL



Genotype-Tissue **Expression** (GTEx) project

Stevens, M et al, Under Review

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Clinical Characteristics of Individuals Carrying 0 or 2 copies of KIF3A alleles

Clinical variables	rs2299007		rs11740584	
	Reference[A] (A)	Alternate[B] (G)	Reference[A] (C)	Alternate[B] (G)
N	36	17	26	27
Black	12 (33%)	1 (6%)	4 (15%)	9 (33%)
Male	23 (64%)	12 (71%)	18 (69%)	17 (63%)
Age	15.1 +-3.7	14.9 +-4.2	15.5 +-4.1	14.6 +-3.4
History of AD	18 (50%)	9 (53%)	13 (50%)	14 (52%)
Current AD	11 (31%)	5 (29%)	8 (31%)	8 (30%)

[A]Reference allele carriers were homozygous for the reference alleles at both SNPs.
[B]Alternate allele carriers were both homozygous and heterozygous.

Are the novel CpG sites methylated?

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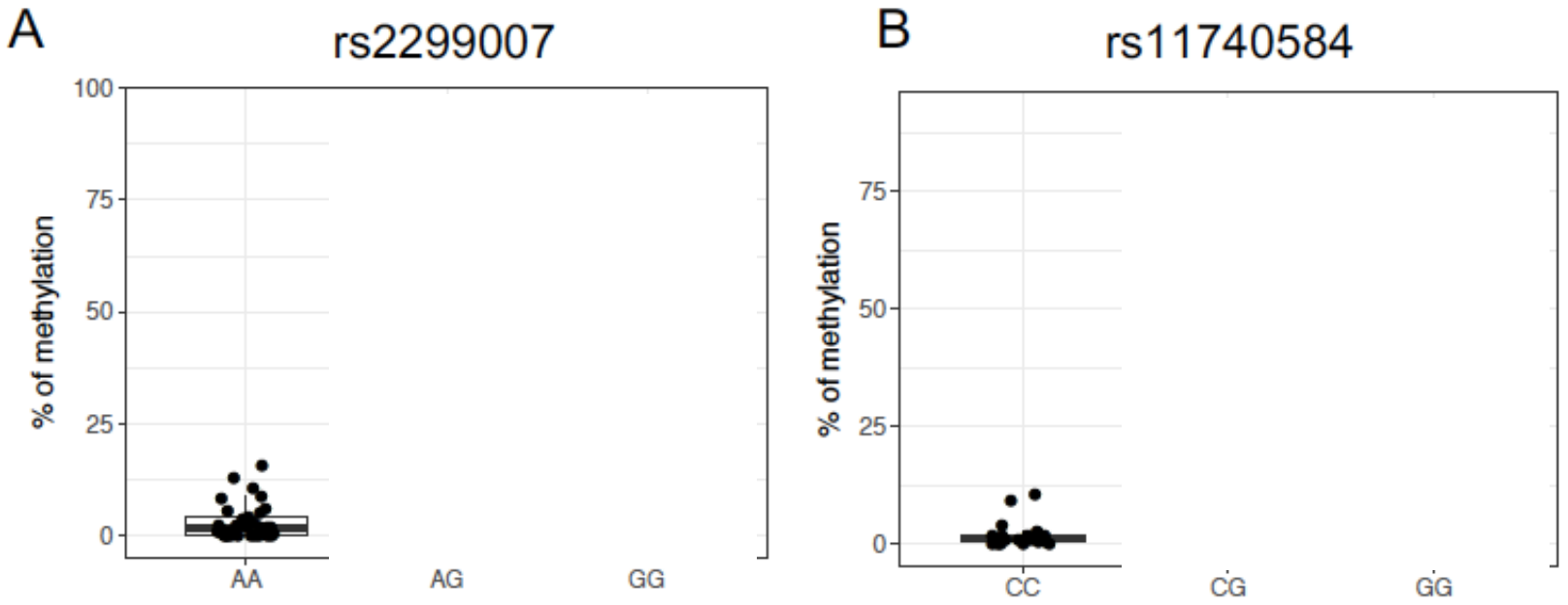
Individuals homozygous for variant alleles have increased methylation at the SNP site



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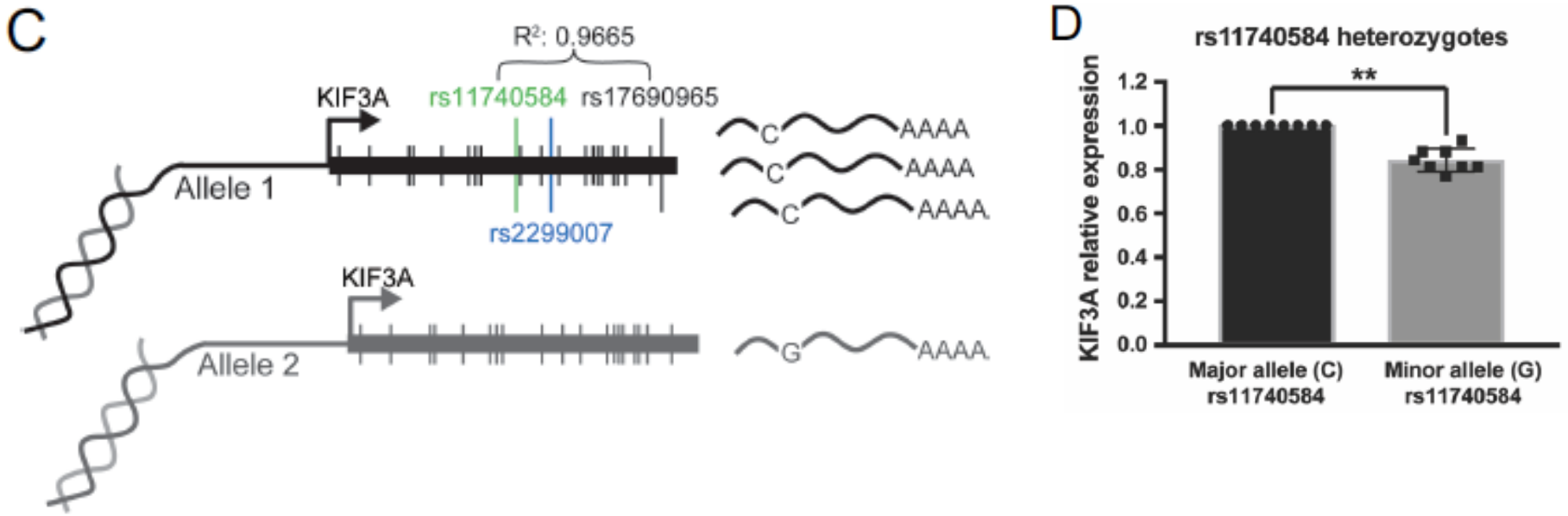
Allele Specific PCR in individuals heterozygous for variant alleles



**Variant alleles have increased CpG methylation and decreased KIF3A expression

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Table 1. *KIF3A* SNPs rs11740584 and rs2299007 alternate allele carriers have higher transepidermal water loss (TEWL)

	Non-lesional TEWL			Lesional TEWL		
	Estimate	St. Error	P value	Estimate	St. Error	P Vale
rs11740584 genotype[A]	-0.15	0.13	0.25	0.35	0.34	0.33
rs2299007 genotype[A]	-0.11	0.15	0.46	0.46	0.30	0.16
rs11740584 methylation	-0.0014	0.0019	0.47	0.0066	0.0023	**0.025**
rs2299007 methylation	-0.0022	0.0022	0.31	0.0067	0.0018	**0.007**

[A]Presence of the alternate allele for the *KIF3A* SNPs rs11740584 and rs2299007.

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Table 2. Non-lesional skin expression of epidermal differentiation complex gene filaggrin (*FLG*) is lower in *KIF3A* SNP rs11740584 alternate allele carriers and is associated with its methylation level

	rs11740584 genotype			rs11740584 methylation	
	Reference[A] allele [Median (IQR)]	Alternate[B] allele [Median (IQR)]	P value	rho	P value
Non-lesional FLG/18S	**5.2 (2.5,9.2)**	**1.3 (0.0,7.4)**	**0.04**	**-0.3**	**0.045**
Lesional FLG/18S	5.0 (0.3, 0.6)	0.1 (0.0,1.7)	0.72	-0.4	0.19

FLG expression values are shown as a multiple of 10^4.
[A]Reference allele carriers were homozygous for the reference allele.
[B]Alternate allele carriers were both homozygous and heterozygous.

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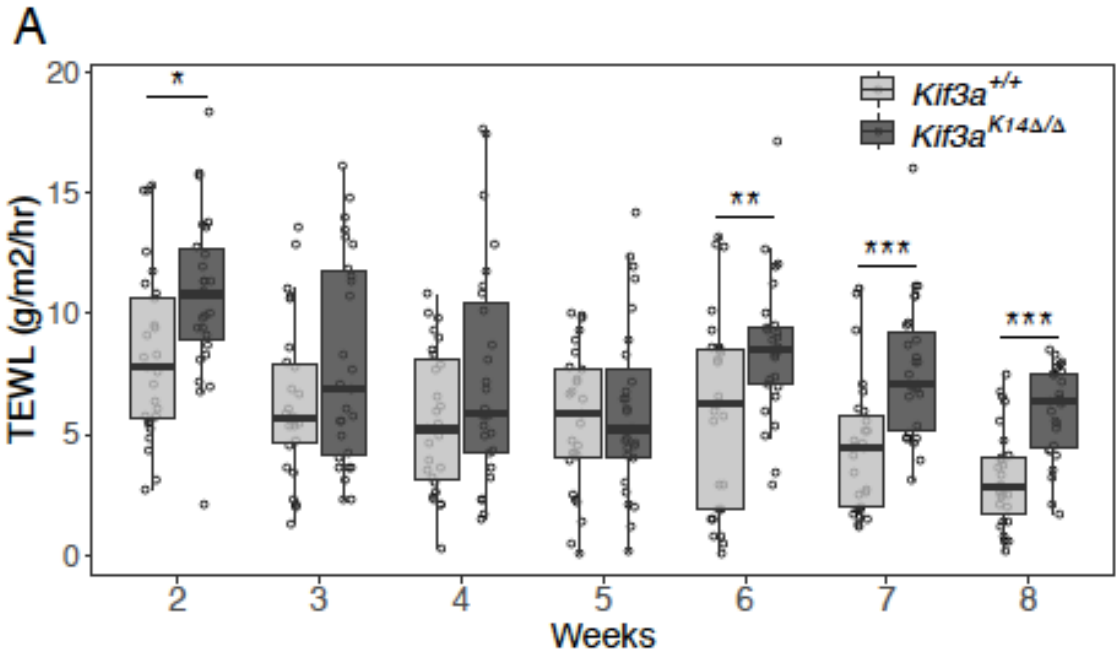
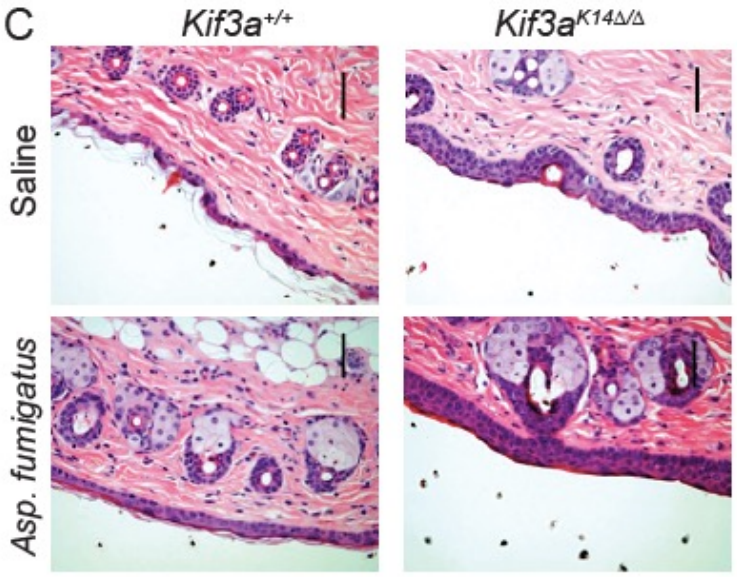
Deficiency of KIF3A in keratinocytes results in barrier dysfunction and susceptibility to AD phenotype after cutaneous allergen





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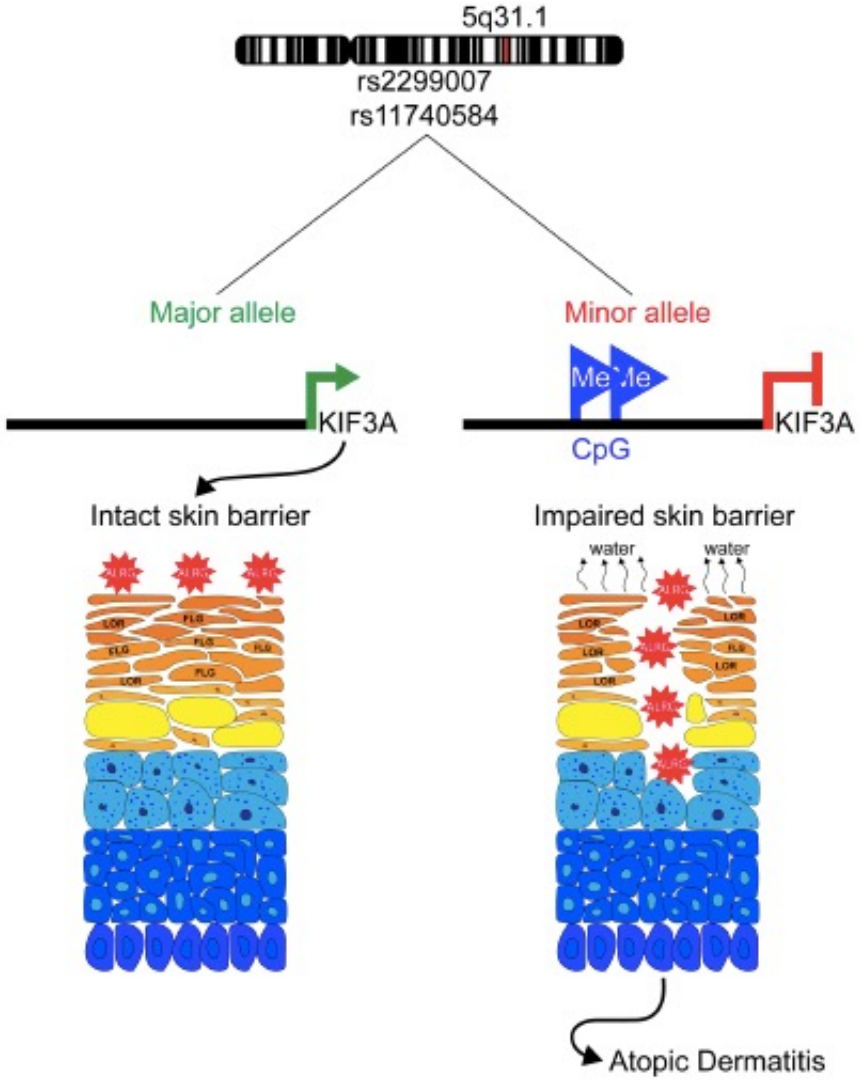

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J Immunol. 2016 December 1; 197(11): 4228–4239. doi:10.4049/jimmunol.1600926.

AIRWAY EPITHELIAL KIF3A REGULATES Th2- RESPONSES TO AEROALLERGENS

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Research Question: What genes regulate filaggrin expression in the skin?

-Deep sequencing of FLG locus in MPAACH is underway

- Data Obtained:
  - Body Fluids
    - Saliva (DNA)
    - Blood (DNA, cellular composition, IgE, cytokines, etc.)
    - Stool microbiome
  - Skin Prick Testing (allergen sensitization)
  - Environment: Household dust samples
  - Skin:
    - Symptom score (SCORAD)
    - Transepidermal water loss (TEWL)
    - Contact plates for skin biome colonies.
    - Lesional & Non-lesional tape strips (DNA, RNA, microbial)

GWAS with eQTL *FLG in* lesional and non-lesional skin

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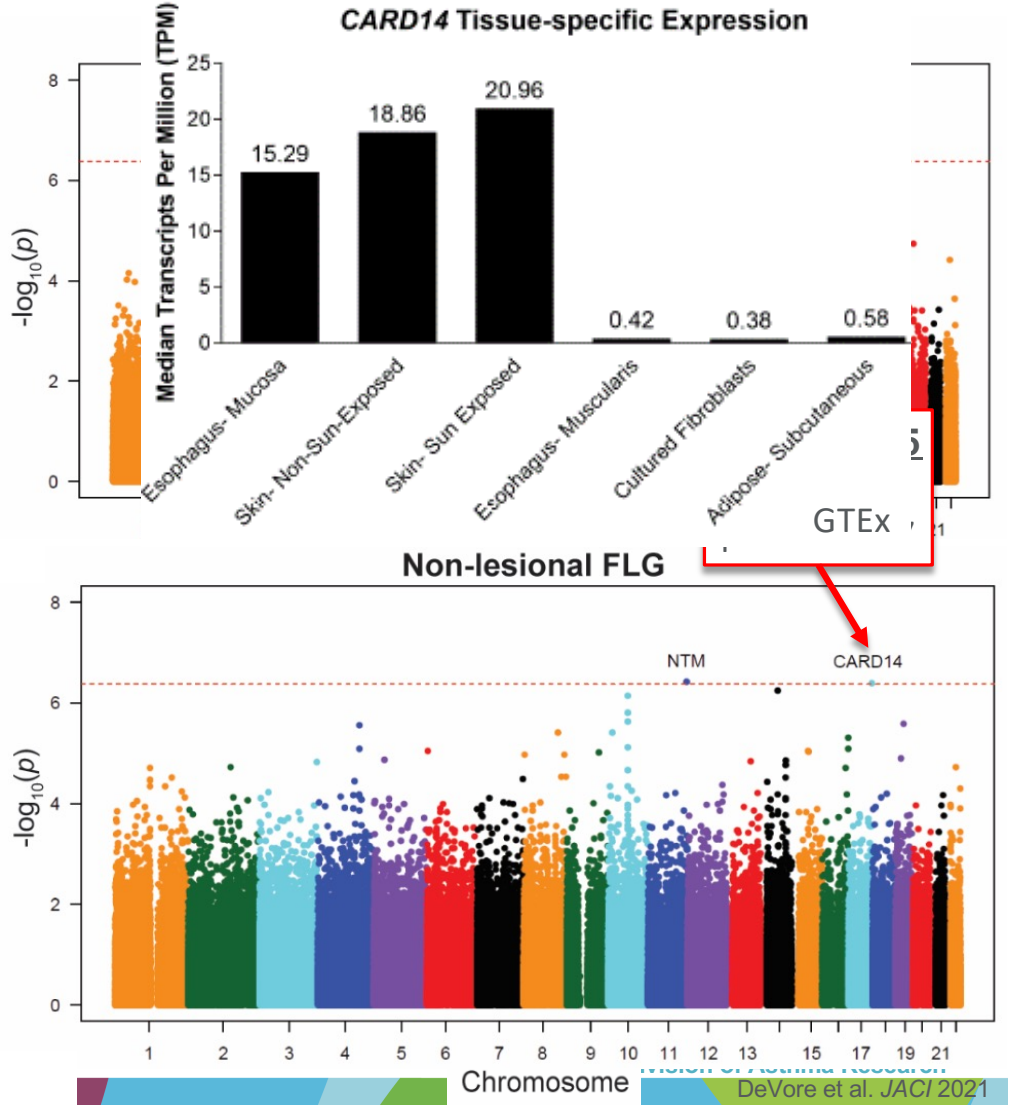
MPAACH Filaggrin GWAS

- N = 279 children with AD
- Analysis:
  - Continuous outcome: FLG mRNA
  - Adjusted for age, sex, race
- Results:
  - Lesional skin: No SNPs identified
  - Non-lesional skin: *CARD14* rs11652075
    - T-allele associated with low FLG mRNA
    - *CARD14* highly expressed in skin and mucosae
    - Exonic
    - Common (47.7% MAF: 49% European, 25% AA)

Hypothesis: *CARD14* rs11652075 is functional, and suppresses *FLG* in a genotype-dependent manner



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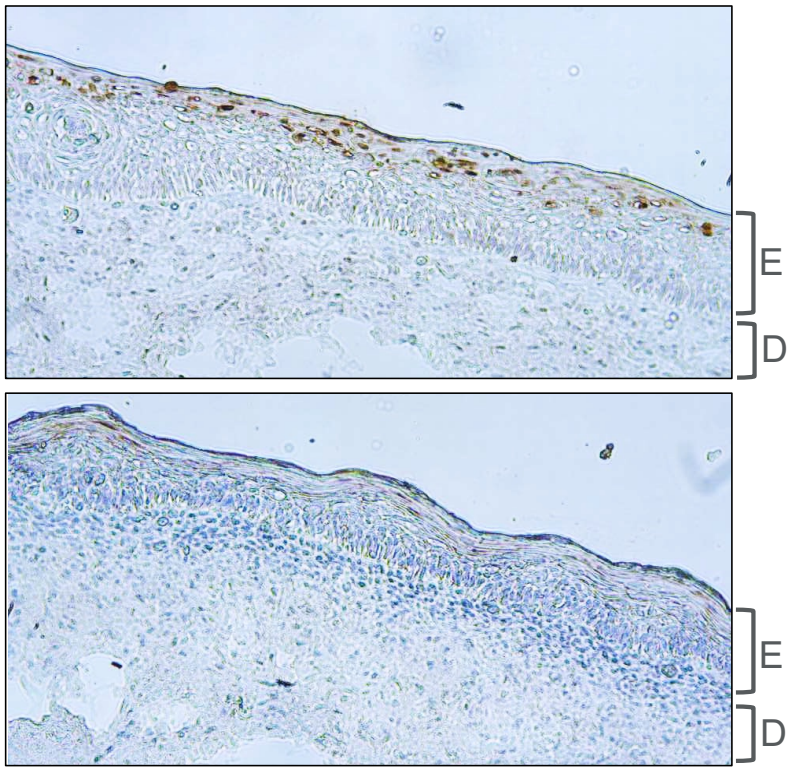
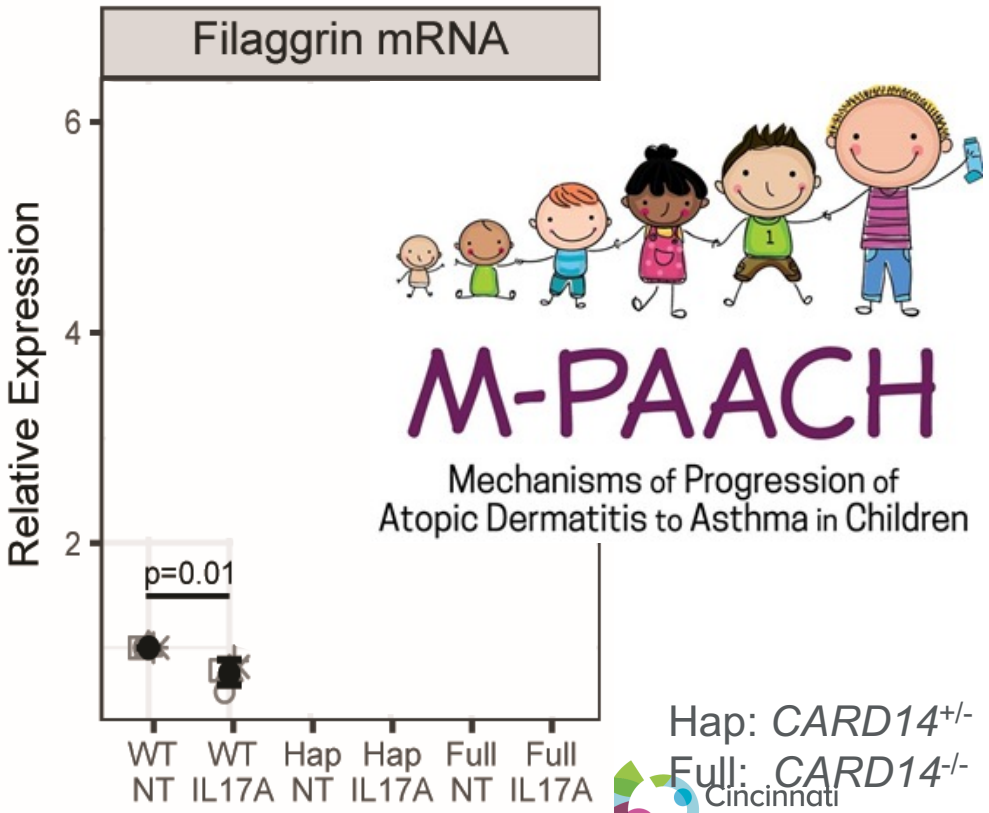
CARD14 mediates *FLG* suppression at baseline and downstream of IL-17A

- IL-17A activates CARD14 signaling (Wang 2018)
- Th17 immunity elevated in pediatric AD (Brunner 2018)
- IL-17A suppresses *FLG* expression (Pfaff 2017)

Engineered Skin Substitute: FLG





M-PAACH

Mechanisms of Progression of Atopic Dermatitis to Asthma in Children

Hap: *CARD14*$^{+/-}$

Full: *CARD14*$^{-/-}$

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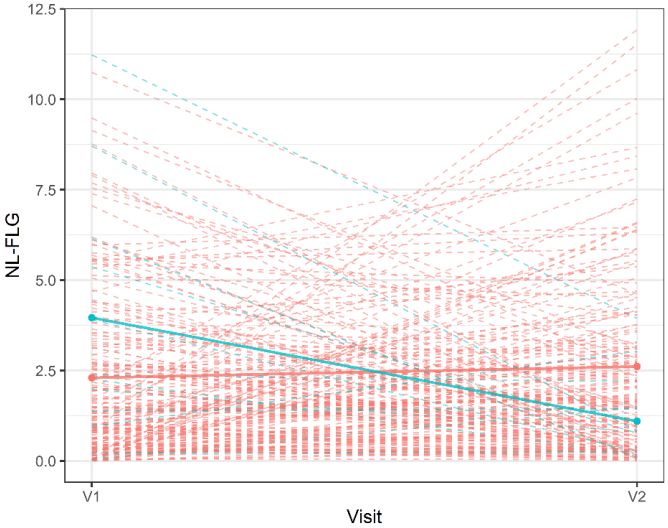
Longitudinal *S. Aureus* Colonization Patterns

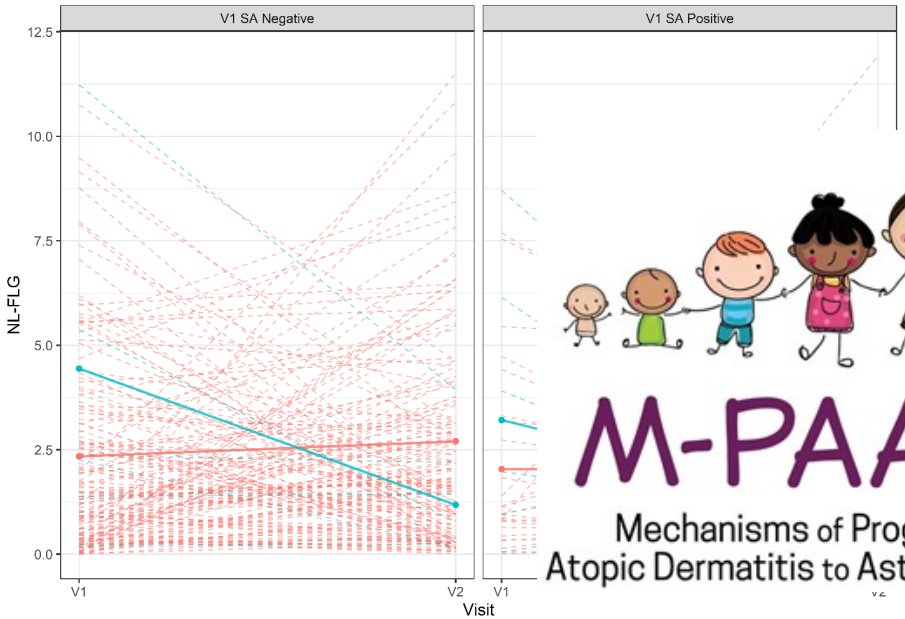
Table 2. Characterization of four longitudinal phenotypes in MPAACH children (N=326) based on *S. aureus* presence (+) or absence (-) at Visit 1 and Visit 2		
	(Visit 1, Visit 2)	N (%)
Negative	(-,-)	264 (81.0)
Transient	(+,-)	38 (11.6)
Late	(-,+)	15 (4.6)
Persistent	(+,+)	9 (2.8)
Total		326

Unpublished Data

In review

Non-lesional *FLG*





If positive for *S. Aureus* at V2, FLG expression lower at V2; if negative at V2, FLG expression remains constant or equal.

If positive at V1, FLG expression lower, but negative or positive similar at V2 if negative at V2.

But if positive for *S. Aureus* at V2, FLG expression → lower at V2 regardless of V1 colonization status. ; if negative at V2, FLG expression remains constant or equal.

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MPAACH Team- current and past

Patients and Families

M-PAACH
Mechanisms of Progression of Atopic Dermatitis to Asthma in Children

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Michael Sherenian, MD

NIH National Institute of Allergy and Infectious Diseases

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