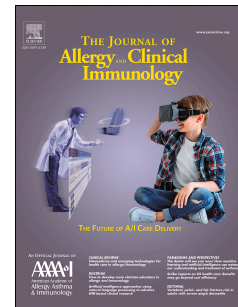


Journal Pre-proof

Longitudinal atopic dermatitis endotypes: An atopic march paradigm that includes Black children

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PII: S0091-6749(21)01555-4

DOI: <https://doi.org/10.1016/j.jaci.2021.09.036>

Reference: YMAI 15311

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 27 April 2021

Revised Date: 14 September 2021

Accepted Date: 17 September 2021

Please cite this article as: Biagini JM, Kroner JW, Baatyrbek kyzy A, Gonzales A, He H, Stevens M, Grashel B, Spagna D, Paul S, Patel R, Bucci A, Sherenian MG, Murrison LB, Martin LJ, Khurana Hershey GK, Longitudinal atopic dermatitis endotypes: An atopic march paradigm that includes Black children, *Journal of Allergy and Clinical Immunology* (2021), doi: <https://doi.org/10.1016/j.jaci.2021.09.036>.

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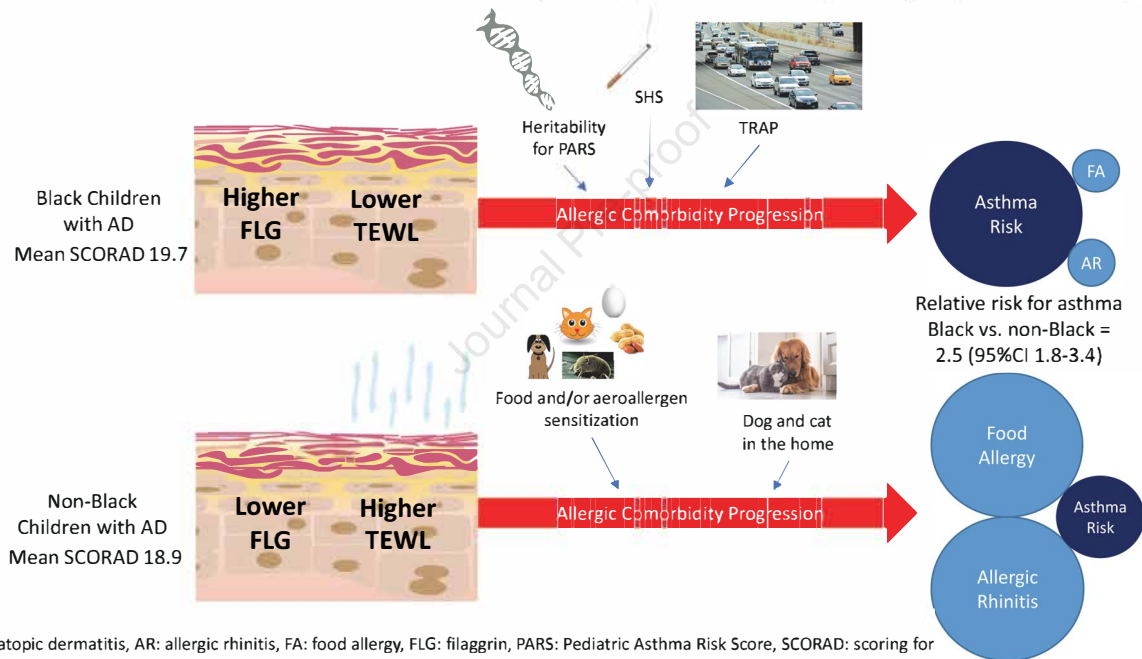
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Atopic March Progression in Children Participating in the Mechanisms of Progression of Atopic Dermatitis to Asthma in Children (MPAACH) Longitudinal Cohort (n=601) Differs by Race

Race-Specific Risk Factors

Progressor Phenotype



AD: atopic dermatitis, AR: allergic rhinitis, FA: food allergy, FLG: filaggrin, PARS: Pediatric Asthma Risk Score, SCORAD: scoring for atopic dermatitis, SHS: secondhand smoke, TEWL: trans-epidermal water loss, TRAP: traffic-related air pollution

Longitudinal atopic dermatitis endotypes: An atopic march paradigm that includes Black children

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Word Count: 3819

Word count abstract: 256

Funding Source: This work was supported by NIH grant U19AI070235 (GKH, JMB, LJM).

The authors have no conflicts of interest.

Abstract (word count 256)

Background. The atopic march has been studied mostly in White populations, biasing our current paradigms.

Objective. To define the atopic march in Black and White children and explore mechanisms for racial differences.

Methods. Utilizing the Mechanisms of Progression of Atopic Dermatitis to Asthma in Children (MPAACH) cohort (N=601), we assessed longitudinal sensitization, food allergy, allergic rhinitis, risk of asthma development (through the Pediatric Asthma Risk Score), SCORAD, transepidermal water loss (TEWL), skin filaggrin (*FLG*) expression, exposures and genetic heritability to define AD progression endotypes in Black and White children.

Results. White MPAACH children were more likely to be sensitized to aero and food allergens ($p=0.0001$) and over 3-times more likely to develop food allergy (FA) and/or allergic rhinitis (AR) without asthma risk ($p<0.0001$). In contrast, Black children were over 6-times more likely to proceed to high asthma risk without FA, sensitization, or AR ($p<0.0001$). White children had higher lesional and non-lesional TEWL (both $p<0.001$) and decreased non-lesional keratinocyte *FLG* expression ($p=0.02$). Black children had increased genetic heritability for asthma risk and higher rates of exposures to secondhand smoke and traffic-related air pollution.

Conclusions. Black and White children with AD have distinct allergic trajectories defined by different longitudinal endotypes. Black children exhibit higher asthma risk despite a more intact skin barrier, and less sensitization, FA and AR. White children have less asthma risk, despite a more dysfunctional skin barrier, and more FA, AR and sensitization. The observed racial differences are likely due, in part, to increased genetic heritability for asthma risk and harmful

environmental exposures in the Black children. Collectively, our findings provide a new paradigm for the atopic march that is inclusive of Black children.

Key Messages

- The atopic march trajectories in Black and White children with atopic dermatitis differ and are defined by distinct longitudinal endotypes.
- Increased genetic heritability for asthma risk (defined by a high Pediatric Asthma Risk Score) and environmental exposures in Black children with AD primarily promote progression to asthma risk alone.
- White children are more likely to have an impaired skin barrier promoting sensitization through the skin and development of food allergy and allergic rhinitis without increased asthma risk.

Capsule Summary

Progression of allergic disease is multi-faceted and differs by race. The traditional atopic march does not exist in most Black children. Our data provide a foundation for a new atopic march paradigm that includes Black children.

Keywords:

Atopic march, atopic dermatitis, race, genetic ancestry, environmental exposure, skin barrier, biomarker

Abbreviations

AD: atopic dermatitis

FA: food allergy

AR: allergic rhinitis

MPAACH: Mechanisms of Progression of Atopic Dermatitis (AD) to Asthma in Children

FLG: filaggrin

CCHMC: Cincinnati Children's Hospital Medical Center

CEQ: Children's Eczema Questionnaire

NVQ: New Visit Questionnaire

SHS: secondhand smoke

DDFC: Demographic Data and Family Contact Form

SCORAD: Scoring for Atopic Dermatitis

TEWL: transepidermal water loss

SPT: skin prick test

PARS: Pediatric Asthma Risk Score

V1: Visit 1

V2: Visit 2

IQR: interquartile range

TRAP: traffic related air pollution

INTRODUCTION

Atopic dermatitis (AD), food allergy (FA), allergic rhinitis (AR), and asthma frequently appear together and usually begin in early life. For nearly two decades, the “atopic march” concept, which describes the sequential development of AD, FA, asthma, and AR has served as a guiding principle, however, a recent NIH workshop concluded that only about 3% of children follow the traditional atopic march¹. While early-life AD remains a major risk factor for the development of any atopic disease, there is significant heterogeneity in the atopic march including the timing and organ(s) affected¹. The atopic march needs to be revised to include this heterogeneity and incorporate the pathogenesis of the various combinations of the atopic march. The Mechanisms of Progression of Atopic Dermatitis (AD) to Asthma in Children (MPAACH) cohort² was designed to meet this need. Further, studies of the atopic march have been almost exclusively conducted in White populations and need to be expanded to include other racial and ethnic groups. MPAACH includes 65% Black children and is one of the only early life cohorts that adequately represents this historically underrepresented and understudied population.

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, and this disparity persists as the child ages even when controlling for socioeconomic status³. Despite these disparities, studies focused on understanding the trajectories of allergic disorders in childhood have been conducted almost exclusively in White populations, so our current paradigms of the atopic march are inherently biased toward White children⁴⁻¹⁵. One recent study focused on African-Americans conducted a secondary analysis of 18,596 subjects with AD identified from health records based on diagnosis codes and found that individuals who identify as Black are more likely to progress from AD to asthma while White subjects progressed from AD to allergic rhinitis¹⁶. This study highlights the racial differences in the atopic march, but they lacked sensitization data, quantitative assessments of the skin barrier, or biospecimens that would enable a deeper understanding of the disparity.

Herein, we utilized the MPAACH cohort (N=601), and its considerable longitudinal data and biospecimens, to define longitudinal endotypes of AD in early life. We study the atopic march in Black and White children including how sensitization patterns and skin barrier assessments affect atopic march progression and the development of allergic co-morbidity. We go on to explore the mechanisms including genetics and environmental exposures that underlie differences in atopic march trajectories by race.

METHODS

Study Subjects

MPAACH is a prospective longitudinal early life cohort of children with AD that has been previously described². Recruitment began in December of 2016 and is ongoing. Briefly, Children in the Greater Cincinnati Area (southwest Ohio and northern Kentucky) were identified through public advertising or the medical chart at Cincinnati Children's Medical Center (CCHMC). Eligible children were aged ≤ 2 years upon enrollment, had a gestation of ≥ 36 weeks and either a diagnosis of AD (based on the Hanifin and Rajka Criteria for Atopic Dermatitis¹⁷) or the parent(s)/legal authorized representative indicated a positive response to each of the 3 questions from the Children's Eczema Questionnaire (CEQ)¹⁸. This study was approved by the Institutional Review Board at CCHMC and all subjects signed informed consent/parental permission prior to participation.

Outcome Definitions

Co-sensitization was defined as a positive SPT to at least one or more aeroallergens **and** one or more foods. Longitudinal sensitization was defined from SPT data from visit 1 (V1) and visit 2 (V2) as follows: 1) non-sensitized (negative to all allergens at V1 and V2); 2) transient (sensitization to allergen(s) at V1 and non-sensitized at V2); 3) acquired (non-sensitized at V1 and sensitized to allergen(s) at V2); 4) persistent (sensitization to ≥ 1 of the same allergen(s) at V1 and V2).

FA was defined based on parental report of a physician diagnosis of food allergy. AR was defined as parental report of "a problem with sneezing or a runny or a blocked nose when he/she DID NOT have a cold or the flu," and/or reported one or more allergy symptoms (itchy red eyes, runny nose, sneezing, itchy nose, congestion) and/or report of the child scratching or itching his/her eyes when he/she is in the same room with a cat, dog, disturbance of dust or near freshly cut grass AND had at least one positive SPT result to an aeroallergen.

The Pediatric Asthma Risk Score (PARS) was calculated as published¹⁹. High asthma risk was defined as a PARS score ≥ 9 . The respiratory symptom burden was defined according to our validated and published respiratory symptom score (maximum weekly symptom frequency of wheeze, cough, chest tightness or shortness of breath)²⁰.

Data Analyses

The cohort was characterized with descriptive statistics. Chi squared and Mann-Whitney tests were applied to evaluate differences between the Black and White children. Multivariate logistic regression was utilized to evaluate associations between race and FA, AR and PARS adjusted for covariates. Heritability was estimated using the Genome-wide Complex Trait Analysis (GCTA) model.

Information on the questionnaires, clinical assessments, biospecimen collection and full data analyses is available in the Online Supplement.

RESULTS

Demographics in MPAACH

There were 601 MPAACH subjects (68% Black) who had completed the first annual MPAACH visit (V1) and 339 who completed their second annual visit (V2) at the time of analysis. A high-level CONSORT diagram is displayed in Supplemental Figure 1 and the sample sizes for each variable in the analyses stratified by race are displayed in Supplemental Table 1. Genetic data were available for 489 of the MPAACH subjects, so we compared parent-reported race to % African ancestry. We observed a strong correlation between % African ancestry and reported race (spearman coefficient 0.81, $p < 0.0001$), therefore we present the analyses with parent-reported race to maximize the sample size. The White children were slightly older (median 2.1, interquartile range (IQR) 1.6-2.4 years compared to median 2.1, IQR 1.3-2.4 for Black, $p = 0.012$, Table I). There were no differences with respect to sex. Most Black participants (93%) reported being on public insurance compared to 31% of the White participants ($p < 0.0001$, Table I).

Development of co-morbid allergic conditions differ by race

At V1, White subjects had a significantly higher prevalence of food allergy (31% vs. 7%, $p < 0.0001$, Figure 2B). The prevalence of AR was also significantly higher in the White compared to the Black children (22% vs. 13%, $p = 0.003$, Figure 2B). Since the children participating in MPAACH are currently too young to have asthma objectively diagnosed, we evaluated respiratory symptoms via the maximum respiratory symptom frequency score²⁰ and PARS (a measure of asthma risk). Black MPAACH children had higher respiratory symptoms frequency scores ($p = 0.017$) and PARS scores (median 7 vs. 4, $p < 0.0001$, Figure 3A-B) compared to White children.

To ensure that the differences we observed between the races in PARS, AR and FA were not due to other covariates, we utilized multivariate logistic regression to adjust for AD severity, early AD onset, age at enrollment, public insurance, cat and dog ownership, daycare attendance,

parental asthma, parental AD and secondhand smoke (SHS) exposure. The parameter estimates and p-value for the race variable for each outcome in the unadjusted and adjusted models are displayed in Supplemental Table 2. For all outcomes, race was still significant even after adjustment for all factors, but the race estimate for PARS was slightly attenuated. Collectively, these data indicate that the racial differences observed were not explained by these other factors.

Black and White children follow distinct multi-morbid trajectories

Progressor phenotypes were defined across V1 and V2. If a child had no comorbidity at V1 and did not yet complete V2 they were excluded (n=145). By Visit 2, 72% (71% of Black and 72% of White) of the MPAACH children developed a co-morbid allergic disease (food allergy, allergic rhinitis, or high asthma risk). Black children were more likely to progress to high asthma risk (with or without FA and/or AR) while White children were more likely to progress to FA and/or AR (Figure 1A). Of the 325 children that developed a co-morbid disease by Visit 2, 63% had high asthma risk, with Black children having almost 5-fold higher asthma risk compared to White children (79% vs. 32%, $p<0.0001$, Figure 1B). When we evaluated children that developed **only** high asthma risk (no food allergy or allergic rhinitis), Black MPAACH children were over 6-times more likely to have high asthma risk alone compared to White children (52% vs. 8%, $p<0.0001$, Figure 1A). In contrast, White children were over 3-times more likely to develop FA and/or AR without high asthma risk (68% vs. 21%, $p<0.0001$, Figure 1B). These data indicate that the allergic comorbidity trajectories in Black and White children with AD are vastly different. We next sought to determine the factors that contribute to AD progression (sensitization, food allergy, allergic rhinitis, asthma risk, skin barrier, environmental exposures, family history) in each race among MPAACH children and define longitudinal AD endotypes.

Black children have lower sensitization rates compared to White children

Although there were no differences between the races with respect to early onset of AD (<3 months of age) or SCORAD at V1 (Table I), we observed vast differences in sensitization prevalence between Black and White children. White children were more likely to be sensitized overall (52% vs. 35%, $p=0.0001$), have aeroallergen sensitization (37% vs. 25%, $p=0.0031$), and have food allergen sensitization (38% vs. 22%, $p<0.0001$, Figure 2A). White children also had almost double the rate of co-sensitization to both aeroallergen(s) and food allergen(s) (23% vs. 12%, $p=0.0008$, Figure 2A) and had a higher sensitization load (IQR 0-1 vs. 0-2, $p<0.0001$, data not shown). This was surprising as sensitization, especially polysensitization has been shown to be a risk factor for asthma²¹⁻²⁴, yet asthma risk was higher in the black children. There were no differences in Total IgE between Black and White children ($p=0.67$).

Black children have higher skin FLG expression and lower TEWL than White children

Given the marked racial differences in disease trajectories, we next examined whether differences in skin barrier function may underlie this as poor skin barrier integrity has been reported to be a risk factor for the development of allergic co-morbidity^{25, 26}. Further, we have previously reported that non-lesional FLG level is most predictive of development of co-sensitization and moderate to severe AD². Therefore, we evaluated objective measures of skin barrier integrity including keratinocyte *FLG* expression level and TEWL. The most common regions sampled were the dorsal arm, intrascapular region and back of the leg for lesional site and abdomen, volar forearm and intrascapular region for non-lesional site. The site of sample did not differ between Black and White children. The median coefficient of variation within child for TEWL was 8.5%. Black children exhibited higher skin barrier quality and function, having higher *FLG* expression in the non-lesional skin ($p=0.02$, Figure 4A) and lower TEWL in both the non-lesional ($p=0.005$) and lesional skin ($p<0.0001$, Figure 4B). There were no differences in the *FLG* expression level between Black and White children in the lesional skin ($p=0.28$, Figure 4A), further supporting the importance of the non-lesional skin in AD.

Genetic heritability for co-morbid allergic disease development differs by race

Given that the trajectories of the atopic march were very heterogeneous by race, we next investigated factors that may be contributing to asthma risk other than sensitization. For PARS, children receive 2 points for Black race/African ancestry¹⁹. We observed a 3-point difference in total PARS score in MPAACH Black children compared to White children, suggesting the observed increase in PARS scores in Black children was not solely due to the 2 points for Black race/African ancestry. As a proxy for genetic factors, we first evaluated parental allergic disease history differences between the races. This increase in PARS score above Black race/African ancestry was being driven by a significant increase in parental asthma (48% vs. 38%, $p=0.032$, Figure 5). Black MPAACH children were also nearly 1.5 times more likely to have a history of parental AD (64% vs. 49%, $p=0.0003$, Figure 5). In contrast, White children had an increased risk of parental environmental allergies/hay fever (80% vs. 57%, $p<0.0001$, Figure 5).

Since the parental histories of allergic diseases were different between Black and White MPAACH children, we next estimated SNP-based heritability of PARS by race. We used a likelihood ratio test to compare two models (with and without genetic data) separately by Black and White. In Black children, there was a significant genetic contribution to PARS (0.66 ± 0.37 ($p=0.019$)). In contrast, the genetic contribution to PARS was not significant in White children (0.43 ± 0.52 ($p=0.10$)). While the standard errors are large, this data in conjunction with the higher parental history of allergic disease in Black children supports that Black children have a higher contribution of genetics to their asthma risk compared to White children.

Environmental exposure risk factors for co-morbid allergic disease development differ by race

We also evaluated environmental exposures as a possible mechanistic contributor to the racial differences we observed in allergic comorbid disease development. White children were significantly more likely to own a dog or cat, both currently and during the first year of life,

compared to Black children (all $p < 0.0001$, Table II). This is relevant as pet ownership in early life may be protective against asthma development²⁷⁻³⁰.

We next evaluated air pollutants that are known to increase asthma risk, specifically SHS exposure and traffic related air pollution (TRAP). A recent meta-analysis of 93 studies concluded that secondhand smoke exposure was significantly associated with asthma, particularly in younger children³¹. In MPAACH, Black children were much more likely to have SHS exposure (57% vs. 34%, $p < 0.0001$, Table II) compared to White children. Accordingly, the median serum cotinine in the Black MPAACH children was almost 2-fold higher than the White children (0.33 vs. 0.17 ng/mL), although this difference did not reach statistical significance due to large variability in the data ($p = 0.108$, Table II). We and others have reported that exposure to TRAP is associated with the development of asthma in children³²⁻³⁴. In MPAACH, Black children had higher estimates of TRAP (0.4g/m³ vs. 0.3g/m³, $p = 0.0001$, Table II) compared to White children.

Racial differences in allergic trajectories are defined by distinct longitudinal endotypes

There are no differences in age of onset or severity of AD between Black and White children, yet the allergic trajectories are vastly different, evident by distinct endotypes. The molecular endotype of AD in the Black children underlying the observed progressor phenotype of high asthma risk independent of FA/AR is characterized by low sensitization, decreased lesional and non-lesional TEWL, increased non-lesional *FLG* expression, higher genetic heritability for asthma, increased SHS and TRAP exposures, and decreased cat and dog exposures (Table III). In contrast, the molecular endotype of AD in the White children underlying the observed progressor phenotype of FA/AR without high asthma risk is characterized by high sensitization, increased lesional and non-lesional TEWL, decreased non-lesional *FLG* expression, decreased exposures to SHS and TRAP and increased ownership of cats and dogs in the first year of life (Table III).

DISCUSSION

Our data provide a foundation for a new atopic march paradigm that includes Black and White children. The allergic comorbid trajectories for Black and White children with AD are vastly different. The progressor phenotype most often observed in the Black children was high asthma risk independent of sensitization, AR and/or FA, while White children were most likely to progress to FA, AR and sensitization to both aeroallergens and foods without high asthma risk, revealing that the traditional atopic march largely does not exist in Black children. When we examined endotypic factors underlying the progressor phenotypes, Black children had increased parental history of AD and asthma, higher genetic heritability for high asthma risk (PARS ≥ 9), and increased environmental exposures to air pollutants, but they did not have increased barrier dysfunction and had less sensitization. In contrast, the endotypic factors underlying progression in the White children were decreased skin barrier quality and function, evident by increased TEWL and decreased keratinocyte *FLG* expression, increased sensitization to food and aero allergens, and increased pet ownership. These data collectively suggest that genetic predisposition and environmental exposures to air pollutants may contribute to progression to asthma in Black children, while White children may be more likely to sensitize through a more dysfunctional skin barrier, promoting the development of FA and AR.

There is a growing body of evidence that sensitization occurs more readily through an impaired skin barrier, particularly in AD^{26, 35, 36}. We have previously reported in MPAACH that children with higher SCORAD scores have higher TEWL and lower skin *FLG* expression, as well as higher rates of co-sensitization to both aero and food allergens, suggesting that both food and aeroallergen sensitization is occurring through the skin². *FLG* is an essential epidermal protein expressed in the outer layers of the epidermis, and plays an important role in maintaining skin barrier integrity²⁶. In murine models, flaky tailed mice with the 5303delA *FLG* mutation (analogous to human *FLG* mutations) treated with topical OVA have increased specific IgE to OVA compared to wild-type mice, supporting antigen transfer through the skin³⁷. We have also shown that total

serum IgE and *A.fumigatus*-specific IgG1 were significantly increased after epicutaneous *A.fumigatus* exposure in mice³⁸. As in *FLG* mutation-induced skin barrier dysfunction, skin exhibiting significantly decreased *FLG* expression levels may allow for penetration of allergens and lead to the development of systemic allergic responses and comorbidities including FA and AR.

Our data show that in MPAACH, the higher rates of sensitization, FA, AR and decreased skin barrier quality are most evident in the White children, despite no differences in SCORAD or age of AD onset by race, suggesting differences in the underlying skin biology. *FLG* loss of function mutations are 6 times more frequent in individuals of European ancestry³⁹. *FLG* deficiency alters the shape of the corneocytes in the skin and leads to decreased stratum corneum hydration and downstream production of acidic metabolites of *FLG* proteolysis, resulting in increased skin pH and skin permeability⁴⁰. The stratum corneum in White skin has been shown to have less corneocyte layers than Black skin, despite no difference in skin thickness⁴¹. In addition, the mean electrical resistance in the skin of White adult subjects is half that of adults with Black skin⁴² and subjects with lighter skin require fewer tape strips to disrupt the epidermal barrier as measured by TEWL⁴³, supporting that White skin may have decreased intercellular cohesion compared to Black skin. These racial differences in the skin barrier quality and biology could, in part, explain the differences in allergen sensitization, FA and AR between the Black and White children in MPAACH.

While the Black MPAACH children had a stronger skin barrier, the parental history of AD and asthma was much higher in the Black children and we observed a higher contribution of genetics to their asthma risk compared to White children. To our knowledge, this is the first report of black children having an increased genetic heritability of high asthma risk. While GWASs have identified many loci reaching genome wide significance for asthma in individuals of European descent, individuals with African ancestry are severely underrepresented in these studies⁴⁴, thus it is difficult to make inferences about the how much genetics plays a role in the risk of asthma in

individuals of African descent. In addition to genetics, other factors are likely to play a role, most notably environmental factors cannot be dismissed⁴⁵.

Indeed, Black MPAACH children had increased exposures to SHS and TRAP and decreased in-home exposures to pets in early life. It is well documented that SHS exposures cause asthma exacerbation and a recent meta-analysis of 93 studies concluded that secondhand smoke exposure was significantly associated with asthma, particularly in younger children³¹. Our observation that Black MPAACH children are 1.7 times more likely to be SHS exposed compared to White children are in line with 2013-2014 NHANES data from 3-11 year olds, showing while overall rates of SHS exposure declined among children since 1999-2014, non-Hispanic Black children were still 1.85 times more likely to be exposed than non-Hispanic White children⁴⁶. Our observation that Black MPAACH children are exposed to disproportionately high levels of TRAP also mirror the racial inequality in air pollution exposure in the United States^{47, 48}. Exposures to ambient air pollution including TRAP, can exacerbate existing asthma^{49, 50}, and we and others have also shown that exposure to TRAP is associated with the development of asthma in children³²⁻³⁴.

In contrast to air pollution, Black MPAACH children are less likely to have pets in the home both currently and in the first year of life. This is highly relevant as pet ownership in early life may be protective against asthma development²⁷⁻³⁰. One study reported that having a dog or cat in the house in the first year of life may protect against childhood asthma and allergy by up to 40%⁵¹. It is hypothesized that pets confer protection from allergy and asthma development by increasing the richness and diversity of the microbiome environment in the home⁵². The "Microbiota Hypothesis" proposes that the environmental microbial diversity (in this case from pet ownership) influences the assemblage process of an infant's gut microbiota ecosystem which subsequently, in partnership with exposure to allergens and microbes, influences the child's immune development and risk for allergies and asthma⁵³.

Limitations of this study include that asthma was not objectively diagnosed due to the young age of the participants. However, children with a PARS score of ≥ 9 have a 40-79% risk of developing asthma by age 7¹⁹. It is also difficult to disentangle race from socioeconomic factors (such as public insurance and income, environmental exposures) and sociocultural factors that may also contribute to the risk of allergic comorbidity development. It is likely that many factors have a concerted role. Black children are disproportionately impacted by asthma prevalence, morbidity, and mortality and studies have shown that this race-asthma association is not eliminated after adjusting for socioeconomic factors^{3, 54} suggesting that race may also serve as a proxy for a critical biologic factor that we do not currently recognize. While race, insurance type, income and education level are likely also contributors and proxies for other relevant exposures, our skin data support an inherent difference in skin biology between the races that contributes to allergic disease progression. In addition, we only had data available for one skin barrier protein (*FLG*). We will include other barrier proteins important in cell proliferation and differentiation, such as occludin, claudins, keratins, transglutaminases and loricrin in the future. Since our study has a high prevalence of Black children, reflective of the surrounding city of Cincinnati⁵⁵ and the increased risk of eczema in Black children⁵⁶, the results may not be generalizable to all children with AD in the US. However, the high number of Black children in MPAACH allows us to investigate factors promoting allergic disease progression in this otherwise greatly understudied population.

These data collectively support that progression of allergic disease is multi-faceted and differs by race. Black children in MPAACH do not follow the traditional atopic march; rather they are most likely to progress straight to high risk of asthma rather than develop sensitization, FA or AR. Our results suggest that these Black children suffer disproportionately from air pollution, have increased genetic heritability of asthma and do not have exposure to pets in the home that confer protection from allergic disease development, culminating in development of asthma. In contrast, White MPAACH children suffer from a poor skin barrier that allows allergen penetration and

subsequent sensitization, leading to the development of primarily FA and AR. Our data support that the traditional atopic march does not exist in Black children and the provides a foundation for a new atopic march paradigm that includes Black children. We will continue to follow the MPAACH participants as they age to determine the allergic trajectories followed by Black and White children with AD. In the future, these unique longitudinal data may inform a risk score for predicting allergic disease progression in children with AD.

Acknowledgements

We thank the participating families and staff on the MPAACH study.

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Table I. Demographics and AD Onset and Severity in Black and White MPAACH Children.

Total N=601	Black n=410	White n=191	p-value
Demographics			
Male Sex	52.4%	52.9%	0.920
Age at enrollment (years), median (IQR)	2.06 (1.29 - 2.39)	2.12 (1.57 - 2.44)	0.012
Public Insurance	93.1%	30.8%	<0.0001
Early AD Onset 0-3 Months	44.5%	44.0%	0.9050
AD Severity			
SCORAD (score) median (IQR)	19.7 (12.3 - 30.7)	18.9 (11.6 - 27.7)	0.295
SCORAD (severity group)			
Mild (SCORAD <25)	62.9%	67.5%	0.469
Moderate (SCORAD ≥25)	32.2%	27.2%	
Severe (SCORAD ≥50)	4.9%	5.2%	

Table II. Environmental Exposures in Black and White MPAACH Children at V1.

Total N=601	Black n=410	White n=191	p-value
Owned a dog in the 1st year of life	21.5%	55.5%	<0.0001
Currently live with a dog	12.2%	48.2%	<0.0001
Owned a cat in the 1st year of life	5.1%	22.5%	<0.0001
Currently live with a cat	3.4%	20.9%	<0.0001
Parental reported SHS exposure (cigarettes/cigars)	56.8%	33.5%	<0.0001
Serum cotinine median (IQR), ng/mL	0.33 (0.0 - 1.46)	0.17 (0.0 - 0.91)	0.108
TRAP median (IQR), ug/m3	0.4 (0.3 - 0.5)	0.3 (0.3 - 0.4)	<0.0001

SHS=secondhand smoke exposure, IQR=interquartile range, TRAP=traffic-related air pollution

Table III. Endotypic and environmental factors underlying the co-morbid allergic progressor phenotypes in Black and White children with AD

	Black Children	White Children	p-value
Primary Progressor Phenotype	High asthma risk independent of sensitization, AR or FA	AR and/or FA without high asthma risk	<0.0001
Factors Underlying Progressor Phenotype			
Endotypic Factors			
Non-lesional FLG Expression	1.66 (IQR 0.64-3.55)	1.15 (IQR 0.32-3.19)	0.02
Non-lesional TEWL*	9.4 (7.2 - 12.9)	10.8 (7.6 - 14.9)	0.005
Lesional TEWL*	11.3 (8.1 - 17.5)	15.4 (10.1 - 24.9)	<0.0001
Sensitization	35.0%	52.4%	<0.0001
Environmental Factors			
SHS	56.8%	33.5%	<0.0001
TRAP (ug/m3)	0.4 (0.3 - 0.5)	0.3 (0.3 - 0.4)	<0.0001
Dog in the first year of life	21.5%	55.5%	<0.0001
Cat in the first year of life	5.1%	22.5%	<0.0001
Genetic Factors			
Heritability for PARS	0.66 ± 0.37	0.43 ± 0.52	n/a

*Published TEWL in healthy control subjects is 7.2 for White children and 5.7 for Black children⁵⁷. AR: allergic rhinitis, FA: food allergy, IQR: interquartile range, FLG: filaggrin, TEWL: trans-epidermal water loss, SHS: secondhand smoke exposure, TRAP: traffic-related air pollution.

Figure Legends

Figure 1. Progressor Phenotypes of Black and White MPAACH Children. A. Progressor phenotype across V1 and V2 by race (n=456). B. Children with at least one co-morbidity across V1 and V2 (n=325). *children that did not have a co-morbidity at V1 and did not yet complete V2 were not included in the non-progressor phenotype (n=145).

Figure 2. Sensitization patterns Food Allergy and Allergic Rhinitis in Black and White MPAACH children at visit 1.

Figure 3. A) maximum respiratory symptom frequency score and B) Pediatric Asthma Risk Scores (PARS) in Black and White MPAACH children at visit 1.

Figure 4. Skin FLG expression and TEWL in non-lesional and lesional skin in Black and White MPAACH children at visit 1.

Figure 5. Parental AD, asthma and environmental allergies/hay fever in Black and White MPAACH children.

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%

Progressor
Phenotypes

