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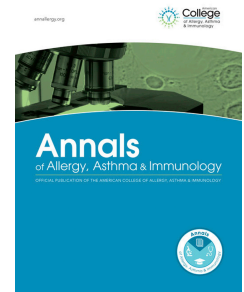
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African American Ancestry Contribution to Asthma and Atopic Dermatitis**Michelle Daya and Kathleen C. Barnes**

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1 Introduction

2 Despite advances in therapeutics and a better understanding of environmental risk factors,
3 racial disparities in both asthma and atopic dermatitis (AD) are profound, and cannot be
4 explained by non-genetic factors alone^{1,2}. Disparities are compounded by a disproportionate
5 under-representation of minority populations in genetic and pharmacogenetic studies of
6 asthma and AD. As a result, genetic risk factors for these clinical conditions are much less well
7 understood in African ancestry populations compared to European populations. Because of
8 their shared as well as different evolutionary histories with regard to environmental exposure,
9 African ancestry populations probably share some genetic underpinnings of disease with other
10 population groups, but distinct genetic risk factors are also likely at play, as evidenced by the
11 increased prevalence and severity of asthma and AD in African ancestry populations, different
12 disease characterization markers, and different efficacy of drugs used to treat disease. Here, we
13 review the literature of GWAS of asthma and AD in African ancestry populations, discuss shared
14 and unique underpinnings of disease, highlight the importance of ancestry-aware
15 pharmacogenetic implementation, and build a case for the urgent need to perform large scale
16 genetic studies of asthma and AD in African ancestry populations.

18 ***Populations of African ancestry suffer disproportionately from asthma and atopic dermatitis.***

19 In the U.S., childhood asthma prevalence is ~twice as high in African Americans compared to
20 European Americans, and African American children are >10 times more likely to die from
21 asthma than whites (<https://minorityhealth.hhs.gov>). Individuals of African ancestry have
22 greater asthma morbidity and mortality both within³ and *outside* the U.S.⁴, and asthma

prevalence is high in African countries and countries with populations of African ancestry^{4,5}, supporting a role for genetics. Similarly, AD is more common among non-Hispanic blacks than whites (~17% vs. 10-11%)⁶, and African Americans suffer greater childhood AD severity^{7,8}, have increased healthcare utilization⁹ and hospitalization¹⁰ compared to white AD patients.

Markers used to characterize asthma and AD phenotypes also differ by race and ethnicity. A consideration in asthma phenotyping is that individuals of African ancestry have 10-15% lower spirometric values (*i.e.*, forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁)) than those of European ancestry, warranting the need for a correction factor for prediction equations¹¹. Biomarkers of the allergic diathesis, relevant to both traits – notably total and specific serum IgE levels – are higher in individuals of African ancestry^{12,13}.

For AD, the measurement of transepidermal water loss (TEWL) is commonly used as a biomarker of skin barrier function, and correlates with disease severity¹⁴. TEWL values are reportedly higher in the *normal skin* of individuals of African ancestry compared to whites^{15,16}, and among *AD patients*, higher in whites compared to blacks, despite more severe disease among black AD patients¹⁴. Also, the ceramide component of the stratum corneum, which is essential for maintaining barrier integrity, differs according to ethnicity and race, wherein individuals of African ancestry have lower ceramide/cholesterol ratios than whites or Asians¹⁷.

AD is characterized by recurrent bacterial skin infections (*i.e.*, *Staphylococcus aureus*), which occur in 55%-90% of AD patients in both lesional and nonlesional skin^{18,19}. Persistent bacterial colonization tracks closely with disease severity²⁰ and higher total serum IgE (tIgE) levels^{19,21}. The prevalence of genes encoding superantigens (SAGs) was examined from AD *S. aureus* isolates collected over a 6-year period as part of the NIAID Atopic Dermatitis Research

Network (ADRN), showing a higher prevalence of *tstH*, the gene encoding toxic shock syndrome toxin 1 (TSST-1), which is associated with *decreased* severity of AD. Interestingly, ~90% of the isolates from African American patients lacked the gene for TSST-1, compared to 76% European Americans and 66% Mexican Americans, and it was proposed that differences in these *S. aureus* virulence factors may predict differences in infection types and disease severity²².

How ancestry influences risk of asthma and AD: lessons learned from genome-wide association studies (GWAS).

Both asthma and AD are highly heritable, with estimates of the contribution of genetic variation to developing disease ranging between 35-95% for asthma and 71-84% for AD²³. With the advent of the technology for interrogating DNA, linkage studies were conducted to identify broad regions of the genome inherited more frequently by affected compared to unaffected family members of patients with asthma and AD. After the assembly of the human reference genome and its catalog of putative protein-coding genes, the field moved towards population-based candidate gene association studies, in which genetic variation in genes hypothesized to play a role in disease were tested for disease association. Subsequently, the development of cost-effective arrays that can genotype hundreds of thousands to millions of genetic variation genome-wide led to the advent of genome-wide association studies (GWAS), the current state-of-the-art method for interrogating the role of genetic variation in disease in an unbiased, hypothesis-generative manner. Results from GWAS are key to increased understanding of genetic risk factors for asthma and AD in common between population groups, as well as genetic risk factors unique to African Americans. An added advantage of GWAS is the use of

genome-wide markers to verify self-reported race (e.g. Black or White) and ethnicity (e.g. Hispanic or non-Hispanic) by estimating ancestral components (e.g. proportions of African, European and Native American ancestry) for each individual, as opposed previous older study designs which typically relied on self-reported status only. In admixed populations, these estimates of ancestral component proportions can also be used to test whether ancestry is correlated with disease outcomes [ref 12]. As reflected in **Table 1**, all asthma and AD GWAS of African ancestry populations reported to date have either verified self-reported status with GWAS data or exclusively relied on GWAS data to classify research subjects according to race and ethnicity.

An ongoing challenge in understanding the role that ancestry plays in risk of asthma and AD is the underrepresentation of non-white populations in federally funded and published studies, including GWAS^{24,25}. This situation is not unique to allergic disease: recently it was concluded that non-European, non-Asian groups combined account for <4% of individuals represented in the international GWAS catalog²⁴, and African ancestry individuals contributed 7% of all catalog associations, despite only comprising 2.4% of the catalog. This report highlights the value of GWAS conducted in African ancestry populations for empowering scientific discoveries. At the time of this review, we estimated that African ancestry individuals comprised 5% of the number of subjects reported for asthma studies in the GWAS Catalog, slightly better than the overall representation across all reported traits; however, AD representation is worse: African ancestry individuals in AD studies only comprised 0.7% of subjects.

In addition to the relative paucity of African American subjects in genetic studies, until fairly recently, genetic studies of African Americans were hampered by a lack of whole genome sequence data from African ancestry individuals. As a result, the first few generations of GWAS arrays provided inadequate coverage of African ancestry genetic variation²⁶. Furthermore, the lack of sequence data also limited genotype imputation of polymorphisms not directly assayed by the arrays. Sequencing efforts of the *International HapMap Project*, *1000 Genomes Project* and the *Consortium on Asthma among African-ancestry Populations in the Americas* (CAAPA) have led to the development of genotyping arrays that better captured African genetic variation, such as Affymetrix's Pan-African array and Illumina's Multi-ethnic Genotyping Array (MEGA). These sequence data also enabled genotype imputation of African American genetic data through their use as imputation reference panels. Further improvements in imputation of low and rare frequency variation in African ancestry populations are now possible through initiatives such as the NHLBI-supported Trans-Omics for Precision Medicine, or TOPMed, program (<https://www.nhlbi.nih.gov/science/trans-omics-precision-medicine-topmed-program>), which has dramatically improved the catalog of African American sequences.

Although relatively small in number and sample size, a number of asthma and one AD GWAS of African ancestry populations have been reported to date (**Table 1**). The genes summarized in Table 1 are plausible candidates for playing a role in the development of asthma, but none of the associations have been replicated by other studies, due to the lack of suitable and suitably sized replication populations. In total, four loci have reached genome-wide significance²⁷⁻²⁹, of which 3 have not been reported by asthma GWAS in non-African populations (**Table 1**). Notably, African ancestry individuals have only been included in one AD

GWAS to date³⁰, and because of the relatively small number of individuals included in this single study, no associations achieved genome-wide significance, and no African ancestry-specific results were reported. Consequently, no data from an unbiased genome-wide investigation of genetic risk factors for AD in African ancestry individuals is available in published literature. In comparison, the largest asthma and AD GWAS's were published by the *Trans-National Asthma Genetic Consortium* (TAGC; 19,954 European asthma cases and 107,715 controls)³¹ and the EARly Genetics & Lifecourse Epidemiology (EAGLE) eczema consortium (18,900 European AD cases and 84,166 controls)³⁰, respectively. In these GWAS, 16 asthma loci and 21 AD loci reached genome-wide significance in Europeans. Given the large European ancestry sample sizes available through these consortia, the relatively large number of European ancestry discoveries are not surprising. The CAAPA program recently performed the largest GWAS of asthma in African ancestry population to date (7,009 asthma cases and 7,645 controls), with findings recapitulating asthma risk loci discovered previously in non-African populations²⁹. Of the 18 loci reported by the TAGC GWAS (whose discovery was largely driven by >90% European ancestry individuals), four loci showed strong evidence for replication in CAAPA: the *IL33* (chromosome 9p24), *RORA* (chromosome 15q22), *STAT6* (chromosome 12q13) and *ORMDL3-GSDMB-PGAP3* (chromosome 17q12-21) gene regions. An additional 7 loci showed some but relatively marginal evidence for replication in CAAPA, and a novel association on chr8p23 not previously identified by any asthma GWAS reached genome-wide significance. The findings from CAAPA are consistent with the Morales et al. study²⁴, which found that some complex disease risk loci generalize across ancestries, while others appear to be ancestry-specific.

In addition to difference in sample size, which affects statistical power to detect associations (*e.g.*, large sample size European ancestry GWAS are better powered to detect associations than small sample size African ancestry GWAS), a number of factors influence between population differences of variants associated with disease: **(1)** differences in allele frequency (genetic impact) – risk alleles that are present at a relatively higher frequency in a particular population have a higher impact on disease risk in that population, with less statistical power to detect association of lower frequency variants; **(2)** differences in effect size (genetic effect) – risk alleles that have a relatively larger increase in risk in a particular population, or a non-zero effect in a particular population but a zero effect in others, or opposite directions of effect *i.e.* increases risk in one population but decreases risk in another; and **(3)** differences in the correlation structure (linkage disequilibrium, or LD) between genetic variants - variants reported by GWAS are not necessarily causal, but may be a “tagging” variant that is correlated with the true causal variant. These factors are illustrated in detail in Figure 1 for asthma related phenotypes. For example, certain allelic variants in asthma and AD candidate genes are more common in people of non-European descent, including variants associated with response to therapy. A classic example is a common coding variant (Gly16Arg) in the gene encoding the beta-2 adrenergic receptor (*ADRB2*), whereby African- or Asian- ancestry asthmatics are more likely to carry the homozygous Arg¹⁶Arg genotype, which is associated with poorer lung function during regular treatment with albuterol³².

An excellent example of the impact of LD structure and differences according to ancestry is the chromosome 17q12-21 locus and associations with asthma³³. Associations in single nucleotide polymorphisms (SNPs) near the *ORMDL3* gene were reported in the first

asthma GWAS³⁴ and subsequently widely replicated in ethnically diverse populations. However, the SNPs significantly associated in the discovery population (European) then replicated elsewhere, but were not significantly associated with asthma in several independent African American populations³³. Recently it was proposed that the strength of associations between SNPs in this locus and asthma is relatively weak in African Americans, and that the reduced strength of association may be due to an overall lower minor allele frequency (MAF) spectrum in African Americans in this region (which would reduce statistical power to detect association), breakdown of LD on African haplotypes, and different asthma endotypes (*i.e.*, viral exposures) in children³³. Although this locus was associated with asthma in CAAPA, it did not reach genome-wide significance when analyzing African American subjects alone, and it was determined that the association was largely driven by other African-admixed populations outside of the U.S. with relatively large European or Native American ancestral components²⁹. In addition, a stratified analysis of African American subjects by the number of copies African ancestry at the chromosome 17q12-21 locus showed that the effect size of putative causal variants in this locus are smaller on African ancestry haplotypes compared to European ancestry haplotypes²⁹.

The role of population history in shaping genetic variation in allergic disease.

One of the strongest evolutionary forces that shaped genetic variation in humans is exposure to pathogens^{35,36}. The immune system has adapted defense mechanisms against a multitude of microorganisms, which the immune system learns to distinguish especially during childhood. Children growing up in modern-day sterile environments have a less educated and less mature

immune system compared to their evolutionary counterparts in history, resulting in immune tolerance and susceptibility to allergies such as asthma and AD (e.g., the 'Hygiene Hypothesis'³⁷). Due to the shared genetic history of human populations, the potential to develop this warped immune response likely shares genetic risk factors and mechanisms, but differences in environmental exposures between population groups in their evolutionary history may also have resulted in distinct genetic risk factors between groups. Among African-admixed populations, the correlation between African ancestry and higher levels of tIgE^{12,13} suggests that genetic variation inherited from an African ancestry background induces a stronger Th2 immune response compared to non-African ancestry, and thus increased genetic risk for allergic disease. A recent study that investigated changes in the transcriptional response upon exposure to a number of pathogens also found that African ancestry was associated with an increased inflammatory response³⁵.

In contrast, disruptive skin barrier loss of function (LOF) mutations in the filaggrin (*FLG*) gene is a major risk factor for developing AD in European populations³⁸, as well as risk of asthma secondary to AD³⁹. In addition to a theory that these *FLG* mutations may have increased immunity during European pandemics due to increased exposure of pathogens to epithelial antigen-presenting cells³⁹, it is thought that the mutations increase vitamin D biosynthesis and thus an evolutionary advantage in the high latitudes of Northern Europe^{40,41}. Interestingly, these LOF *FLG* mutations that are relatively common in populations of Northern European descent have a much lower prevalence in African Americans (and are likely inherited from their European ancestral component), are absent or very rare in continental African populations assessed to date, and are not associated with AD in African Americans⁴². However,

recent reports suggest that skin barrier function disruption certainly play a role in development of AD in African ancestry individuals, but is probably caused by alternative genetic mutations^{42,43} (i.e., *FLG*⁴³ and possibly rare LOF mutations identified by alternate sequencing technologies⁴⁴).

Clinical implications. Similar to genetic studies, there is a lack of diversity of ancestral groups in federally funded clinical trials, limiting our understanding of the efficacy of targeted therapeutics for asthma and AD. In a recent, comprehensive review of all randomized clinical trials (RCTs) between 2010 to 2015 targeting dermatologic conditions, nearly 75% of the study participants were white⁴⁵. The statistics are worse for respiratory trials, which include less than 5% non-whites (<https://undark.org/2016/04/28/confronting-legacy-keeps-african-americans-away-clinical-trials/>).

Pharmacogenetics is a rapidly expanding area in personalized medicine that studies how genetic makeup determines a patient's drug response with the goal to optimize drug efficacy and reduce toxicity. Multiple candidate gene studies have identified variants in genes in the leukotriene, glucocorticoid, and beta-2 adrenergic receptor pathways associated with therapeutic responsiveness in asthmatics⁴⁶. A number of studies have suggested that significant differences in risk allele frequency between blacks and whites could account for differences in response to therapy, exacerbations, and severity of exacerbations. Far fewer pharmacogenetics studies have been performed on AD. Oral corticosteroids are a cornerstone of management of both severe asthma and AD, and there is increasing evidence of corticosteroid resistance; however, to date the data supporting specific genetic variants

associated with oral corticosteroid response is limited. In one of several studies on nephrotic syndrome among children, polymorphisms in the gene encoding multidrug resistance mutation 1, or *MDR1* (also known as adenosine triphosphate-binding cassette B1 (*ABCB1*)), were associated with increased disease susceptibility and steroid resistance⁴⁷. Perhaps surprisingly, the frequency of the allele associated with increased disease susceptibility and resistance to steroids is found at *low* frequency in African populations, but *high* frequency in European populations (rs2032582; A allele frequency in Thousand Genomes Europeans=0.41, Africans = 0.02), which would suggest that individuals of African descent may be better responders to steroids. Clearly, robustly designed studies to further investigate the role of variants in *MDR1* and response to steroids according to ethnicity are warranted, and should be extended to use of oral steroids in allergic disease.

Tacrolimus (FK506) is a calcineurin inhibitor that suppresses eotaxin 1 and RANTES expression in lesional skin⁴⁸, and is used to treat AD. There is considerable interpatient pharmacokinetic variability in tacrolimus concentrations, and the role of genetic polymorphisms on tacrolimus metabolism is of particular interest. Several polymorphisms have been associated with lower tacrolimus concentrations, including those in the genes encoding cytochrome P450 oxidoreductase (*POR*), cytochrome (CYP) 3A5 (*CYP3A5*) and *MDR1*, but most studies have focused on patients with nephrological conditions^{49,50}. Importantly, there is more genetic diversity in CYP distribution among African ancestry populations, and recently a protocol incorporating African American specific CYP3A5 genotype-guided tacrolimus dosing was developed for kidney transplant recipients receiving tacrolimus⁵⁰.

Conclusion

It is hoped that the recent development of institutional biobanks with access to multi-ethnic patient populations⁵¹, as well as efforts by institutions such as the National Institute of Health to reduce health and research disparities⁵² will greatly expand representation of well-characterized African American patients in future genetic studies. Despite the current challenge of underrepresentation of African Americans in genetic studies, such studies have huge potential for elucidating complex disease etiology. One of the techniques that can be used to identify genetic risk factors for complex disease in admixed populations is admixture mapping, which identifies regions of the genome from where ancestry from a particular ancestral population with a higher risk of disease is inherited more frequently in affected versus unaffected individuals. A major advantage of admixture mapping over traditional GWAS is a reduced burden of correcting for multiple statistical tests, and thus smaller sample size requirements compared to GWAS. While admixture mapping has been used in disease gene discovery of a number of diseases in African Americans including prostate cancer and kidney disease⁵³, no successful African American admixture mapping studies have been reported in the literature for asthma and AD, which implies that either these studies did not yield interesting results and thus suffers from publication bias, or that this tool has not been employed widely by asthma and AD investigators. (CAAPA reported an admixture mapping study as part of their asthma GWAS, and although 1 genome-wide significant association was identified, replication was unsuccessful, possibly due to the limited sample size of the replication data sets available.) Admixture mapping may therefore yet be an untapped resource for identifying genetic risk factors for asthma and AD in African Americans. In addition to admixture mapping, African

American GWAS will likely lead to the identification of genetic variation at play in disease etiology that are not detectable in non-African populations, as suggested by others²⁴. Multi-ethnic fine-mapping of associations present across ancestries is a powerful tool towards identifying causal variants in regions identified by GWAS, and shorter blocks of LD present in African ancestry populations can further enhance these efforts through reducing the number of variants included in the credible set of variants constructed by these analyses⁵⁴. The possible polygenic and even omigenic genetic architecture of complex disease⁵⁵ are receiving much attention in the field of genetics, and the potential clinical application of this hypothesis is evidenced by recent success in building polygenic risk scores (PRS) for individuals at high risk for coronary artery disease, atrial fibrillation, type 2 diabetes, inflammatory bowel disease, and breast cancer⁵⁶. However, as large samples are required to build PRS, and as PRS are not transferrable across populations⁵⁷, African American asthma and AD patients will not benefit from these applications until large-scale African American GWAS have become a reality.

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Table 1: Summary of findings from asthma and atopic dermatitis GWAS of African ancestry. Novel genes with genome-wide significant associations not reported by other GWAS are highlighted in bold, underlined font.

First Author	Year	Disease	Population and discovery sample size	Reported genes (lead SNP p-value)	Gene functions relevant to disease	Reference
Mathias	2010	Asthma	935 African American cases and controls & 929 African Caribbean asthmatics and family members from Barbados ²	<i>ADRA1B</i> (p=4E-6) <i>PRNP</i> (p=2E-6) <i>DPP10</i> (p=3E-6)	May be associated with pro-inflammatory responses Has been shown to be involved in immune cell activation Murine models have linked airway hyper-responsiveness in mice to the mouse homolog of human <i>DPP10</i>	58
Torgerson ¹	2011	Asthma	1,612 African American and African Caribbean cases (number of controls not reported as some studies were family-based) ²	<u>PYHIN1</u> (p=4E-9 when combined with replication data set)	The pyrin domain is a protein-protein interaction domain that is present in many interferon-inducible proteins that functions in both apoptotic and inflammatory pathways	27
Paternoster ¹	2015	Atopic dermatitis	422 African American cases and 844 African American controls ²	None (results for African American GWAS not available, no African American specific findings reported)		30
White	2016	Childhood onset asthma	812 African American cases and 415 African American controls ²	<i>PTCHD3</i> (p=2E-7)	PTCHD1 up-regulation has been shown to induce a Th2 phenotype in peripheral CC4+ T-cells	59

Almoguera ¹	2016	Asthma	3,037 African American cases and 4,360 African American controls ³	<i>PTGES</i> (p=4E-8)	Prostaglandin E2 may mediate airway remodeling in asthma	28
Demenais ¹	2017	Asthma	2,149 African American cases and 6,055 African American controls ²	African ancestry results were reported in a supplementary table. One association had p<1E-6: <i>TSN2-C2orf84-NCOA1</i> (p=2E-7)	NCOA1 plays a role in inflammatory and metabolic pathways ⁶⁰	31
Daya	2019	Asthma	7,009 African ancestry cases and 7,645 African ancestry controls (3,786 cases and 4,438 controls are African American) ²	<i>ARHGEF10-MYOM2</i> (p=3E-8) <i>TATDN1</i> (p=3E-7) <i>STAT6</i> (p=9E-7) <i>RORA</i> (p=2E-7) <i>ORMDL3-GSDMB</i> (p=4E-12)	<i>ARHGEF10</i> has been associated with exacerbations in chronic obstructive pulmonary disease; genetic variants in <i>MYOM2</i> are predictive of lung function in an isolated European ancestry (Hutterite) population Increased expression of <i>TATDN1</i> in human airway smooth muscle cells stimulated with interleukin 17A Genome-wide significant in the Demenais multi-ethnic meta-analysis Genome-wide significant in the Demenais multi-ethnic meta-analysis Genome-wide significant in the Demenais multi-ethnic	29

meta-analysis

¹ Multi-ethnic studies that included non-African populations. Only results in African ancestry populations are summarized.

² Self-reported ethnicity of African ancestry subjects verified using ancestry estimates from genetic data.

³ Ancestry

Figure 1: Illustration of factors that influence between population differences of variants associated with asthma related phenotypes

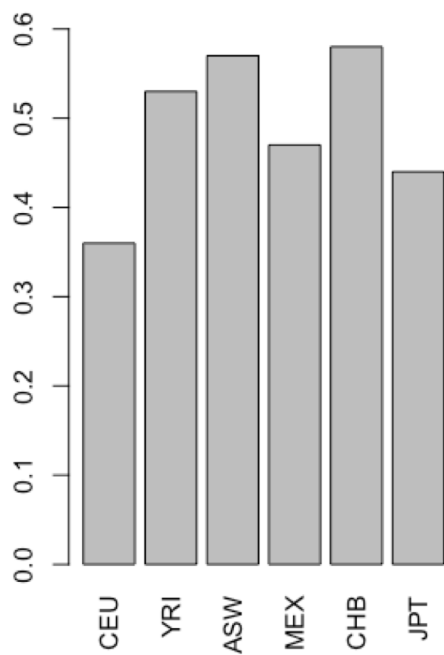
A). Genetic Impact – differences in allele frequency. African- or Asian-ancestry asthmatics are more likely to carry the homozygous Arg16Arg genotype of a common coding variant (Gly16Arg) in the gene encoding the beta-2 adrenergic receptor (ADRB2, which is associated with poorer lung function during regular treatment with albuterol [Ortega, V. E. *J Allergy Clin Immunol* (2014)]). Allele frequencies from the 1000 Genomes Project are shown. CEU=Utah residents with ancestry from northern and western Europe; YRI=Individuals from Yoruba in Ibadan, Nigeria; ASW=African Americans from the southwest United States; MEX=Mexican Americans from Los Angeles, CA; CHB=Han Chinese from Beijing, China; JPT=Japanese from Tokyo, Japan.

B). Genetic effect - differences in effect size. i.) The *IL1RI1* rs10173081 asthma risk allele odds ratio is larger in European Americans and Latinos compared to African American and African-Caribbean populations [Torgerson, D.G. *Nat Genet* (2011)] ii.) rs335016 is associated with asthma in Latinos but have zero effect (odds ratio = 1) in African American and African-Caribbean populations [Torgerson, D.G. *Nat Genet* (2011)]. iii). The minor allele of SNP rs2786098 located in the *CRB1* gene is protective for asthma in European ancestry children (odds ratio < 1), but increases risk for asthma in African American children (odds ratio > 1) [Sleiman, P. M. *N Engl J Med* (2010)]

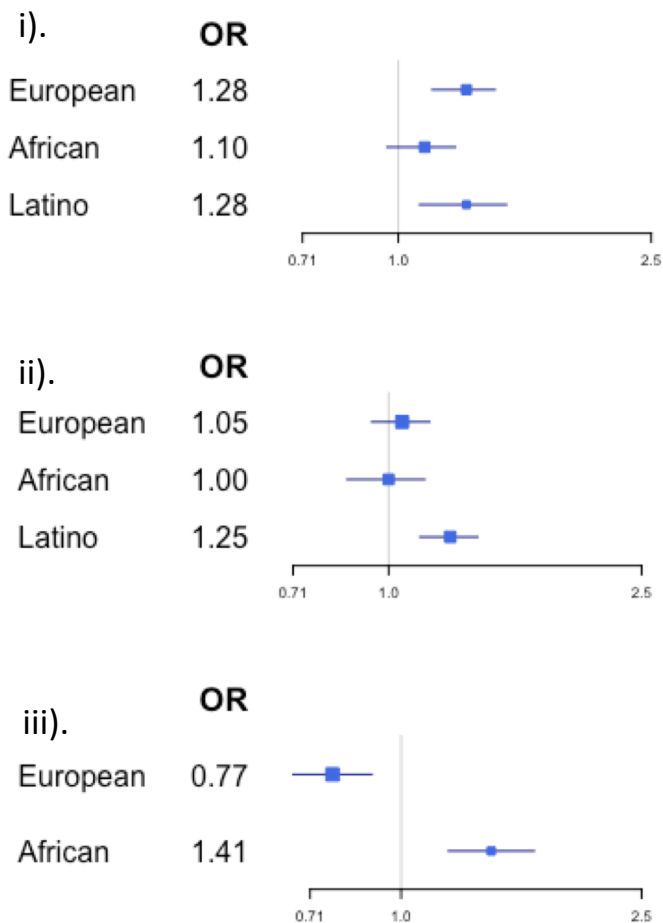
A). Differences in linkage disequilibrium. Variants reported by GWAS are not necessarily causal, but may be a “tagging” variant that is correlated with the true causal variant. The pairwise correlation between genome-wide significant SNPs in the chr17q21-12 locus from the TAGC meta-analysis [Demenais, F. *Nat Genet* (2018)] is shown in European (CEU) vs. African (YRI) ancestry populations from the *1000 Genomes Project*. The

correlation structure between asthma associated variants is markedly different in the two populations.

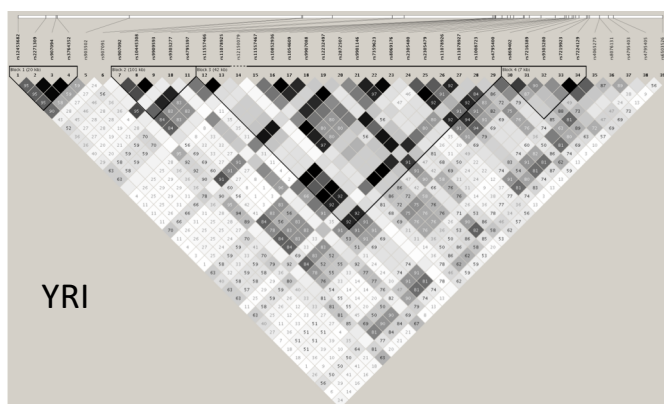
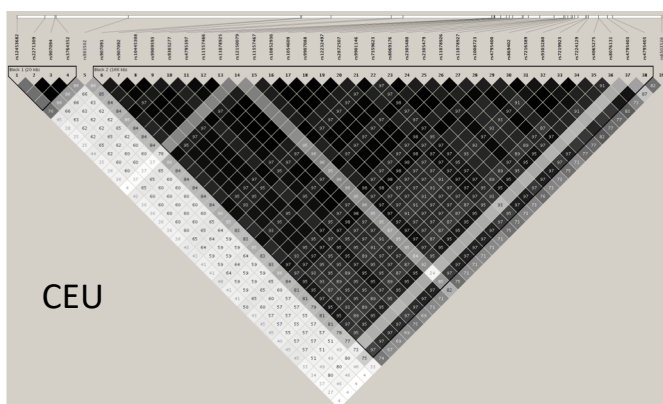
A).



B).



C).



Key Messages

- African Americans suffer disproportionately from asthma and atopic dermatitis (AD), and are under-represented in genetic studies of asthma and AD
- Similar to other complex diseases, some genetic variants conferring risk of asthma and AD and identified in non-African populations are relevant in African ancestry populations
- Because of differences in environmental exposures in the evolutionary history of Africans and Europeans, it is likely that some genetic risk factors for asthma and AD are ancestry specific, *e.g.*, novel asthma loci have been reported in genome-wide association studies (GWAS) on African ancestry asthmatics, and common loss of function mutations in the filaggrin gene associated with AD in European populations may be less relevant in African American AD patients
- Pharmacogenetic studies, which focus on how genetic makeup determines a patient's drug response, have identified differences in polymorphisms in genes that alter therapeutic efficacy according to ancestry, but success in this area is hampered by the limited representation of African Americans in dermatologic and respiratory clinical trials and in genetic research in general
- Large-scale GWAS of asthma and AD in African Americans have not yet been realized, but are essential to reduce research and health disparities and empower scientific discoveries