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Genetic architecture of asthma in African American Patients

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Abstract

Background: Asthma is a chronic inflammatory disorder with a strong genetic inheritance. Although over one hundred loci were reported through the genome-wide association study of European populations, the genetic underpinning of asthma in African Americans remains largely elusive.

Objective: We aimed to identify genetic loci associated with asthma in African Americans.

Methods: Three cohorts were genotyped at the Children's Hospital of Philadelphia (CHOP) using the Illumina SNP array platform. Genotype imputation was performed using the TOPMed reference panel including whole genome sequencing data from over 100,000 individuals. Meta-analysis of three CHOP cohorts and ten CAAPA cohorts totaling 19,628 subjects was conducted to identify genetic loci associated with asthma in African Americans.

Results: Our study identified 12 loci surpassing the classical genome-wide significant threshold (5×10^{-8}). Eight of them reached the stricter significant threshold (3×10^{-8}). The 9p24.1 locus (rs10975467, $P = 1.63 \times 10^{-8}$) has been previously associated with asthma in Europeans. Six

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Conflicts of interest

The authors declare that they have no conflict of interest.

loci are associated with enhancer activities, two loci are in DNase I hypersensitive regions, and all of them are associated with regulatory motifs. Moreover, locus 11q13.4 (rs7480008) is an eQTL (expression quantitative trait loci) of *XRRA1* in lung ($P = 9.4 \times 10^{-10}$), and locus 13q14.3 (rs1543525) is a sQTL (splicing quantitative trait loci) of *DHRS12* in lung ($P = 1.1 \times 10^{-13}$).

Conclusions: Our findings provide candidate genetic loci for therapeutic target identification and prioritization for African populations.

Capsule Summary:

This GWAS analysis adds to our understanding of the pathogenesis of Asthma in African populations and provides candidate genes for further functional studies aimed at the development of novel therapeutic strategies.

Keywords

asthma; African Americans; GWAS

INTRODUCTION

The largest genome-wide association study (GWAS) of asthma has uncovered over one hundred genetic loci from the meta-analysis of over 536,000 subjects[1]. However, asthma GWASs have been performed mostly in European populations. There is an urgent need to study non-European populations such as African American populations, which have notably higher prevalence and greater severity of asthma compared to European Americans[2]. To further elucidate the genetic architecture of asthma in African Americans, we performed the largest meta-analysis, using three cohorts collected at the Children's Hospital of Philadelphia (CHOP) and ten cohorts from the Consortium on Asthma among African-ancestry Populations in the Americas (CAAPA), including 19,628 African American subjects.

RESULTS AND DISCUSSION

Cases and controls were determined by a phenotyping algorithm successfully applied in our previous study[3] (Methods and Supplementary file). This algorithm accrued 8,618 cases and 5,553 controls, who self-reported as African Americans. Participants were genotyped using Illumina SNP arrays, and further divided into three cohorts according to different versions of SNP arrays (HM: HumanHap550/610 arrays; GSA: Global Screening arrays; OMNI: OmniExpress/Omni-2.5 arrays). After quality control measures (Methods), 4182 (2638 cases and 1544 controls), 6483 (3876 cases and 2607 controls) and 739 (461 cases and 278 controls) subjects were kept in the HM cohort, GSA cohort and OMNI cohort, respectively. Demographic data of each cohort including age and sex are documented in Table I. We further imputed our genotyping data by using the TOPMed reference panel[4], and performed GWAS on each cohort (Methods).

As no genome-wide significant loci were detected from each of the three cohorts individually, we next performed a meta-analysis combining the three cohorts (6975 cases and 4429 controls in total). Our results demonstrate that a locus in the intergenic region

between *RFX6* and *VGLL2* at 6q22.1 (rs144763329, $P = 3.35 \times 10^{-8}$) was significantly associated with Asthma in African Americans. We next meta-analyzed our three data sets, together with GWAS summary statistics from ten African-American data sets (3786 cases and 4438 controls in total)[2], obtained from the CAAPA consortium, using the sample size based meta-analysis[5]. The inverse variance based meta-analysis was not suitable here[6], because the CAAPA data were tested by a logistic mixed effects model as previously described[2], while our data were tested by the conventional logistic regression model. Meta-analysis of the 13 data sets yielded 12 GWAS loci surpassing the classical genome-wide significant threshold (5×10^{-8}). However, considering that a large amount of imputed variants were tested, we also applied a more stringent threshold of 3×10^{-8} used by the GWAS of Ferreira et al[7]. Eight loci reached the significant threshold of 3×10^{-8} (Fig 1 and Table II). No additional independent association signals were detected by the conditional analysis. Among loci uncovered, 9p24.1 (*IL33*, rs10975467, $P = 1.63 \times 10^{-8}$, Table II and Fig E1), was previously reported in Europeans, reaching genome-wide significance in African Americans for the first time in our analysis. Locus 1p36.32 locus was reported to be modestly associated with asthma in the Finnish population (rs79408112, $P = 2.2 \times 10^{-3}$, Table E1) and locus 8q24.12 was modestly associated with obesity related asthma (rs6982340, $P = 1.7 \times 10^{-3}$, Table E1). We next investigated the potential functional consequences of the top SNP and SNPs in LD with the top SNP from each locus uncovered by querying the HaploReg database[8] (Supplementary file). HaploReg annotations indicated most of the tested SNPs are located in regulatory regions of the genome. Among the 12 assessed loci, six loci were associated with enhancer activities, two loci were in DNase I hypersensitive regions, and all of them were associated with regulatory motifs (Table E2). We subsequently performed an enrichment analysis with GARFIELD[9] to assess whether the associated SNPs lie in cell-type-specific elements of the genome. The associated variants were enriched in DNase I hypersensitivity site hotspots and peaks in several tissues including blood, lung and epithelium (Fig E2 and Table E3) and were also enriched in a repertoire of immune cells from the blood tissue, such as GM12864 and GM12865 B cells and CD3+ and CD4+ T cells (Table E3). Moreover, the 11q13.4 locus (rs7480008) is an eQTL (expression quantitative trait loci) of multiple nearby genes in multiple tissues including lung (*XRRA1*, $P = 9.4 \times 10^{-10}$, Table E4) according to GTEx[10]. Locus 13q14.3 (rs1543525) is a sQTL (splicing quantitative trait loci) of nearby gene *DHRS12* in lung ($P = 1.1 \times 10^{-13}$, Table E4) and other tissues according to GTEx[10]. It is also an eQTL of *DHRS12* in CD4+ lymphocytes ($P = 2 \times 10^{-5}$, Table E2), suggesting a potential role of these variants in gene regulation in asthma. In consistent with this, *XRRA1* was associated with resting-state white blood cell count, which is a marker of inflammation and immune system health[11]. Differential methylation at *DHRS12* was also reported in B cells from patients with rheumatoid arthritis[12].

In addition to locus 9p24.1, the known locus in Europeans, 5q31.1 (*IL13*, rs2706349, $P = 9.89 \times 10^{-8}$, Table III), showed associations close to genome-wide significance (5×10^{-8}). Since none of the reported loci of asthma in Africans was detected in our study (Table E5), we next investigated the reported loci in the largest GWAS of Asthma[1], which included all the known asthma loci in Europeans so far. We used LocusCompare[13] to visualize if association signals were co-localized between African-Americans and Europeans. Moreover,

we used a stringent threshold for the replication analysis (that is, either the lead SNP in the European GWAS has a *P*-value < 0.01 in the African GWAS or its proxy SNP has a *P*-value < 0.001 in the African GWAS (Supplementary file)). For example, the lead SNP rs10040192 of the 5q13.2 locus in the European GWAS is located within a LD block of approximately 200Kb, with many associated SNPs highly correlated with each other. In comparison, the *P* value of rs10040192 is 5.99×10^{-5} in the African GWAS, and many SNPs in LD with rs10040192 have a *P*-value < 0.05. Another example, although the lead SNP rs10178845 of 2p25.1 locus in the European GWAS are not significantly associated in the African GWAS, a few SNPs in LD with the lead SNP such as rs391934 display a P-value < 0.001. A total of 43 loci showed evidence of associations (Table III and Fig E3) in our GWAS of African Americans, including the well-established loci, 5q22.1 (*TSLP*) and 11q13.5 (*C11orf30*/*LRRC32*), indicating genetic risk factors of asthma are partially shared by African American and European populations. Interestingly, eight of them showed associations in the opposite direction to that previously reported in Europeans (Table III), suggesting the other allele may be relevant to asthma risk, or that there may be opposite or different mechanism resulting in asthma between Africans and Europeans.

This study has limitations. First, the eQTL and sQTL data are mainly based on European populations. Potential cis-eQTL effects should be further verified in African populations when available. Second, our meta-analysis includes both pediatric and adult data. Future studies focusing on pediatric or adult asthma may detect genetic loci associated with a specific subtype of asthma.

Taken together, this study extends our understanding of the genetic architecture of asthma in African American populations adding eight novel asthma risk loci to the current asthma loci repertoire. It is evident from this study that more genetic loci contributing to asthma in African Americans can be detected though GWAS with a larger sample size. This study also provides evidence that some genetic risk factors in asthma may be shared among populations of African and European descent, whereas most of them appear to be population-specific. It is also likely that integrative analysis combining GWAS results and linkage disequilibrium information from European and African populations will identify culprit genes and causal variants at these shared loci.

METHODS

Study subjects

Study subjects from Children's Hospital of Philadelphia (CHOP) were selected from the biorepository at the Center for Applied Genomics (CAG), which includes internal pediatric blood samples and genotyping arrays linked to subjects' electronic medical records (EMR). Cases and controls subjects were determined based on EMR by a phenotyping algorithm independently validated by two other sites (Lyam Vazquez, John Connolly. CHOP. Asthma. PheKB; 2013 Available from: https://phekb.org/phenotype/146)[3]. Cases were individuals of four years of age and older, with a diagnostic history of one or more relevant asthma medications (Table E6) and a history of asthma as determined by ICD9 codes (493.x, J45) and chart review (Supplementary file and Table E7). Controls were individuals of four years of age or older, with no diagnosis codes for asthma (493.x, J45) and no history of relevant

medications (Supplementary file, Table E6 and E8). The institutional review board at CHOP reviewed and approved the project. Written informed consent for participation in the study was obtained from all participants and their parents or guardians.

Statistics

EIGENSTRAT was used to detect potential population substructures and outliers[14]. Participants of African American ancestry were verified by visually comparing the first two principal components (PCs) of participants and reference populations from 1000 Genomes (Fig E4). Pairwise identity-by-descent values were calculated by PLINK[15] to remove cryptic relatedness and duplicated samples. SNP markers were filtered with genotype missing rate (< 5%), minor allele frequency (MAF > 1%), and Hardy-Weinberg equilibrium *P* value ($> 1\times10^{-6}$). Genotype imputation was performed using the TOPMed Imputation Server using the minimac4 imputation algorithm and the TOPMed freeze 5b reference panel of 50253 whole genomes including 14438 (28.7%) individuals of African ancestry[4], which achieved a significant improvement in imputation qualities and accuracies of low frequency variants (MAF < 5%) in African populations. Common variants (MAFs > 1%) with high imputation confidence (Rsq (imputation quality metric) > 0.5) were retained for association analysis (Table E9 and E10). Association analyses were implemented by PLINK using logistic regression with an additive model on the imputed dosage of the effect allele while adjusting for sex, age and the first ten PCs[15]. Scree plots show that most variance can be captured by the first two or three PCs, so correction for the first ten PCs can guarantee that the association results are not influenced by population structures (Fig E5). Meta-analysis was performed by METAL[5]. No genomic inflation was detected (Fig E6). The summary statistics are available through GWAS Catalog under accession numbers GCST90131434, GCST90131435 and GCST90131436. Details about the numbers of samples and variants in each analytical step were summarized in Table E11.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

CHOP	Children's Hospital of Philadelphia
GWAS	Genome-wide association study
TOPMed	Trans-Omics for Precision Medicine

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Key Messages

- This study uncovered eight genome-wide significant loci through the largest GWAS of asthma to date in African Americans.
- This study provides evidence that genetic risk factors in asthma are partially shared among populations of African and European descent.

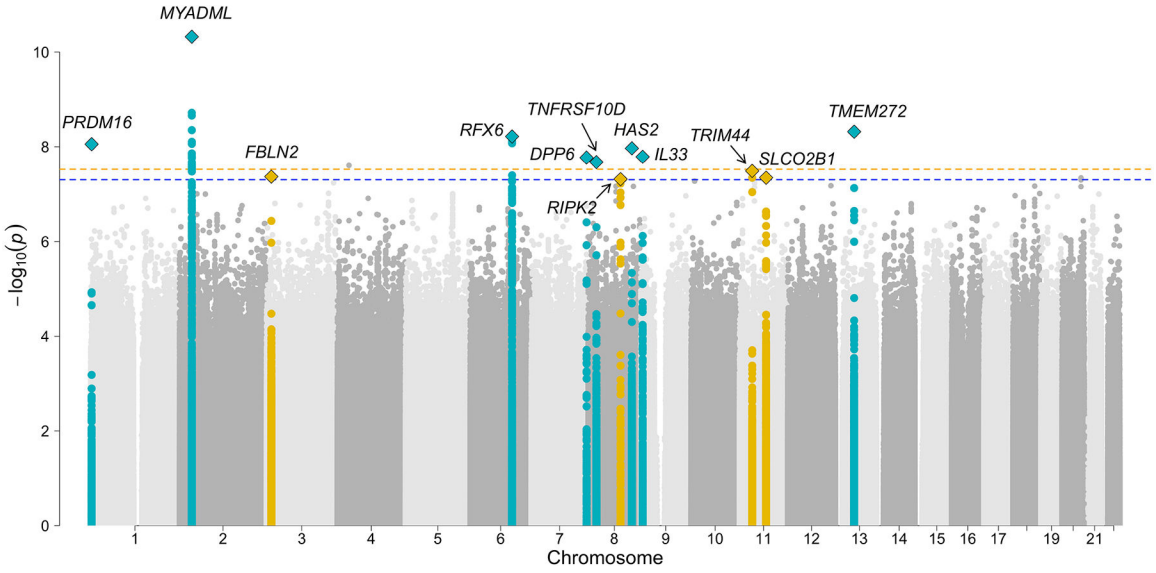

Fig 1.

Manhattan plot of the GWAS meta-analysis of the CHOP and CAAPA cohorts. Loci passing significant threshold (3×10^{-8}) are colored in blue and loci passing significant threshold (5×10^{-8}) are colored in yellow.

Table I.

Demographics of analyzed African-American cases and controls.

Phenotypic Variables	HM		GSA		OMNI		CAAPA		ALL	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Contr
Number (N)	2638	1544	3876	2607	461	278	3786	4438	10761	8867
Age in years, mean (SD)	14.02 years (3.79)	14.74 years (4.07)	11.00 years (4.57)	13.38 years (5.07)	13.07 years (3.78)	14.30 years (3.99)	38.18 years (0.56)	27.83 years (0.69)	21.75 years (3.52)	20.8 years (3.37
Percent male	1420 (53.8%)	687 (44.5%)	2117 (54.6%)	1193 (45.8%)	280 (60.7%)	168 (60.4%)	1504 (39.7%)	1655 (37.3%)	5321 (49.4%)	3703 (41.8%
Genotyping Array	Illumina HumanHap550/610	Illumina HumanHap550/610	Illumina GSA	Illumina GSA	Illumina Omni Express/ Omni-2.5	Illumina OmniExpress/ Omni-2.5	ADPC, Illumina MEGA/ OmniExpress/ Omni-2.5/ HumanHap1M, Affymetrix 6.0/Axiom	ADPC, Illumina MEGA/ OmniExpress/ Omni-2.5/ HumanHap1M, Affymetrix 6.0/Axiom		

Table II.

Associations of the associated loci identified in the meta-analyses

Locus	GENE	SNP	CHR	POS	EA/NEA	EAF	BETA	SE	*P*
1p36.32	*PRDM16*	rs79408112	1	3435611	A/G	0.05	0.137	0.0239	8.84E-09
2p22.3	*MYADML*	rs73926864	2	34078378	A/G	0.91	−0.120	0.0183	4.76E-11
3p25.1	*FBLN2*	rs79980658	3	13561699	A/T	0.97	−0.174	0.0319	4.30E-08
6q22.1	*RFX6*	rs144763329	6	117071395	A/T	0.15	0.088	0.0151	6.09E-09
7q36.2	*DPP6*	rs76556931	7	154835628	A/G	0.91	−0.107	0.0190	1.70E-08
8q24.12	*HAS2*	rs6982340	8	121320840	T/C	0.97	−0.186	0.0325	1.08E-08
8p21.3	*TNFRSF10D*	rs7014637	8	23151624	A/C	0.34	−0.063	0.0113	2.12E-08
8q21.3	*RIPK2*	rs311656	8	89598206	A/G	0.05	0.139	0.0256	4.86E-08
9p24.1	*IL33*	rs10975467	9	6159758	T/C	0.12	0.092	0.0162	1.63E-08
11p13	*TRIM44*	rs77231114	11	35865269	T/C	0.05	0.133	0.0241	3.26E-08
11q13.4	*SLCO2B1*	rs7480008	11	75123789	A/G	0.58	0.060	0.0109	4.54E-08
13q14.3	*TMEM272*	rs1543525	13	51814629	T/C	0.82	−0.083	0.0141	4.82E-09

GENE: nearest gene

SNP: rsID number

CHR: chromosome number

POS: genomic coordinate (GRCh38)

EA: effect allele

NEA: non-effect allele

EAF: effect allele frequency

BETA: effect size

SE: standard error of effect size

P: *P* value of the meta-analysis of three CHOP cohorts and ten CAAPA cohorts

Table III.

Replication of 43 loci reported in studies of Europeans

Locus	Gene	SNP	CHR	POS	EA/ NEA	EUR				AFR				
						EAF	BETA	SE	*P*	EAF	BETA	SE	*P*	*P*
1p36.22	*PEX14*	rs6687430	1	10573188	A/G	0.54	0.014	0.0019	8.11E-13	0.30	0.031	0.0105	2.89E-03	0.
1p35.2	*COL16A1*	rs2228552	1	31699894	T/G	0.63	0.011	0.0020	2.15E-08	0.29	0.027	0.0108	0.012	1.
		rs10914471 (R2 = 0.912)	1	31712335	T/C	0.35	−0.010	0.0020	3.63E-07	0.21	−0.045	0.0119	1.45E-04	0.
1q21.3	*IL6R*	rs4129267	1	154453788	T/C	0.40	0.017	0.0020	1.17E-17	0.13	0.035	0.0140	0.013	1.
		rs12128408 (R2 = 0.358)	1	154516057	A/G	0.37	−0.009	0.0020	2.10E-05	0.82	−0.048	0.0124	1.15E-04	0.
1q23.3	*FCER1G*	rs2070901	1	161215268	T/G	0.28	0.017	0.0022	6.48E-16	0.40	0.036	0.0098	2.29E-04	0.
1q25.1	*TNFSF4*	rs10912564	1	173201479	T/C	0.31	0.017	0.0021	1.54E-16	0.67	0.032	0.0103	1.79E-03	0.
1q32.1[†]	*ADORA1*	rs7555556	1	203121848	T/C	0.33	−0.017	0.0021	7.29E-16	0.10	0.039	0.0161	0.015	1.
		rs1494486 (R2 = 0.995)	1	203125076	T/C	0.33	−0.016	0.0021	1.16E-15	0.18	0.043	0.0125	5.92E-04	0.
1q32.3	*BATF3*	rs906364	1	212685406	T/C	0.82	−0.014	0.0025	2.78E-08	0.87	−0.058	0.0139	2.46E-05	4.9
2p25.1	*LINC00299*	rs10178845	2	8303673	A/G	0.29	−0.024	0.0021	3.73E-29	0.12	−0.019	0.0147	0.206	1.
		rs391934 (R2 = 0.35)	2	8304364	T/C	0.47	0.013	0.0019	4.58E-11	0.30	0.046	0.0104	9.75E-06	1.9
2q12.1[#]	*IL1RL1*	rs3771180	2	102337157	T/G	0.14	−0.063	0.0028	5.83E-116	0.26	−0.009	0.0107	0.408	1.
		rs11406702 (R2 = 0.985)	2	102299506	A/A T	0.86	0.061	0.0028	9.37E-109	0.76	0.043	0.0111	1.21E-04	0.
2q36.1	*AP1S3*	rs13383994	2	223802975	A/G	0.41	0.013	0.0020	1.72E-10	0.44	0.029	0.0096	2.30E-03	0.
2q36.3	*CCL20*	rs7423358	2	227840005	T/C	0.25	−0.017	0.0022	9.88E-15	0.40	−0.017	0.0105	0.107	1.
		rs11899826 (R2 = 0.247)	2	227869104	A/G	0.51	0.010	0.0019	8.24E-07	0.42	0.036	0.0100	3.92E-04	0.
3q13.2[†]	*CD200R1*	rs7622814	3	112931584	T/G	0.46	0.012	0.0019	4.09E-10	0.30	−0.008	0.0103	0.408	1.
		rs11718878 (R2 = 0.423)	3	112877808	A/G	0.66	0.012	0.0020	1.25E-08	0.80	−0.040	0.0118	7.18E-04	0.
5q13.2[*]	*PTCD2*	rs10040192	5	72400053	T/C	0.52	−0.015	0.0026	3.20E-08	0.81	−0.049	0.0122	5.99E-05	0.
5q22.1(1)[#]	*TSLP*	rs1898671	5	111072304	T/C	0.34	0.038	0.0020	7.57E-78	0.10	0.044	0.0157	4.93E-03	0.
5q22.1(2)[#]	*TSLP*	rs9784728	5	110878104	A/G	0.20	0.023	0.0024	2.36E-21	0.39	0.040	0.0100	7.34E-05	0.
5q31.1[#]	*IL13*	rs848	5	132660808	A/C	0.19	0.037	0.0024	8.54E-53	0.50	−0.010	0.0099	0.294	1.
		rs2706349 (R2 = 0.2206)	5	132571068	A/G	0.20	0.033	0.0024	6.79E-43	0.61	0.053	0.0099	9.89E-08	2.0
6p22.2	*HIST1H4H*	rs6900665	6	26486941	T/C	0.13	0.019	0.0029	5.03E-11	0.17	0.049	0.0124	8.53E-05	0.
6p22.1[#]	*TRIM27*	rs1233578	6	28744470	A/G	0.82	−0.021	0.0025	1.47E-17	0.59	−0.013	0.0095	0.169	1.
		rs13211507 (R2 = 0.397)	6	28289600	T/C	0.89	−0.022	0.0031	1.70E-12	0.94	−0.081	0.0203	7.01E-05	0.
6p21.31[*]	SCUBE3	rs9348970	6	35185788	G/C	0.81	−0.021	0.0034	7.10E-10	0.47	−0.018	0.0095	0.055	1.
		rs13210323 (R2 = 0.1)	6	35037307	A/C	0.72	−0.013	0.0029	9.40E-06	0.66	−0.036	0.0099	2.27E-04	0.

Locus	Gene	SNP	CHR	POS	EA/ NEA	EUR				AFR				
						EAF	BETA	SE	*P*	EAF	BETA	SE	*P*	*P*
6q21[†]	*SESN1*	rs11759732	6	109048803	A/G	0.85	0.017	0.0027	2.52E-10	0.75	−0.034	0.0110	2.08E-03	0.
6q25.1	*ZC3H12D*	rs431362	6	149466242	A/G	0.36	0.013	0.0020	1.65E-10	0.46	0.020	0.0094	0.034	1.
		rs409099 (R2 = 0.433)	6	149445727	T/G	0.50	−0.008	0.0019	4.08E-05	0.15	−0.054	0.0132	4.49E-05	9.0
9p24.1[#]	*IL33*	rs992969	9	6209697	A/G	0.25	0.049	0.0022	7.69E-107	0.31	−0.006	0.0103	0.548	1.
		rs10975467 (R2 = 0.2045)	9	6159758	T/C	0.25	0.030	0.0022	4.84E-42	0.12	0.081	0.0144	1.63E-08	3.2
9q32	*TNFSF15*	rs4978607	9	114746157	T/C	0.12	−0.016	0.0030	4.53E-08	0.17	−0.049	0.0127	9.60E-05	0.
9q33.3	*NEK6*	rs10986311	9	124309214	T/C	0.63	−0.014	0.0020	2.09E-12	0.68	−0.028	0.0102	7.20E-03	1.
10q11.21	*RASGEF1A*	rs12769745	10	43254252	A/G	0.28	0.012	0.0022	2.45E-08	0.21	0.016	0.0117	0.180	1.
		rs1864406 (R2 = 0.349)	10	43105416	A/T	0.71	−0.005	0.0021	0.01791	0.65	−0.037	0.0099	1.75E-04	0.
10q22.2	*FUT11*	rs12256103	10	73785493	A/G	0.29	−0.012	0.0021	3.37E-08	0.47	−0.033	0.0095	5.45E-04	0.
10q23.33	*KIF11*	rs7918084	10	92669710	T/C	0.56	0.014	0.0019	3.48E-12	0.66	0.011	0.0101	0.261	1.
		rs6583826 (R2 = 0.634)	10	92588073	A/G	0.53	0.011	0.0019	5.89E-09	0.50	0.035	0.0095	2.50E-04	0.
11q12.2	*FADS1*	rs174551	11	61806212	T/C	0.66	0.018	0.0020	5.95E-18	0.92	−0.002	0.0175	0.915	1.
		rs174465 (R2 = 0.29)	11	61891328	T/C	0.68	0.012	0.0021	2.12E-09	0.19	0.045	0.0122	2.43E-04	0.
11q13.5[#]	*LRRC32*	rs7936323	11	76582714	A/G	0.47	0.038	0.0019	7.39E-86	0.36	0.040	0.0099	4.30E-05	8.6
13q14.11[*,†]	COG6	rs34270626	13	39779253	G/G T	0.35	−0.017	0.0027	6.00E-10	0.52	0.008	0.0095	0.372	1.
		rs7335495 (R2 = 0.67)	13	39805134	A/T	0.72	0.017	0.0029	4.80E-09	0.80	−0.043	0.0118	2.81E-04	0.
13q32.3	*UBAC2*	rs34259893	13	99377209	C/C A	0.69	0.025	0.0028	9.3E-19	0.34	−0.009	0.0101	0.363	1.
		rs4238216 (R2 = 0.37)	13	99412716	C/T	0.15	−0.029	0.0037	5.20E-15	0.53	0.038	0.0099	1.46E-04	0.
14q23.1[†]	*PRKCH*	rs3751289	14	61517225	A/G	0.78	−0.013	0.0023	1.49E-08	0.66	−0.010	0.0100	0.332	1.
		rs1119016 (R2 = 0.371)	14	61505232	C/G	0.89	−0.012	0.0031	6.31E-05	0.87	0.054	0.0145	2.14E-04	0.
14q32.12[†]	*RIN3*	rs10131290	14	92549134	A/C	0.67	−0.018	0.0028	1.12E-10	0.20	0.034	0.0118	3.67E-03	0.
15q15.1[†]	*RTF1*	rs1942	15	41482225	A/G	0.46	−0.014	0.0019	1.37E-12	0.15	−0.011	0.0140	0.453	1.
		rs3101436 (R2 = 0.309)	15	40995491	A/G	0.48	0.010	0.0019	3.36E-07	0.78	−0.040	0.0115	5.23E-04	0.
17q12	*GSDMB*	rs2305479	17	39905964	T/C	0.50	−0.043	0.0019	7.86E-112	0.17	−0.003	0.0126	0.801	1.
		rs7224908 (R2 = 0.299)	17	39930601	A/G	0.22	−0.028	0.0023	4.92E-32	0.10	−0.064	0.0159	6.19E-05	0.
17q21.31	*SPATA32*	rs7224548	17	45259769	T/G	0.70	−0.016	0.0021	8.43E-15	0.85	0.017	0.0135	0.217	1.
		rs117574138 (R2 = 0.241)	17	45371815	C/G	0.90	−0.017	0.0032	1.52E-07	0.98	−0.130	0.0375	5.01E-04	0.
17q21.33[#]	*ZNF652*	rs17637472	17	49384071	A/G	0.39	0.022	0.0020	6.25E-28	0.07	0.026	0.0181	0.152	1.

Locus	Gene	SNP	CHR	POS	EA/ NEA	EUR				AFR				
						EAF	BETA	SE	*P*	EAF	BETA	SE	*P*	P_{a}
		rs12150526 (R2 = 0.498)	17	49366218	T/C	0.45	0.018	0.0019	1.01E-19	0.41	0.035	0.0096	2.71E-04	0.
17q25.1	*UNC13D*	rs111365807	17	75829382	C/G	0.12	0.017	0.0030	3.49E-08	0.13	0.011	0.0142	0.446	1.
		rs74410877 (R2 = 0.912)	17	75836303	T/C	0.12	0.016	0.0030	8.31E-08	0.02	0.136	0.0332	3.84E-05	7.7
18q21.2	*SMAD4*	rs12453988	18	51055548	T/C	0.37	0.012	0.0020	2.20E-09	0.17	0.030	0.0127	0.018	1.
		rs1789229 (R2 = 0.436)	18	50887961	A/G	0.63	−0.010	0.0020	2.07E-07	0.72	−0.037	0.0107	4.66E-04	0.
19p13.3	*SBNO2*	rs892225	19	1152657	A/G	0.62	−0.011	0.0020	1.12E-08	0.67	−0.042	0.0112	1.86E-04	0.
20q13.2†	*LOC101927770*	rs2766667	20	53555865	T/C	0.26	0.016	0.0022	1.84E-13	0.30	−0.046	0.0110	3.24E-05	6.5
21q22.12	*RUNX1*	rs2242900	21	35081540	A/G	0.86	−0.025	0.0028	2.11E-18	0.98	−0.062	0.0304	0.042	1.
		rs73207404 (R2 = 0.321)	21	35138436	T/C	0.08	0.020	0.0036	3.52E-08	0.03	0.105	0.0289	2.76E-04	0.
22q13.2	*ACO2*	rs1972057	22	41558247	A/G	0.80	−0.016	0.0024	1.22E-11	0.86	−0.036	0.0134	7.24E-03	1.

GENE: nearest gene

SNP: rsID number

CHR: chromosome number

POS: genomic coordinate (GRCh38)

EA: effect allele

NEA: non-effect allele

EAF: effect allele frequency

BETA: effect size

SE: standard error of effect size

P: *P* value of European GWAS (Han et al[1]) or African GWAS

P_{adjust}: *P* value of African GWAS corrected by the Bonferroni procedure for multiple comparisons (202 tested variants)

*: loci only reported in the UK biobank data

#: loci reported in the TAGC data

†: opposite directions of associations between Europeans and Africans