PLOS ONE

RESEARCH ARTICLE

Evidence of selection as a cause for racial disparities in fibroproliferative disease

Jacklyn N. Hellwege[1,2], Eric S. Torstenson[1,2], Shirley B. Russell[2], Todd L. Edwards[1,2]*, Digna R. Velez Edwards[2,3]*

1 Division of Epidemiology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, United States of America, **2** Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, United States of America, **3** Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, TN, United States of America

* todd.l.edwards@vanderbilt.edu (TLE); digna.r.velez.edwards@vanderbilt.edu (DRVE)

Citation: Hellwege JN, Torstenson ES, Russell SB, Edwards TL, Velez Edwards DR (2017) Evidence of selection as a cause for racial disparities in fibroproliferative disease. PLoS ONE 12(8): e0182791. https://doi.org/10.1371/journal.pone.0182791

Editor: Giorgio Sirugo, Ospedale San Pietro Fatebenefratelli, ITALY

Received: April 12, 2017

Accepted: July 25, 2017

Published: August 8, 2017

Data Availability Statement: 1000 Genomes data is publically available and may be downloaded via FTP (ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/), Aspera, or Globus GridFTP (http://www.internationalgenome.org/data#download). Genotype data from BioVU used in this study is publically available, and can be found in dbGaP, accession number phs001409.v1.p1. Phenotype data from BioVU is available to researchers, who meet the criteria for access to confidential data, upon request and clearance from Vanderbilt University Medical Center Institutional Review

Abstract

Fibroproliferative diseases are common complex traits featuring scarring and overgrowth of connective tissue which vary widely in presentation because they affect many organ systems. Most fibroproliferative diseases are more prevalent in African-derived populations than in European populations, leading to pronounced health disparities. It is hypothesized that the increased prevalence of these diseases in African-derived populations is due to selection for pro-fibrotic alleles that are protective against helminth infections. We constructed a genetic risk score (GRS) of fibroproliferative disease risk-increasing alleles using 147 linkage disequilibrium-pruned variants identified through genome-wide association studies of seven fibroproliferative diseases with large African-European prevalence disparities. A comparison of the fibroproliferative disease GRS between 1000 Genomes Phase 3 populations detected a higher mean GRS in AFR (mean = 148 risk alleles) than EUR (mean = 136 risk alleles; T-test p-value = 1.75×10^{-123}). To test whether differences in GRS burden are systematic and may be due to selection, we employed the quantitative trait loci (QTL) sign test. The QTL sign test result indicates that population differences in risk-increasing allele burdens at these fibroproliferative disease variants are systematic and support a model featuring selective pressure (p-value = 0.011). These observations were replicated in an independent sample and were more statistically significant (T-test p-value = 7.26×10^{-237}, sign test p-value = 0.015). This evidence supports the role of selective pressure acting to increase frequency of fibroproliferative alleles in populations of African relative to European ancestry populations.

Introduction

Fibroproliferative diseases are a consequence of dysregulated scarring and connective tissue overgrowth, affect many organ systems, vary widely in presentation, and are very common in humans[1, 2]. Uterine fibroids, keloid scars, pulmonary fibrosis, cirrhosis, Crohn's disease, and atherosclerosis are examples of diseases with fibroproliferative features. Many fibroproliferative diseases are more prevalent in recently African-derived populations than in European populations[3], collectively contributing to pronounced overall health disparity (Table 1). For

Board and BioVU. Interested and eligible researchers may contact the BioVU data access team at biovu@vanderbilt.edu for more detailed information regarding access to phenotype data from BioVU.

Funding: This project was supported by National Institutes of Health grants R01HD074711 (DRVE), R03HD078567 (DRVE), R21AR067938 (DRVE), and R21HL121429 (TLE and DRVE), as well as the Vanderbilt Molecular and Genetic Epidemiology of Cancer (MAGEC) training program, which was funded by the US National Cancer Institute grant number R25 CA160056 (PI: X.-O. Shu). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

example, keloids are more common in those with darker pigmentation[4], and systemic scleroderma[5, 6], nephrosclerosis[7], and sarcoidosis[8] are more prevalent in African American individuals. However, this is not the case for all fibroproliferative diseases. Dupuytren contracture is a disease predominantly affecting European American individuals[9], as are pulmonary fibrosis[10] and multiple sclerosis[11], though they are not uncommon in those of recent African ancestry.

Beyond the large prevalence disparities across continental ancestral groups, there is observational association study evidence to suggest that these conditions are heritable[12–17]. Genome-wide association studies (GWAS) have identified many common susceptibility variants for several fibroproliferative diseases[18, 19]. However, like most phenotypes, these studies have been performed predominantly in European American populations.

It has been suggested that fibroproliferative diseases may share a common genetic background[20]. There is also evidence for pathological similarities across fibroproliferative phenotypes[1, 2]. A recent review by Russell et al presents the hypothesis and presents evidence for the increased prevalence of fibroproliferative diseases in African American populations as a result of selection for anti-helminthic, pro-fibrotic alleles in response to helminth infections on the African continent[3]. Similar scenarios of diseases arising due to selective response to pathogens in African populations have been seen in sickle cell disease conferring resistance to malaria[21, 22], and the increased frequency of chronic kidney disease in carriers of Apolipoprotein L1 (*APOL1*) variants, which offer enhanced ability to resist trypanosome infections that cause African sleeping sickness[23].

When a trait is under adaptive selective pressure, allele frequencies at all loci with an influence on that trait will change over generations. In contrast, under neutrality allele frequencies will drift randomly. Thereby, if individuals with higher values for the trait enjoy higher relative fitness, then trait-increasing alleles will tend to become more common over generations, and the effect of selection on allele frequency will be proportional to the effect of the allele on the trait under selection. For a complex trait under selection with many genetic determinants with subtle effects, small changes in allele frequency will occur with relatively undetectable differences in linkage disequilibrium (LD) and haplotype diversity, as has been seen in human height[24]. Across trait loci, systematic differences in trait- or risk-increasing allele frequencies that are consistent with the disparity between two populations are detectable, given a sufficient number of known causal loci and precision to estimate allele frequencies[25, 26]. In this study, we were able to assess systematic frequency differences of known fibroproliferative risk-increasing alleles across populations; however, we could not assume or assess proportionality of effect sizes to allele frequency differences between African and other continental populations. The available effect size estimates for these alleles are not for their putative protective effects on helminth infections, but for their consequences across organ systems in various fibroproliferative traits.

Results and discussion

This study sought to determine whether allele frequency differences at known fibroproliferative risk loci are consistent with evidence for selective pressure and may explain racial disparities associated with fibroproliferative diseases (and related quantitative phenotypes) through evaluating loci implicated by genome wide association studies (GWAS). To do this, a genetic risk score (GRS) utilizing single nucleotide polymorphisms (SNPs) from the GWAS catalog [19] was constructed for seven fibroproliferative diseases with increased prevalence (>2 fold on average) in African ancestry populations compared to European ancestry populations (Table 1). The total number of LD-pruned (r^2<0.2) independent SNPs included in the GRS

Table 1. Fibroproliferative diseases with increased prevalence in African-derived populations.

Disease	Prevalence Ratio (AA:EA)	Number of SNPs included in GRS[1]
Nephrosclerosis	3–20[35–41]	69
Keloids	20[42]	3
Sarcoidosis	3–17[43–51]	1
Hypertension[2]	1.4–7[52–57]	42
Glaucoma	4–5[58, 59]	21
Scleroderma	3[43, 60–62]	8
Uterine Fibroids	1.5–3[63–66]	3

Table modified from Russell et al, 2015[3]. AA-African American; EA-European American

[1]Number of loci reaching genome-wide significance in the NHGRI/EBI GWAS Catalog (www.ebi.ac.uk/gwas). Complete list of SNPs is contained in S1 Table

[2]Hypertension is associated with a systemic inflammatory state which can lead to target organ fibrosis[67–70], and also occurs in the presence of atherosclerosis which is itself fibroproliferative[71–73]. There are shared characteristics between hypertension and other fibroproliferative diseases[54, 74–78], and fibrotic growth factors are often upregulated in hypertension as well[53, 55, 79, 80]. Hypertension has been presented as a fibroproliferative condition in other publications[1, 3, 81], which discuss the evidence for this in more detail.

https://doi.org/10.1371/journal.pone.0182791.t001

(excluding the *HLA* region) was 147 (S1 Table). This unweighted GRS was calculated in all 1000 Genomes[27] (a sample without phenotypic selection bias) samples as the number of risk-increasing alleles in each individual. The individual-level GRS burdens ranged from 114 to 174 risk alleles (Table 2, Fig 1, S2 Table). Overall, the burden of risk alleles was consistently higher in African-derived (AFR) populations (mean GRS = 148.07) than European-derived (EUR) populations (mean GRS = 136.03), which have the lowest overall GRS burden (Fig 1). The difference in the mean GRS values between the EUR and AFR populations was 12.04 risk alleles (t-test *p*-value = 1.75x10−123). This result became marginally more significant when limiting the AFR population to only continental African populations (difference in means = 12.69 risk alleles, *p*-value = $1.37x10^{-125}$).

This was replicated in a larger independent population consisting of uterine fibroids cases and controls from BioVU, an electronic health record-linked DNA biorepository (Table 2, Fig 2), ascertained as part of another study[28]. In BioVU, the mean GRS in the African American samples was 145.11 (N = 1382; range: 117.41–167.47), while the mean in European American samples was 136.34 (N = 2359; range: 113.20–162.18). Cases and controls had similar means within racial groups, which were not significantly different from each other (African American controls mean = 145.05, African American cases mean = 145.20, t-test *p*-value = 0.69; European American controls mean = 136.55, European American cases mean = 136.13, t-test *p*-value = 0.16). The difference between African American and European American in this set was also highly significant (t-test *p*-value = $7.26x10^{-237}$), and remained so when evaluating controls only, as cases may be enriched for fibroproliferative alleles above those in the general population (t-test *p*-value = $6.38x10^{-127}$).

We further evaluated whether there are systematic differences in allele frequency at fibroproliferative disease risk alleles in the same direction as the prevalence disparity between African ancestry and European ancestry populations. Many approaches to evaluate selective pressure at multiple loci with small effects rely upon the proportionality assumption between disease effect sizes and allele frequency differences[26, 29]. However, those tests require that the disease of interest is itself under selective pressure, which is inconsistent with the hypothesis of selection in fibroproliferative diseases.

Table 2. Summary statistics for fibroproliferative GRS among AFR and EUR populations from 1000 Genomes, and among BioVU samples.

Population	N	Mean GRS	Minimum GRS	Maximum GRS
AFR	**661**	**148.07**		
ACB	96	146.57	120	169
ASW	61	145.00	131	160
ESN	99	149.90	133	168
GWD	113	147.61	129	163
LWK	99	148.71	134	166
MSL	85	149.69	133	165
YRI	108	148.06	135	161
BioVU AA (combined)	**1382**	**145.11**		
BioVU AA cases	578	145.20	126.44	167.47
BioVU AA controls	804	145.05	117.41	164.25
EUR	**503**	**136.03**		
CEU	99	135.34	117	156
FIN	99	136.07	114	156
GBR	91	136.67	122	156
IBS	107	135.01	116	150
TSI	107	137.10	119	156
BioVU EA (combined)	**2359**	**136.34**		
BioVU EA cases	1195	136.13	113.20	162.18
BioVU EA controls	1164	136.55	113.94	161.10

GRS: Genetic risk score; AA: African American; EA: European American; CEU: Utah Residents (CEPH) with Northern and Western Ancestry; TSI: Toscani in Italia; FIN: Finnish in Finland; GBR: British in England and Scotland; IBS: Iberian Population in Spain; YRI: Yoruba in Ibadan, Nigeria; LWK: Luhya in Webuye, Kenya; GWD: Gambian in Western Divisions in the Gambia; MSL: Mende in Sierra Leone; ESN: Esan in Nigeria; ASW: Americans of African Ancestry in SW USA; ACB: African Caribbeans in Barbados

https://doi.org/10.1371/journal.pone.0182791.t002

Therefore, evidence for selection was examined using the quantitative trait loci (QTL) sign test, which evaluates whether the number of variants at higher frequency in one population compared to the other deviates from neutrality under a binomial distribution[30]. This approach does not utilize phenotypic effect sizes, which is ideal for this study sample in which phenotypes are not observed and in this scenario where the effects of alleles on helminth infections have not been estimated. In this analysis, 85 of the 147 SNPs had risk alleles at higher frequency in African-derived populations than in European-derived populations (S3 Table), which is significant from the QTL sign test with a *p*-value of 0.011. Differences in risk allele frequency ranged from 0.006 to 0.73, with greater than 35% of the variants with an African-European frequency difference of 0.2 or larger. Thirty-three of the 53 variants (62%) with the largest (>0.2) differences were more common in African-derived populations (p-value = 0.022). The number of SNPs at higher frequency (and therefore the *p*-value for the sign test) did not change when limiting to samples from continental Africa. The sign test analysis also replicated in BioVU, with 84 of the 147 SNPs available in this dataset being more common in the African American samples compared to European American samples (*p*-value = 0.015).

Conclusion

Overall, this analysis supports the possibility that selective pressure on an as-yet undetermined phenotype may have impacted genetic variants predisposing to seven fibroproliferative diseases. The observation made in the present study of higher genetic burden of fibroproliferative

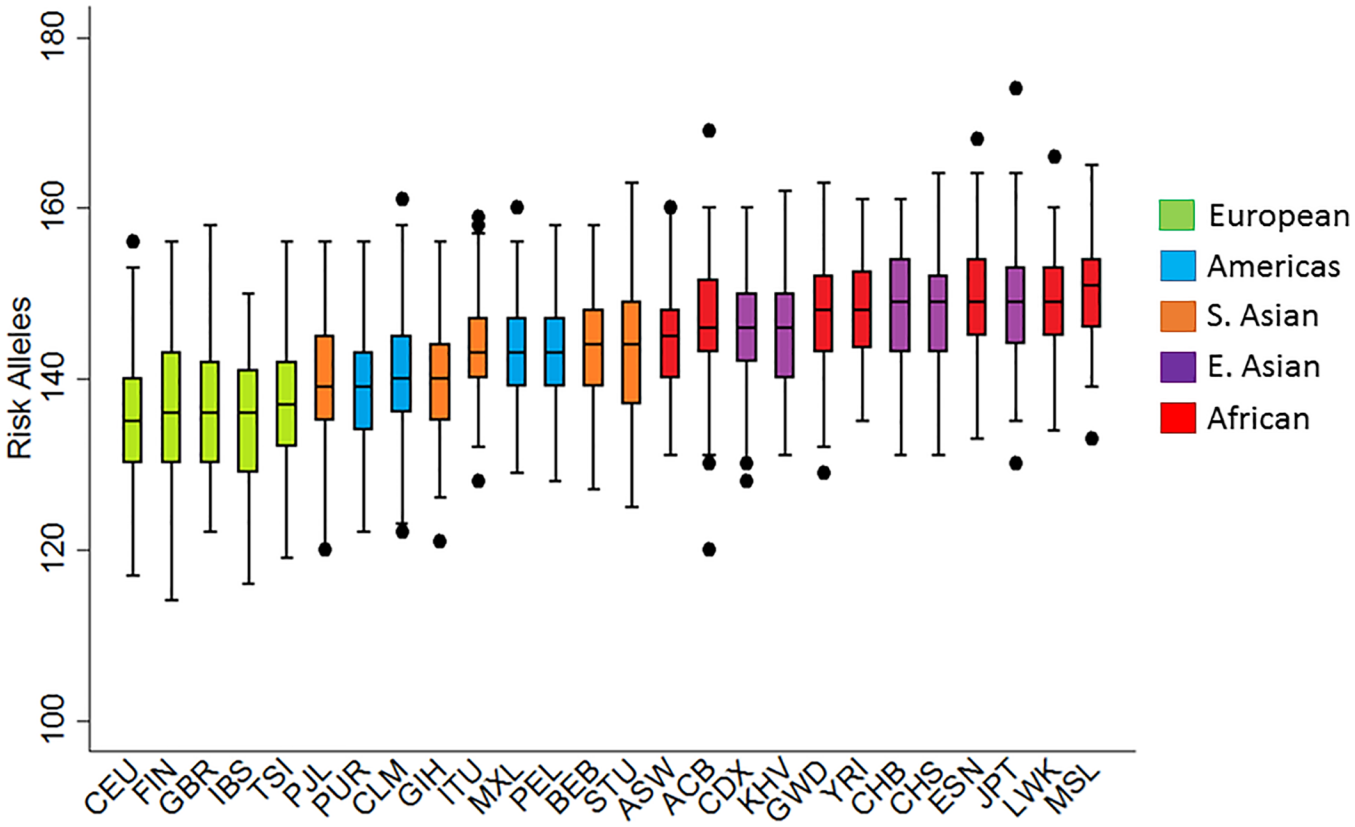

Fig 1. Distribution of fibroproliferative disease GRS in populations from 1000 Genomes. Results are sorted by median risk allele burden. Bars represent the 25th and 75th percentiles and are color coded by super-population (Green = EUR, Blue = AMR, Orange = SAS, Purple = EAS, Red = AFR).

https://doi.org/10.1371/journal.pone.0182791.g001

alleles was observed in both a population-based sample as well as within an independent sample ascertained from a hospital-based biobank. It is of note that nearly all of the genetic variants identified though GWAS (and thus included in the GRS) were implicated through studies of European or East Asian populations. This supports our conclusion, and identification of additional fibroproliferative risk variants that are more common in African populations will likely make the trends observed between these two population groups even more apparent.

Methods

Samples and genotypes

The discovery phase of these analyses utilized publically available genotype and population data from phase 3 of the 1000 Genomes Project was downloaded from ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/[31]. Individual population and super-population assignments were the only non-genetic information evaluated.

For replication individuals with imaging-confirmed uterine fibroids and genome-wide genotype data were included from BioVU, Vanderbilt University Medical Center's de-identified biorepository linked to electronic health records. The phenotyping algorithms used to identify case and control subjects have been previously published [28]. Briefly, this algorithm used a combination of demographic inclusion and exclusion criteria, International Classification of Diseases 9th edition (ICD-9) diagnostic codes, Current Procedural Terminology (CPT)

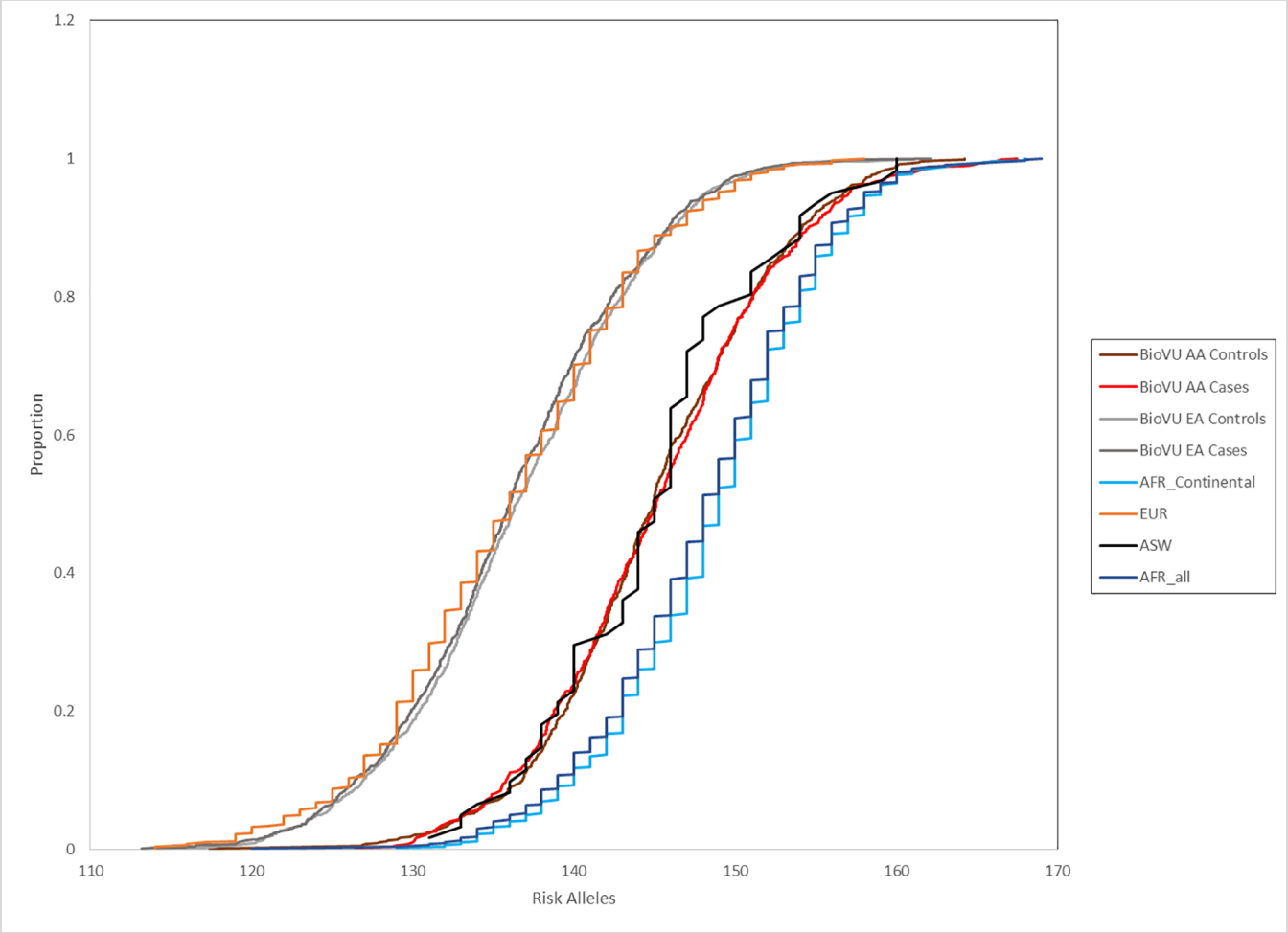

Fig 2. Cumulative distribution of GRS in 1000 Genomes AFR, EUR, ASW, and BioVU populations. *AFR includes only the continental African populations.

https://doi.org/10.1371/journal.pone.0182791.g002

codes, and keywords exclusions from specific notes and reports of a participant in order to identify cases and controls. Cases required evidence of a fibroid diagnosis defined by either an ICD-9 code indicating the presence of fibroids or ICD and CPT codes indicating a history of fibroid treatment procedures (e.g. myomectomy or uterine artery embolization). An individual was included as a control if they had two imaging events on separate dates and did not have a fibroid diagnosis or history of fibroid treatment procedures. Excluded from controls were women without an intact uterus (e.g. having had a prior hysterectomy) based on CPT procedural codes and text mentions of hysterectomy. This study was reviewed and approved by the Vanderbilt University Institutional Review Board (#161378).

BioVU subjects were genotyped using both the Affymetrix BioBank array (European American and African American subjects) and the Axiom World array 2 (Affymetrix Inc., Santa Clara, CA) was additionally genotyped in the African Americans in order to attain better coverage for African-derived variants. Genotype quality control was performed separately for European American and African American datasets, including a 95% SNP and individual call rate threshold, removal of related individuals, gender checks, alignment of alleles to the genomic '+' strand, and visualization of ancestry by principal components analysis using Eigenstrat

software [32]. The genotype data were imputed to the 1000 Genomes phase 3 reference panel using SHAPEIT2 [33] for haplotype phasing and IMPUTE2 [34] for genotype imputation, with phasing and imputation performed separately for each dataset.

Genetic risk score construction

A genetic risk score (GRS) utilizing single nucleotide polymorphisms (SNPs) from the GWAS catalog[19] was constructed for seven fibroproliferative diseases with increased prevalence (>2 fold on average) in African ancestry populations compared to European ancestry populations (Table 1). The total number of LD-pruned (r^2<0.2) independent SNPs included in the GRS (excluding the *HLA* region) was 147 (S1 Table). This unweighted GRS was calculated in all 1000 Genomes[27] as the number of risk-increasing alleles in each individual. The GRS was also computed across the imputed BioVU data utilizing the dosage data to account for the number of risk-increasing alleles. Of the 147 variants evaluated, 70 were directly genotyped in the African American set, and 63 were genotyped in the European American set. Mean info scores among imputed SNPs were 0.979 and 0.971 in African American and European American sets, respectively.

Supporting information

S1 Table. List of SNPs included in the GRS.
(PDF)

S2 Table. Descriptive characteristics of the GRS by 1000 Genomes super-populations and BioVU samples.
(PDF)

S3 Table. Frequencies of GRS SNPs in 1000 Genomes super-populations and BioVU samples. AFR (cont.) represents continental AFR samples only (i.e. not including ACB and ASW populations).
(PDF)

Author Contributions

Conceptualization: Shirley B. Russell, Todd L. Edwards, Digna R. Velez Edwards.

Data curation: Jacklyn N. Hellwege, Eric S. Torstenson.

Formal analysis: Jacklyn N. Hellwege.

Funding acquisition: Todd L. Edwards, Digna R. Velez Edwards.

Project administration: Todd L. Edwards, Digna R. Velez Edwards.

Writing – original draft: Jacklyn N. Hellwege.

Writing – review & editing: Jacklyn N. Hellwege, Shirley B. Russell, Todd L. Edwards, Digna R. Velez Edwards.

References

1. Wynn TA. Common and unique mechanisms regulate fibrosis in various fibroproliferative diseases. J Clin Invest. 2007; 117(3):524–9. Epub 2007/03/03. https://doi.org/10.1172/JCI31487 PMID: 17332879; PubMed Central PMCID: PMCPMC1804380.
2. Huang C, Ogawa R. Fibroproliferative disorders and their mechanobiology. Connective tissue research. 2012; 53(3):187–96. Epub 2012/02/15. https://doi.org/10.3109/03008207.2011.642035 PMID: 22329637.

3. Russell SB, Smith JC, Huang M, Trupin JS, Williams SM. Pleiotropic Effects of Immune Responses Explain Variation in the Prevalence of Fibroproliferative Diseases. PLoS Genet. 2015; 11(11): e1005568. Epub 2015/11/06. https://doi.org/10.1371/journal.pgen.1005568 PMID: 26540410.
4. Ud-Din S, Bayat A. Strategic management of keloid disease in ethnic skin: a structured approach supported by the emerging literature. The British journal of dermatology. 2013; 169 Suppl 3:71–81. Epub 2013/10/23. https://doi.org/10.1111/bjd.12588 PMID: 24098903.
5. Gelber AC, Manno RL, Shah AA, Woods A, Le EN, Boin F, et al. Race and association with disease manifestations and mortality in scleroderma: a 20-year experience at the Johns Hopkins Scleroderma Center and review of the literature. Medicine. 2013; 92(4):191–205. Epub 2013/06/25. https://doi.org/10.1097/MD.0b013e31829be125 PMID: 23793108; PubMed Central PMCID: PMCPMC4553970.
6. Mayes MD, Lacey JV Jr., Beebe-Dimmer J, Gillespie BW, Cooper B, Laing TJ, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis and rheumatism. 2003; 48(8):2246–55. Epub 2003/08/09. https://doi.org/10.1002/art.11073 PMID: 12905479.
7. Meyrier A. Nephrosclerosis: a term in quest of a disease. Nephron. 2015; 129(4):276–82. Epub 2015/04/15. https://doi.org/10.1159/000381195 PMID: 25871843.
8. Mirsaeidi M, Machado RF, Schraufnagel D, Sweiss NJ, Baughman RP. Racial difference in sarcoidosis mortality in the United States. Chest. 2015; 147(2):438–49. Epub 2014/09/05. https://doi.org/10.1378/chest.14-1120 PMID: 25188873; PubMed Central PMCID: PMCPMC4314818.
9. Saboeiro AP, Porkorny JJ, Shehadi SI, Virgo KS, Johnson FE. Racial distribution of Dupuytren's disease in Department of Veterans Affairs patients. Plastic and reconstructive surgery. 2000; 106(1):71–5. Epub 2000/07/07. PMID: 10883614.
10. Swigris JJ, Olson AL, Huie TJ, Fernandez-Perez ER, Solomon J, Sprunger D, et al. Ethnic and racial differences in the presence of idiopathic pulmonary fibrosis at death. Respiratory medicine. 2012; 106 (4):588–93. Epub 2012/02/03. https://doi.org/10.1016/j.rmed.2012.01.002 PMID: 22296740; PubMed Central PMCID: PMCPMC3294009.
11. Cree BA, Khan O, Bourdette D, Goodin DS, Cohen JA, Marrie RA, et al. Clinical characteristics of African Americans vs Caucasian Americans with multiple sclerosis. Neurology. 2004; 63(11):2039–45. Epub 2004/12/15. PMID: 15596747.
12. Luoto R, Kaprio J, Rutanen EM, Taipale P, Perola M, Koskenvuo M. Heritability and risk factors of uterine fibroids—the Finnish Twin Cohort study. Maturitas. 2000; 37(1):15–26. Epub 2000/12/02. PMID: 11099869.
13. Marneros AG, Norris JE, Olsen BR, Reichenberger E. Clinical genetics of familial keloids. Archives of dermatology. 2001; 137(11):1429–34. Epub 2001/11/16. PMID: 11708945.
14. Satko SG, Sedor JR, Iyengar SK, Freedman BI. Familial clustering of chronic kidney disease. Seminars in dialysis. 2007; 20(3):229–36. Epub 2007/06/09. https://doi.org/10.1111/j.1525-139X.2007.00282.x PMID: 17555489.
15. Sverrild A, Backer V, Kyvik KO, Kaprio J, Milman N, Svendsen CB, et al. Heredity in sarcoidosis: a registry-based twin study. Thorax. 2008; 63(10):894–6. Epub 2008/06/07. https://doi.org/10.1136/thx.2007.094060 PMID: 18535119.
16. Allanore Y, Wipff J, Kahan A, Boileau C. Genetic basis for systemic sclerosis. Joint, bone, spine: revue du rhumatisme. 2007; 74(6):577–83. Epub 2007/09/15. https://doi.org/10.1016/j.jbspin.2007.04.005 PMID: 17855142.
17. Teikari JM. Genetic factors in open-angle (simple and capsular) glaucoma. A population-based twin study. Acta ophthalmologica. 1987; 65(6):715–20. Epub 1987/12/01. PMID: 3434238.
18. Welter D, MacArthur J, Morales J, Burdett T, Hall P, Junkins H, et al. The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. Nucleic Acids Res. 2014; 42(Database issue):D1001–6. Epub 2013/12/10. https://doi.org/10.1093/nar/gkt1229 PMID: 24316577; PubMed Central PMCID: PMCPMC3965119.
19. The NHGRI-EBI Catalog of published genome-wide association studies. [Internet]. [cited 02/08/2016].
20. Wenzke KE, Cantemir-Stone C, Zhang J, Marsh CB, Huang K. Identifying common genes and networks in multi-organ fibrosis. AMIA Joint Summits on Translational Science proceedings AMIA Summit on Translational Science. 2012; 2012:106–15. Epub 2012/07/11. PMID: 22779061; PubMed Central PMCID: PMCPMC3392050.
21. Elguero E, Delicat-Loembet LM, Rougeron V, Arnathau C, Roche B, Becquart P, et al. Malaria continues to select for sickle cell trait in Central Africa. Proc Natl Acad Sci U S A. 2015; 112(22):7051–4. Epub 2015/05/06. https://doi.org/10.1073/pnas.1505665112 PMID: 25941403; PubMed Central PMCID: PMCPMC4460506.

22. Williams TN, Mwangi TW, Roberts DJ, Alexander ND, Weatherall DJ, Wambua S, et al. An immune basis for malaria protection by the sickle cell trait. PLoS Med. 2005; 2(5):e128. Epub 2005/05/27. https://doi.org/10.1371/journal.pmed.0020128 PMID: 15916466; PubMed Central PMCID: PMCPMC1140945.

23. Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science (New York, NY). 2010; 329 (5993):841–5. https://doi.org/10.1126/science.1193032 PMID: 20647424; PubMed Central PMCID: PMCPMC2980843.

24. Lohmueller KE. The impact of population demography and selection on the genetic architecture of complex traits. PLoS Genet. 2014; 10(5):e1004379. Epub 2014/05/31. https://doi.org/10.1371/journal.pgen.1004379 PMID: 24875776; PubMed Central PMCID: PMCPMC4038606.

25. Joshi PK, Esko T, Mattsson H, Eklund N, Gandin I, Nutile T, et al. Directional dominance on stature and cognition in diverse human populations. Nature. 2015; 523(7561):459–62. Epub 2015/07/02. https://doi.org/10.1038/nature14618 PMID: 26131930; PubMed Central PMCID: PMCPMC4516141.

26. Berg JJ, Coop G. A population genetic signal of polygenic adaptation. PLoS Genet. 2014; 10(8): e1004412. Epub 2014/08/08. https://doi.org/10.1371/journal.pgen.1004412 PMID: 25102153; PubMed Central PMCID: PMCPMC4125079.

27. Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE, et al. An integrated map of genetic variation from 1,092 human genomes. Nature. 2012; 491(7422):56–65. https://doi.org/10.1038/nature11632 PMID: 23128226; PubMed Central PMCID: PMCPMC3498066.

28. Feingold-Link L, Edwards TL, Jones S, Hartmann KE, Velez Edwards DR. Enhancing uterine fibroid research through utilization of biorepositories linked to electronic medical record data. Journal of women's health (2002). 2014; 23(12):1027–32. https://doi.org/10.1089/jwh.2014.4978 PMID: 25495367; PubMed Central PMCID: PMCPMC4267124.

29. Turchin MC, Chiang CW, Palmer CD, Sankararaman S, Reich D, Hirschhorn JN. Evidence of widespread selection on standing variation in Europe at height-associated SNPs. Nat Genet. 2012; 44 (9):1015–9. Epub 2012/08/21. https://doi.org/10.1038/ng.2368 PMID: 22902787; PubMed Central PMCID: PMCPMC3480734.

30. Orr HA. Testing natural selection vs. genetic drift in phenotypic evolution using quantitative trait locus data. Genetics. 1998; 149(4):2099–104. Epub 1998/08/05. PMID: 9691061; PubMed Central PMCID: PMCPMC1460271.

31. Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, Korbel JO, et al. A global reference for human genetic variation. Nature. 2015; 526(7571):68–74. Epub 2015/10/04. https://doi.org/10.1038/nature15393 PMID: 26432245; PubMed Central PMCID: PMCPMC4750478.

32. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet. 2006; 38(8):904–9. Epub 2006/07/25. https://doi.org/10.1038/ng1847 PMID: 16862161.

33. Delaneau O, Marchini J, Zagury JF. A linear complexity phasing method for thousands of genomes. Nat Methods. 2012; 9(2):179–81. Epub 2011/12/06. https://doi.org/10.1038/nmeth.1785 PMID: 22138821.

34. Duan Q, Liu EY, Auer PL, Zhang G, Lange EM, Jun G, et al. Imputation of coding variants in African Americans: better performance using data from the exome sequencing project. Bioinformatics. 2013; 29(21):2744–9. https://doi.org/10.1093/bioinformatics/btt477 PMID: 23956302; PubMed Central PMCID: PMCPMC3799474.

35. August P, Suthanthiran M. Transforming growth factor beta and progression of renal disease. Kidney international Supplement. 2003;(87):S99–104. Epub 2003/10/09. PMID: 14531781.

36. Ferguson R, Grim CE, Opgenorth TJ. The epidemiology of end-state renal disease: the six-year South-Central Los Angeles experience, 1980–85. American journal of public health. 1987; 77(7):864–5. Epub 1987/07/01. PMID: 3592045; PubMed Central PMCID: PMCPMC1647229.

37. Tracy RE, Bhandaru SY, Oalmann MC, Guzman MA, Newmann WP, 3rd. Blood pressure and nephrosclerosis in black and white men and women aged 25 to 54. Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc. 1991; 4(5):602–9. Epub 1991/09/01. PMID: 1758872.

38. Freedman BI, Bowden DW, Rich SS, Valis CJ, Sale MM, Hicks PJ, et al. A genome scan for all-cause end-stage renal disease in African Americans. Nephrol Dial Transplant. 2005; 20(4):712–8. Epub 2005/02/11. https://doi.org/10.1093/ndt/gfh704 PMID: 15701670.

39. URD S. USRDS 2003 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2003.

40. URDS U. 1998 Annual Data Report. Bethesda, MD: The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1998.

41. Toto RB. Hypertensive nephrosclerosis in African Americans. Kidney Int. 2003; 64(6):2331–41. Epub 2003/11/25. https://doi.org/10.1046/j.1523-1755.2003.00333.x PMID: 14633170.

42. Barrett J. Keloid. In: Bergsma D, editor. Birth Defect Compendium. Baltimore: Williams and Wilkins Company; 1973. p. 553.

43. Polednak AP. Connective tissue responses in blacks in relation to disease: further observations. American journal of physical anthropology. 1987; 74(3):357–71. Epub 1987/11/01. https://doi.org/10.1002/ajpa.1330740308 PMID: 3322033.

44. Rybicki BA, Maliarik MJ, Major M, Popovich J Jr., Iannuzzi MC. Epidemiology, demographics, and genetics of sarcoidosis. Seminars in respiratory infections. 1998; 13(3):166–73. Epub 1998/10/09. PMID: 9764947.

45. Terris M, Chaves AD. An epidemiologic study of sarcoidosis. The American review of respiratory disease. 1966; 94(1):50–5. Epub 1966/07/01. https://doi.org/10.1164/arrd.1966.94.1.50 PMID: 5945340.

46. Keller AZ. Hospital, age, racial, occupational, geographical, clinical and survivorship characteristics in the epidemiology of sarcoidosis. Am J Epidemiol. 1971; 94(3):222–30. Epub 1971/09/01. PMID: 5093653.

47. Sartwell PE, Edwards LB. Epidemiology of sarcoidosis in the U.S. Navy. Am J Epidemiol. 1974; 99 (4):250–7. Epub 1974/04/01. PMID: 4818715.

48. Rybicki BA, Major M, Popovich J Jr., Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. Am J Epidemiol. 1997; 145(3):234–41. Epub 1997/02/01. PMID: 9012596.

49. Rybicki BA, Harrington D, Major M, Simoff M, Popovich J Jr., Maliarik M, et al. Heterogeneity of familial risk in sarcoidosis. Genet Epidemiol. 1996; 13(1):23–33. Epub 1996/01/01. https://doi.org/10.1002/(SICI)1098-2272(1996)13:1<23::AID-GEPI3>3.0.CO;2-7 PMID: 8647376.

50. Kucera GP, Rybicki BA, Kirkey KL, Coon SW, Major ML, Maliarik MJ, et al. Occupational risk factors for sarcoidosis in African-American siblings. Chest. 2003; 123(5):1527–35. Epub 2003/05/13. PMID: 12740270.

51. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med. 2007; 357(21):2153–65. Epub 2007/11/23. https://doi.org/10.1056/NEJMra071714 PMID: 18032765.

52. Polednak AP. Various chronic disorders and other conditions. Racial and Ethnic Differences in Disease. New York: Oxford University Press; 1989. p. 228–9,46–47.

53. Suthanthiran M, Li B, Song JO, Ding R, Sharma VK, Schwartz JE, et al. Transforming growth factor-beta 1 hyperexpression in African-American hypertensives: A novel mediator of hypertension and/or target organ damage. Proc Natl Acad Sci U S A. 2000; 97(7):3479–84. Epub 2000/03/22. https://doi.org/10.1073/pnas.050420897 PMID: 10725360; PubMed Central PMCID: PMCPMC16265.

54. Dustan HP. Does keloid pathogenesis hold the key to understanding black/white differences in hypertension severity? Hypertension. 1995; 26(6 Pt 1):858–62. Epub 1995/12/01. PMID: 7490140.

55. August P, Leventhal B, Suthanthiran M. Hypertension-induced organ damage in African Americans: transforming growth factor-beta(1) excess as a mechanism for increased prevalence. Current hypertension reports. 2000; 2(2):184–91. Epub 2000/09/12. PMID: 10981147.

56. Racial/ethnic disparities in prevalence, treatment, and control of hypertension—United States, 1999–2002. MMWR Morbidity and mortality weekly report. 2005; 54(1):7–9. Epub 2005/01/14. PMID: 15647724.

57. Lackland DT, Keil JE. Epidemiology of hypertension in African Americans. Seminars in nephrology. 1996; 16(2):63–70. Epub 1996/03/01. PMID: 8668862.

58. Racette L, Wilson MR, Zangwill LM, Weinreb RN, Sample PA. Primary open-angle glaucoma in blacks: a review. Survey of ophthalmology. 2003; 48(3):295–313. Epub 2003/05/15. PMID: 12745004.

59. Tielsch JM, Sommer A, Katz J, Royall RM, Quigley HA, Javitt J. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. Jama. 1991; 266(3):369–74. Epub 1991/07/17. PMID: 2056646.

60. Mayes MD. Scleroderma epidemiology. Rheumatic diseases clinics of North America. 2003; 29 (2):239–54. Epub 2003/07/05. PMID: 12841293.

61. Masi AT, D'Angelo WA. Epidemiology of fatal systemic sclerosis (diffuse scleroderma). A 15-year survey in Baltimore. Annals of internal medicine. 1967; 66(5):870–83. Epub 1967/05/01. PMID: 6025228.

62. Arnett FC, Cho M, Chatterjee S, Aguilar MB, Reveille JD, Mayes MD. Familial occurrence frequencies and relative risks for systemic sclerosis (scleroderma) in three United States cohorts. Arthritis and rheumatism. 2001; 44(6):1359–62. Epub 2001/06/16. https://doi.org/10.1002/1529-0131(200106)44:6<1359::AID-ART228>3.0.CO;2-S PMID: 11407695.

63. Flake GP, Andersen J, Dixon D. Etiology and pathogenesis of uterine leiomyomas: a review. Environmental health perspectives. 2003; 111(8):1037–54. Epub 2003/06/27. PMID: 12826476; PubMed Central PMCID: PMCPMC1241553.

64. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. American journal of obstetrics and gynecology. 2003; 188(1):100–7. Epub 2003/01/28. PMID: 12548202.

65. Christopherson WM, Nealon NA. Uterine cancer: a comparative study of black and white women. Progress in clinical and biological research. 1981; 53:185–95. Epub 1981/01/01. PMID: 7465586.

66. Marshall LM, Spiegelman D, Barbieri RL, Goldman MB, Manson JE, Colditz GA, et al. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. Obstetrics and gynecology. 1997; 90(6):967–73. Epub 1997/12/16. PMID: 9397113.

67. Zanchetti A. Impact of hypertension and antihypertensive treatment on organ damage. Am J Cardiol. 1999; 84(2a):18k–24k. Epub 1999/08/07. PMID: 10437740.

68. Muller DN, Kvakan H, Luft FC. Immune-related effects in hypertension and target-organ damage. Current opinion in nephrology and hypertension. 2011; 20(2):113–7. Epub 2011/01/20. https://doi.org/10.1097/MNH.0b013e3283436f88 PMID: 21245763.

69. McMaster WG, Kirabo A, Madhur MS, Harrison DG. Inflammation, immunity, and hypertensive end-organ damage. Circ Res. 2015; 116(6):1022–33. Epub 2015/03/15. https://doi.org/10.1161/CIRCRESAHA.116.303697 PMID: 25767287; PubMed Central PMCID: PMCPMC4535695.

70. Irigoyen MC, De Angelis K, Dos Santos F, Dartora DR, Rodrigues B, Consolim-Colombo FM. Hypertension, Blood Pressure Variability, and Target Organ Lesion. Current hypertension reports. 2016; 18 (4):31. Epub 2016/03/24. https://doi.org/10.1007/s11906-016-0642-9 PMID: 27002717.

71. Ross R. Atherosclerosis is an inflammatory disease. Am Heart J. 1999; 138(5 Pt 2):S419–20. Epub 1999/10/28. PMID: 10539839.

72. Sakakura K, Nakano M, Otsuka F, Ladich E, Kolodgie FD, Virmani R. Pathophysiology of atherosclerosis plaque progression. Heart, lung & circulation. 2013; 22(6):399–411. Epub 2013/04/02. https://doi.org/10.1016/j.hlc.2013.03.001 PMID: 23541627.

73. Lan TH, Huang XQ, Tan HM. Vascular fibrosis in atherosclerosis. Cardiovascular pathology: the official journal of the Society for Cardiovascular Pathology. 2013; 22(5):401–7. Epub 2013/02/05. https://doi.org/10.1016/j.carpath.2013.01.003 PMID: 23375582.

74. Silver MA, Raghuvir R, Fedirko B, Elser D. Systemic hypertension among women with uterine leiomyomata: potential final common pathways of target end-organ remodeling. Journal of clinical hypertension (Greenwich, Conn). 2005; 7(11):664–8. Epub 2005/11/10. PMID: 16278524.

75. Boynton-Jarrett R, Rich-Edwards J, Malspeis S, Missmer SA, Wright R. A prospective study of hypertension and risk of uterine leiomyomata. Am J Epidemiol. 2005; 161(7):628–38. Epub 2005/03/23. https://doi.org/10.1093/aje/kwi072 PMID: 15781952; PubMed Central PMCID: PMCPMC4586055.

76. Okolo S. Incidence, aetiology and epidemiology of uterine fibroids. Best practice & research Clinical obstetrics & gynaecology. 2008; 22(4):571–88. Epub 2008/06/07. 10.1016/j.bpobgyn.2008.04.002. PMID: 18534913. https://doi.org/10.1016/j.bpobgyn.2008.04.002

77. Haan YC, Oudman I, de Lange ME, Timmermans A, Ankum WM, van Montfrans GA, et al. Hypertension risk in Dutch women with symptomatic uterine fibroids. Am J Hypertens. 2015; 28(4):487–92. Epub 2014/09/23. https://doi.org/10.1093/ajh/hpu183 PMID: 25241046.

78. Huang C, Ogawa R. The link between hypertension and pathological scarring: does hypertension cause or promote keloid and hypertrophic scar pathogenesis? Wound repair and regeneration: official publication of the Wound Healing Society [and] the European Tissue Repair Society. 2014; 22(4):462–6. Epub 2014/06/06. https://doi.org/10.1111/wrr.12197 PMID: 24899409.

79. Dustan HP. Growth factors and racial differences in severity of hypertension and renal diseases. Lancet. 1992; 339(8805):1339–40. Epub 1992/05/30. PMID: 1350001.

80. August P, Suthanthiran M. Transforming growth factor beta signaling, vascular remodeling, and hypertension. N Engl J Med. 2006; 354(25):2721–3. Epub 2006/06/23. https://doi.org/10.1056/NEJMcibr062143 PMID: 16790709.

81. Wernig G, Chen SY, Cui L, Van Neste C, Tsai JM, Kambham N, et al. Unifying mechanism for different fibrotic diseases. Proc Natl Acad Sci U S A. 2017; 114(18):4757–62. Epub 2017/04/21. https://doi.org/10.1073/pnas.1621375114 PMID: 28424250; PubMed Central PMCID: PMCPMC5422830.

SNP	Disease	Chromosome	Position (hg19)	Risk Allele	Other Allele
rs880315	Hypertension	1	10796866	C	T
rs17367504	Hypertension	1	11862778	G	A
rs2275247	Systemic sclerosis	1	35908451	C	T
rs3753841	Glaucoma	1	103379918	G	A
rs12136063	Nephrosclerosis	1	110014170	A	G
rs10745332	Hypertension	1	113189053	A	G
rs17030613	Hypertension	1	113190807	C	A
rs267734	Nephrosclerosis	1	150951477	T	C
rs2049805	Nephrosclerosis	1	155194980	C	T
rs4656461	Glaucoma	1	165687205	G	A
rs3850625	Nephrosclerosis	1	201016296	G	A
rs873549	Keloid	1	222271767	C	T
rs2802729	Nephrosclerosis	1	243501763	A	C
rs807601	Nephrosclerosis	2	15793014	T	G
rs6431731	Nephrosclerosis	2	15863002	C	T
rs1260326	Nephrosclerosis	2	27730940	T	C
rs3213787	Glaucoma	2	45646824	A	G
rs7583877	Nephrosclerosis	2	100460654	C	T
rs11123170	Nephrosclerosis	2	113978940	G	C
rs17830558	Nephrosclerosis	2	160878364	T	G
rs16849225	Hypertension	2	164906820	C	T
rs1446468	Hypertension	2	164963486	T	C
rs4667594	Nephrosclerosis	2	170008506	A	T
rs4972593	Nephrosclerosis	2	174462854	A	T
rs7601754	Systemic sclerosis	2	191940451	A	G
rs2712184	Nephrosclerosis	2	217682779	A	C
rs6795744	Nephrosclerosis	3	13906850	A	G
rs820430	Hypertension	3	27548900	A	G
rs1717027	Hypertension	3	41987920	T	C
rs319690	Hypertension	3	47927484	C	T
rs9810888	Hypertension	3	53635595	G	T
rs13069000	Nephrosclerosis	3	66798950	G	C
rs1511412	Keloid	3	138713704	A	G
rs16833934	Hypertension	3	163737250	G	A
rs419076	Hypertension	3	169100886	T	C
rs16853722	Nephrosclerosis	3	169150632	C	T
rs9682041	Nephrosclerosis	3	170091902	C	T
rs6445055	Glaucoma	3	171992387	A	G
rs10513801	Nephrosclerosis	3	185822353	T	G
rs10937329	Nephrosclerosis	3	187713718	T	A
rs4619890	Glaucoma	4	7853160	G	A
rs3775948	Nephrosclerosis	4	9995182	C	G
rs871606	Hypertension	4	54799245	T	C
rs10032549	Nephrosclerosis	4	77398015	G	A
rs1902859	Hypertension	4	81157703	C	T
rs2725220	Nephrosclerosis	4	88959922	C	G

SNP	Disease	Chromosome	Position (hg19)	Risk Allele	Other Allele
rs228611	Nephrosclerosis	4	103561709	G	A
rs1173771	Hypertension	5	32815028	G	A
rs11959928	Nephrosclerosis	5	39397132	A	T
rs2233287	Systemic sclerosis	5	150440097	A	G
rs9313772	Hypertension	5	157804457	C	T
rs6420094	Nephrosclerosis	5	176817636	A	G
rs2745572	Glaucoma	6	1548369	G	A
rs11969985	Glaucoma	6	1922907	G	A
rs198846	Hypertension	6	26107463	G	A
rs7759001	Nephrosclerosis	6	27341409	G	A
rs3130573	Systemic sclerosis	6	31106268	G	A
rs3828890	Nephrosclerosis	6	31440669	G	C
rs805303	Hypertension	6	31616366	G	A
rs443198	Systemic sclerosis	6	32190406	G	A
rs9296015	Systemic sclerosis	6	32218989	A	G
rs9272729	Nephrosclerosis	6	32609594	A	G
rs881858	Nephrosclerosis	6	43806609	A	G
rs13209747	Hypertension	6	127115454	T	C
rs1936800	Nephrosclerosis	6	127436064	T	C
rs17080102	Hypertension	6	151004770	G	C
rs2279463	Nephrosclerosis	6	160668389	A	G
rs316009	Nephrosclerosis	6	160675764	T	C
rs10277115	Nephrosclerosis	7	1285195	T	A
rs59072263	Glaucoma	7	8152067	G	T
rs17428471	Hypertension	7	27337867	T	G
rs3750082	Nephrosclerosis	7	32919927	T	A
rs6465825	Nephrosclerosis	7	77416439	T	C
rs7801190	Hypertension	7	100458093	C	G
rs17477177	Hypertension	7	106411858	T	C
rs10258482	Glaucoma	7	116150095	A	C
rs7805747	Nephrosclerosis	7	151407801	A	G
rs6459680	Nephrosclerosis	7	156258568	T	G
rs1015213	Glaucoma	8	52887541	T	C
rs284491	Glaucoma	8	105958633	T	C
rs2071518	Hypertension	8	120435812	T	C
rs7827545	Hypertension	8	135566567	T	C
rs4744712	Nephrosclerosis	9	71434707	C	A
rs2487032	Glaucoma	9	107703934	A	G
rs8176743	Glaucoma	9	136131415	T	C
rs1044261	Nephrosclerosis	10	1065710	C	T
rs10795433	Nephrosclerosis	10	16969923	A	C
rs4373814	Hypertension	10	18419972	C	G
rs11014166	Hypertension	10	18708798	A	T
rs10994860	Nephrosclerosis	10	52645424	T	C
rs1530440	Hypertension	10	63524591	T	C
rs9663362	Hypertension	10	95895177	G	C

SNP	Disease	Chromosome	Position (hg19)	Risk Allele	Other Allele
rs12416687	Hypertension	10	104629011	T	C
rs7913069	Uterine fibroids	10	105714399	T	C
rs2782980	Hypertension	10	115781527	C	T
rs2280543	Uterine fibroids	11	203788	C	T
rs163160	Nephrosclerosis	11	2789955	A	G
rs7129220	Hypertension	11	10350538	A	G
rs381815	Hypertension	11	16902268	C	T
rs11024102	Glaucoma	11	17008605	C	T
rs10767873	Nephrosclerosis	11	30768678	C	T
rs12419342	Glaucoma	11	47468545	C	T
rs747782	Glaucoma	11	47940925	C	T
rs479777	Sarcoidosis	11	64107477	T	C
rs504915	Nephrosclerosis	11	64464085	T	A
rs4014195	Nephrosclerosis	11	65506822	C	G
rs633185	Hypertension	11	100593538	G	C
rs11222084	Hypertension	11	130273230	T	A
rs1106766	Nephrosclerosis	12	57809456	T	C
rs626277	Nephrosclerosis	13	72347696	C	A
rs17536527	Nephrosclerosis	15	45719187	C	G
rs491567	Nephrosclerosis	15	53946593	C	A
rs8032158	Keloid	15	56194877	C	T
rs3825942	Glaucoma	15	74219582	A	G
rs893818	Glaucoma	15	74229195	A	G
rs6495122	Hypertension	15	75125645	A	C
rs7172677	Systemic sclerosis	15	75424593	A	C
rs1394125	Nephrosclerosis	15	76158983	A	G
rs2521501	Hypertension	15	91437388	T	A
rs12437854	Nephrosclerosis	15	94141833	G	T
rs13329952	Nephrosclerosis	16	20366507	T	C
rs11864909	Nephrosclerosis	16	20400839	C	T
rs889472	Nephrosclerosis	16	79645989	C	A
rs12711490	Systemic sclerosis	16	85973028	T	C
rs164748	Nephrosclerosis	16	89708292	C	G
rs11656696	Glaucoma	17	10033679	A	C
rs2453580	Nephrosclerosis	17	19438321	T	C
rs7208487	Nephrosclerosis	17	37543449	T	G
rs12946454	Hypertension	17	43208121	T	A
rs17608766	Hypertension	17	45013271	T	C
rs16948048	Hypertension	17	47440466	G	A
rs11868441	Nephrosclerosis	17	59239221	G	A
rs8068318	Nephrosclerosis	17	59483766	C	T
rs7227483	Nephrosclerosis	18	43187130	G	A
rs8091180	Nephrosclerosis	18	77164243	A	G
rs12460876	Nephrosclerosis	19	33356891	C	T
rs11666497	Nephrosclerosis	19	38464262	C	T
rs3116139	Glaucoma	19	51879034	C	T

SNP	Disease	Chromosome	Position (hg19)	Risk Allele	Other Allele
rs1327235	Hypertension	20	10969030	G	A
rs6088580	Nephrosclerosis	20	33285053	C	G
rs6066043	Nephrosclerosis	20	45288453	A	G
rs17216707	Nephrosclerosis	20	52732362	T	C
rs6026584	Nephrosclerosis	20	57469073	C	T
rs6015450	Hypertension	20	57751117	G	A
rs35934224	Glaucoma	22	19872645	C	T
rs2239785	Nephrosclerosis	22	36661330	G	A
rs12484776	Uterine fibroids	22	40652873	G	A

SNP	AFR	AFR (cont.)	ACB + ASW	EUR	AMR	SAS	EAS	EA Controls	EA Cases	AA Controls	AA Cases
rs6431731	0.002	0.000	0.010	0.036	0.014	0.005	0.001	0.057	0.049	0.011	0.017
rs1511412	0.005	0.001	0.016	0.111	0.065	0.104	0.036	0.107	0.103	0.022	0.019
rs6066043	0.006	0.002	0.019	0.141	0.221	0.272	0.546	0.139	0.153	0.048	0.040
rs11024102	0.017	0.001	0.067	0.258	0.268	0.329	0.371	0.294	0.276	0.062	0.060
rs3116139	0.018	0.008	0.051	0.288	0.297	0.359	0.284	0.263	0.263	0.068	0.078
rs16853722	0.027	0.023	0.041	0.125	0.094	0.176	0.296	0.127	0.111	0.055	0.053
rs1530440	0.036	0.037	0.035	0.190	0.232	0.154	0.194	0.198	0.173	0.072	0.074
rs7129220	0.052	0.056	0.041	0.129	0.068	0.044	0.001	0.114	0.106	0.079	0.079
rs9272729	0.053	0.049	0.067	0.106	0.118	0.076	0.052	0.121	0.125	0.071	0.072
rs17030613	0.064	0.069	0.045	0.235	0.278	0.210	0.442	0.195	0.199	0.090	0.076
rs12484776	0.065	0.057	0.092	0.194	0.434	0.301	0.287	0.210	0.205	0.099	0.113
rs12946454	0.067	0.058	0.096	0.283	0.197	0.305	0.224	0.248	0.251	0.093	0.094
rs11868441	0.068	0.035	0.175	0.797	0.754	0.886	0.756	0.812	0.803	0.208	0.194
rs1106766	0.082	0.076	0.099	0.194	0.310	0.101	0.079	0.247	0.230	0.103	0.108
rs1902859	0.089	0.076	0.131	0.310	0.311	0.259	0.366	0.320	0.310	0.118	0.132
rs13069000	0.090	0.088	0.096	0.184	0.133	0.060	0.196	0.196	0.179	0.098	0.129
rs1260326	0.094	0.089	0.108	0.411	0.362	0.200	0.481	0.395	0.422	0.146	0.133
rs316009	0.101	0.103	0.096	0.109	0.069	0.134	0.041	0.108	0.100	0.091	0.088
rs17367504	0.110	0.102	0.137	0.139	0.078	0.188	0.123	0.167	0.152	0.101	0.131
rs10277115	0.117	0.100	0.169	0.755	0.533	0.679	0.308	0.757	0.756	0.238	0.252
rs13209747	0.120	0.106	0.162	0.451	0.362	0.417	0.489	0.428	0.440	0.171	0.179
rs7759001	0.123	0.112	0.156	0.235	0.231	0.260	0.413	0.236	0.224	0.145	0.129
rs8091180	0.125	0.111	0.169	0.597	0.601	0.457	0.784	0.561	0.574	0.194	0.178
rs2745572	0.150	0.144	0.169	0.364	0.382	0.484	0.493	0.339	0.360	0.179	0.179
rs17428471	0.154	0.165	0.118	0.069	0.081	0.026	0.037	0.089	0.078	0.115	0.122
rs7601754	0.154	0.124	0.252	0.819	0.787	0.880	0.855	0.823	0.817	0.279	0.257
rs880315	0.165	0.159	0.185	0.357	0.513	0.398	0.636	0.341	0.348	0.195	0.174
rs7913069	0.166	0.174	0.143	0.038	0.117	0.069	0.085	0.021	0.019	0.156	0.138
rs8176743	0.169	0.176	0.150	0.084	0.048	0.233	0.194	0.062	0.074	0.158	0.166
rs893818	0.178	0.180	0.172	0.319	0.307	0.309	0.522	0.337	0.322	0.210	0.203
rs12437854	0.179	0.187	0.156	0.079	0.153	0.127	0.215	0.065	0.063	0.158	0.143
rs873549	0.181	0.179	0.188	0.283	0.369	0.434	0.352	0.284	0.287	0.200	0.170
rs633185	0.196	0.199	0.185	0.277	0.421	0.500	0.484	0.271	0.294	0.235	0.222

SNP	AFR	AFR (cont.)	ACB + ASW	EUR	AMR	SAS	EAS	EA Controls	EA Cases	AA Controls	AA Cases
rs11656696	0.201	0.199	0.207	0.414	0.337	0.249	0.489	0.416	0.421	0.241	0.247
rs6015450	0.205	0.202	0.213	0.127	0.059	0.051	0.000	0.124	0.124	0.187	0.187
rs11222084	0.209	0.209	0.207	0.330	0.330	0.217	0.022	0.366	0.352	0.225	0.221
rs2233287	0.213	0.218	0.194	0.082	0.091	0.047	0.003	0.082	0.083	0.182	0.172
rs10994860	0.222	0.216	0.242	0.202	0.110	0.200	0.047	0.174	0.172	0.230	0.206
rs2521501	0.223	0.218	0.239	0.319	0.183	0.232	0.095	0.304	0.299	0.237	0.226
rs10032549	0.225	0.205	0.287	0.516	0.484	0.337	0.273	0.536	0.528	0.272	0.260
rs6795744	0.231	0.222	0.258	0.158	0.133	0.037	0.081	0.154	0.152	0.223	0.202
rs9663362	0.232	0.225	0.255	0.528	0.369	0.488	0.300	0.523	0.531	0.283	0.298
rs4656461	0.256	0.261	0.242	0.141	0.135	0.043	0.009	0.125	0.115	0.218	0.208
rs9296015	0.266	0.266	0.268	0.220	0.236	0.194	0.299	0.197	0.176	0.240	0.221
rs12136063	0.269	0.256	0.309	0.689	0.818	0.714	0.957	0.714	0.704	0.351	0.341
rs12460876	0.270	0.255	0.319	0.423	0.375	0.445	0.639	0.387	0.403	0.285	0.273
rs11123170	0.278	0.285	0.258	0.394	0.367	0.471	0.333	0.373	0.383	0.312	0.292
rs11959928	0.287	0.289	0.280	0.451	0.395	0.377	0.174	0.432	0.441	0.305	0.334
rs9682041	0.291	0.308	0.236	0.121	0.111	0.163	0.060	0.121	0.121	0.260	0.253
rs7172677	0.293	0.290	0.303	0.301	0.246	0.267	0.201	0.269	0.266	0.298	0.280
rs3828890	0.296	0.295	0.299	0.124	0.140	0.055	0.032	0.115	0.101	0.315	0.306
rs6088580	0.311	0.302	0.341	0.465	0.314	0.401	0.408	0.441	0.456	0.342	0.349
rs10795433	0.313	0.295	0.373	0.836	0.591	0.739	0.594	0.841	0.833	0.392	0.385
rs8032158	0.315	0.325	0.283	0.280	0.300	0.432	0.304	0.317	0.324	0.313	0.313
rs7805747	0.325	0.336	0.287	0.288	0.173	0.071	0.003	0.272	0.269	0.313	0.327
rs3750082	0.330	0.323	0.350	0.635	0.700	0.497	0.656	0.630	0.658	0.410	0.390
rs881858	0.338	0.332	0.357	0.695	0.761	0.756	0.773	0.708	0.686	0.361	0.363
rs1015213	0.338	0.365	0.252	0.101	0.055	0.108	0.014	0.093	0.084	0.268	0.298
rs4972593	0.349	0.352	0.338	0.134	0.104	0.403	0.214	0.164	0.160	0.310	0.298
rs17536527	0.350	0.357	0.325	0.480	0.644	0.598	0.909	0.424	0.443	0.353	0.342
rs1394125	0.350	0.350	0.350	0.342	0.233	0.229	0.083	0.357	0.362	0.340	0.342
rs805303	0.357	0.341	0.408	0.633	0.572	0.698	0.631	0.624	0.638	0.410	0.420
rs6445055	0.362	0.380	0.306	0.174	0.278	0.205	0.339	0.161	0.162	0.332	0.348
rs7827545	0.370	0.352	0.427	0.335	0.398	0.460	0.673	0.320	0.311	0.352	0.362
rs10258482	0.398	0.415	0.344	0.258	0.208	0.191	0.009	0.272	0.288	0.357	0.350
rs16948048	0.408	0.434	0.325	0.371	0.244	0.140	0.211	0.363	0.386	0.402	0.373

SNP	AFR	AFR (cont.)	ACB + ASW	EUR	AMR	SAS	EAS	EA Controls	EA Cases	AA Controls	AA Cases
rs3825942	0.410	0.419	0.382	0.177	0.169	0.268	0.140	0.148	0.166	0.368	0.376
rs747782	0.424	0.437	0.385	0.193	0.170	0.163	0.259	0.204	0.202	0.386	0.403
rs2712184	0.442	0.427	0.490	0.572	0.627	0.457	0.533	0.567	0.591	0.488	0.486
rs443198	0.471	0.478	0.446	0.364	0.378	0.502	0.562	0.381	0.378	0.475	0.486
rs6459680	0.482	0.468	0.528	0.754	0.741	0.723	0.628	0.753	0.752	0.558	0.549
rs3130573	0.488	0.492	0.475	0.347	0.317	0.324	0.184	0.351	0.344	0.442	0.458
rs2802729	0.490	0.506	0.440	0.445	0.396	0.571	0.319	0.463	0.464	0.487	0.484
rs6465825	0.493	0.494	0.490	0.574	0.689	0.638	0.780	0.595	0.599	0.507	0.522
rs1327235	0.494	0.489	0.510	0.462	0.264	0.490	0.542	0.482	0.479	0.503	0.510
rs1936800	0.535	0.547	0.497	0.480	0.510	0.484	0.492	0.510	0.525	0.517	0.539
rs2782980	0.538	0.536	0.545	0.697	0.777	0.806	0.862	0.711	0.722	0.563	0.547
rs419076	0.550	0.558	0.526	0.482	0.369	0.473	0.151	0.470	0.492	0.528	0.522
rs9810888	0.551	0.559	0.529	0.489	0.405	0.409	0.417	0.520	0.499	0.546	0.544
rs7583877	0.568	0.572	0.554	0.269	0.401	0.226	0.365	0.316	0.304	0.540	0.560
rs2071518	0.592	0.589	0.599	0.225	0.189	0.308	0.161	0.262	0.270	0.506	0.539
rs2453580	0.600	0.598	0.605	0.593	0.732	0.833	0.787	0.601	0.603	0.613	0.597
rs4744712	0.601	0.605	0.586	0.623	0.751	0.688	0.545	0.587	0.601	0.575	0.599
rs16833934	0.604	0.612	0.576	0.272	0.179	0.151	0.216	0.261	0.267	0.540	0.534
rs4373814	0.613	0.619	0.592	0.466	0.514	0.431	0.504	0.425	0.424	0.557	0.585
rs491567	0.617	0.617	0.615	0.203	0.404	0.276	0.531	0.226	0.221	0.567	0.546
rs2049805	0.617	0.599	0.675	0.523	0.689	0.547	0.757	0.519	0.508	0.633	0.629
rs7227483	0.620	0.622	0.615	0.745	0.741	0.805	0.845	0.735	0.714	0.635	0.612
rs4667594	0.623	0.631	0.599	0.512	0.647	0.488	0.135	0.541	0.543	0.603	0.574
rs319690	0.627	0.639	0.589	0.300	0.404	0.347	0.285	0.307	0.304	0.608	0.592
rs12419342	0.653	0.685	0.551	0.302	0.313	0.162	0.341	0.298	0.292	0.567	0.564
rs13329952	0.657	0.657	0.656	0.784	0.744	0.681	0.914	0.803	0.810	0.652	0.658
rs7208487	0.659	0.648	0.694	0.838	0.764	0.921	0.762	0.836	0.840	0.655	0.669
rs3775948	0.663	0.661	0.672	0.755	0.575	0.684	0.581	0.761	0.740	0.657	0.677
rs889472	0.676	0.688	0.640	0.376	0.517	0.532	0.595	0.392	0.390	0.633	0.652
rs626277	0.689	0.706	0.634	0.417	0.587	0.629	0.876	0.407	0.382	0.649	0.652
rs35934224	0.691	0.686	0.707	0.846	0.856	0.814	0.967	0.841	0.839	0.725	0.721
rs2239785	0.694	0.716	0.621	0.219	0.160	0.162	0.204	0.217	0.195	0.636	0.639
rs1717027	0.704	0.717	0.662	0.191	0.186	0.173	0.149	0.174	0.172	0.632	0.639

SNP	AFR	AFR (cont.)	ACB + ASW	EUR	AMR	SAS	EAS	EA Controls	EA Cases	AA Controls	AA Cases
rs284491	0.719	0.740	0.650	0.341	0.416	0.272	0.406	0.328	0.341	0.647	0.673
rs2275247	0.720	0.730	0.688	0.050	0.367	0.241	0.766	0.038	0.037	0.633	0.638
rs11969985	0.741	0.739	0.745	0.851	0.833	0.859	0.822	0.848	0.862	0.763	0.738
rs7801190	0.750	0.742	0.774	0.946	0.937	0.956	0.998	0.957	0.954	0.785	0.777
rs59072263	0.756	0.749	0.777	0.858	0.911	0.880	0.908	0.849	0.853	0.782	0.775
rs6495122	0.775	0.796	0.710	0.470	0.512	0.873	0.818	0.429	0.432	0.726	0.708
rs10745332	0.783	0.789	0.764	0.756	0.865	0.879	0.811	0.741	0.752	0.784	0.774
rs871606	0.792	0.796	0.780	0.863	0.859	0.664	0.801	0.890	0.898	0.791	0.812
rs1173771	0.795	0.799	0.783	0.581	0.591	0.613	0.661	0.619	0.607	0.767	0.775
rs2725220	0.801	0.817	0.752	0.486	0.395	0.405	0.241	0.490	0.481	0.744	0.736
rs8068318	0.803	0.818	0.755	0.272	0.579	0.529	0.632	0.277	0.284	0.688	0.728
rs381815	0.810	0.812	0.806	0.705	0.710	0.872	0.842	0.742	0.719	0.808	0.796
rs228611	0.812	0.819	0.787	0.518	0.683	0.403	0.514	0.529	0.525	0.750	0.739
rs2279463	0.814	0.806	0.841	0.872	0.934	0.916	0.918	0.870	0.868	0.810	0.815
rs6420094	0.815	0.821	0.793	0.668	0.721	0.698	0.787	0.682	0.674	0.804	0.776
rs6026584	0.818	0.829	0.780	0.665	0.719	0.752	0.748	0.666	0.658	0.783	0.789
rs4014195	0.819	0.812	0.841	0.649	0.785	0.654	0.763	0.659	0.672	0.792	0.792
rs807601	0.822	0.832	0.787	0.323	0.434	0.561	0.783	0.356	0.353	0.739	0.757
rs2487032	0.833	0.844	0.796	0.498	0.484	0.560	0.492	0.502	0.496	0.761	0.776
rs9313772	0.846	0.858	0.806	0.664	0.650	0.629	0.830	0.621	0.622	0.813	0.816
rs4619890	0.859	0.875	0.806	0.466	0.597	0.619	0.704	0.476	0.477	0.824	0.824
rs10937329	0.866	0.873	0.844	0.681	0.736	0.813	0.606	0.700	0.684	0.822	0.837
rs11014166	0.867	0.866	0.869	0.678	0.784	0.708	0.880	0.666	0.669	0.845	0.854
rs17080102	0.880	0.876	0.892	0.930	0.806	0.831	0.920	0.933	0.934	0.900	0.897
rs198846	0.881	0.880	0.885	0.822	0.865	0.926	0.965	0.835	0.838	0.891	0.884
rs12416687	0.887	0.896	0.857	0.746	0.814	0.925	0.821	0.751	0.748	0.853	0.856
rs479777	0.914	0.923	0.885	0.660	0.634	0.778	0.834	0.693	0.647	0.879	0.855
rs16849225	0.914	0.923	0.885	0.775	0.800	0.712	0.595	0.766	0.770	0.891	0.882
rs11864909	0.927	0.932	0.911	0.706	0.718	0.690	0.866	0.723	0.727	0.889	0.882
rs10767873	0.929	0.941	0.892	0.502	0.588	0.743	0.672	0.529	0.549	0.864	0.872
rs12711490	0.930	0.940	0.898	0.805	0.831	0.944	0.926	0.781	0.769	0.899	0.893
rs504915	0.935	0.959	0.857	0.287	0.585	0.389	0.781	0.313	0.313	0.847	0.818
rs2280543	0.935	0.933	0.943	0.967	0.961	0.895	0.845	0.952	0.956	0.935	0.937

SNP	AFR	AFR (cont.)	ACB + ASW	EUR	AMR	SAS	EAS	EA Controls	EA Cases	AA Controls	AA Cases
rs164748	0.937	0.952	0.885	0.523	0.672	0.805	0.984	0.549	0.554	0.886	0.882
rs163160	0.938	0.942	0.927	0.821	0.813	0.742	0.792	0.823	0.819	0.907	0.933
rs11666497	0.940	0.940	0.940	0.805	0.857	0.794	0.890	0.800	0.810	0.924	0.929
rs17477177	0.941	0.947	0.920	0.777	0.843	0.701	0.864	0.801	0.800	0.924	0.924
rs3753841	0.951	0.980	0.857	0.388	0.245	0.414	0.297	0.369	0.396	0.820	0.868
rs17830558	0.959	0.985	0.876	0.466	0.713	0.746	0.656	0.445	0.468	0.887	0.882
rs1446468	0.961	0.978	0.908	0.488	0.667	0.596	0.462	0.474	0.470	0.864	0.883
rs1044261	0.962	0.964	0.955	0.934	0.957	0.993	1.000	0.917	0.929	0.960	0.954
rs17216707	0.965	0.974	0.936	0.773	0.648	0.785	0.957	0.817	0.804	0.918	0.931
rs820430	0.980	0.993	0.940	0.610	0.627	0.623	0.329	0.618	0.598	0.920	0.911
rs10513801	0.988	0.994	0.968	0.862	0.921	0.875	0.937	0.872	0.870	0.958	0.959
rs17608766	0.990	0.999	0.962	0.826	0.942	0.958	0.999	0.876	0.872	0.979	0.977
rs3213787	0.990	0.988	0.997	0.967	0.863	0.894	0.864	0.961	0.959	0.989	0.988
rs267734	0.993	0.997	0.981	0.806	0.906	0.946	0.974	0.799	0.798	0.960	0.954
rs3850625	0.995	1.000	0.978	0.882	0.912	0.802	0.960	0.878	0.889	0.983	0.981

	AFR (cont.)	AFR	ACB + ASW	EAS	SAS	AMR	EUR	EA Controls	EA Cases	AA Controls	AA Cases
N Samples	504	661	157	504	489	347	503	1164	1195	804	578
min	0.000	0.002	0.010	0.000	0.005	0.014	0.036	0.021	0.019	0.011	0.017
mean	0.506	0.504	0.497	0.502	0.483	0.480	0.463	0.464	0.463	0.497	0.497
median	0.494	0.493	0.497	0.504	0.471	0.434	0.451	0.428	0.440	0.506	0.522
max	1.000	0.995	0.997	1.000	0.993	0.961	0.967	0.961	0.959	0.989	0.988
sd	0.321	0.315	0.300	0.312	0.279	0.270	0.258	0.260	0.261	0.291	0.293