Genetic Determinants of Radiographic Knee Osteoarthritis in African Americans

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ABSTRACT. ***Objective.*** The etiology of knee osteoarthritis (OA), the most common form of arthritis, is complex and may differ by race or ethnicity. In recent years, genetic studies have identified many genetic variants associated with OA, but nearly all the studies were conducted in European whites and Asian Americans. Few studies have focused on the genetics of knee OA in African Americans.

Methods. We performed a genome-wide association study of radiographic knee OA in 1217 African Americans from 2 North American cohort studies: 590 subjects from the Johnston County Osteoarthritis Project and 627 subjects from the Osteoarthritis Initiative. Analyses were conducted in each cohort separately and combined in an inverse variance fixed effects metaanalysis, which were then included in pathway analyses. We additionally tested 12 single-nucleotide polymorphisms robustly associated with OA in European white populations for association in African Americans.

Results. We identified a genome-wide significant variant in *LINC01006* (minor allele frequency 12%; $p = 4.11 \times 10^{-9}$) that is less common in European white populations (minor allele frequency < 3%). Five other independent loci reached suggestive significance ($p < 1 \times 10^{-6}$). In pathway analyses, dorsal/ventral neural tube patterning and iron ion transport pathways were significantly associated with knee OA in African Americans (false discovery rate < 0.05). We found no evidence that previously reported OA susceptibility variants in European whites were associated with knee OA in African Americans.

Conclusion. These results highlight differences in the genetic architecture of knee OA between African American and European whites. This finding underscores the need to include more diverse populations in OA genetics studies. (J Rheumatol First Release September 15 2017; doi:10.3899/jrheum.161488)

Key Indexing Terms:
KNEE OSTEOARTHRITIS
ETHNICITY
GENETICS
GENOME-WIDE ASSOCIATION STUDY

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The Genetic Components of Knee Osteoarthritis project was supported by the American Recovery and Reinvestment Act through grant no. RC2-AR-058950 from the US National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)/National Institutes of Health (NIH). The Osteoarthritis Initiative is a public-private partnership composed of 5 contracts (N01-AR-2-2258, N01-AR-2-2259, N01-AR-2-2260, N01-AR-2-2261, N01-AR-2-2262) funded by the NIH. The Johnston County Osteoarthritis Project is supported in part by S043, S1734, and S3486 from the US Centers for Disease Control/Association of Schools of Public Health; 5-P60-AR30701 and 5-P60-AR49465-03 from NIAMS/NIH, and Algynomics Inc. Partial analysis support was provided by P30 DK072488. MSY was supported by the US National Institute on Aging (NIA)/NIH T32AG00262, Arthritis Foundation Doctoral Dissertation Award (6081), NIA/NIH T32AG023480, and Friends of Hebrew SeniorLife.

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Accepted for publication June 27, 2017.

Osteoarthritis (OA) is a multifactorial joint disease characterized by cartilage degradation and structural changes in the subchondral bone, which often leads to joint pain, activity limitations, and physical disability. The etiopathogenesis of OA is complex; family studies indicate that at least part of OA susceptibility is under genetic control[1]. The heritability of radiographic knee OA has been estimated in twin studies to be 39%[2]. Knee OA is also strongly influenced by environmental factors, such as history of injuries and overweight, making it difficult to identify the genetic mechanisms behind knee OA pathogenesis[3]. Identifying genes underlying OA susceptibility is important because the implicated genes may reveal insights into disease pathogenesis and identify potential targets for prevention or therapy. At least a dozen robustly replicated OA susceptibility variants have been identified to date; most of these association studies have been carried out in European whites[4,5,6,7,8,9,10,11,12].

Studies focused on African Americans are important because African Americans experience a higher prevalence of knee OA[13] than white Americans and there is disparity in the incidence of total knee arthroplasty for knee OA, with higher rates in white Americans than African Americans[14]. It is currently unknown whether these differences are due to biological or sociocultural differences or both. The goal of our report is 2-fold: first, to identify single-nucleotide polymorphisms (SNP) associated with radiographic knee OA in African Americans through a genome-wide association analysis, and second, to determine whether SNP robustly associated with OA in European white populations are also associated with radiographic knee OA in African Americans. To address these goals, we performed association analyses in 2 large population-based studies of knee OA that included substantial numbers of African Americans.

MATERIALS AND METHODS

The analyses presented are based on African American participants of the Johnston County Osteoarthritis Project (JoCo) and the Osteoarthritis Initiative (OAI).

The JoCo is an ongoing, community-based cohort study of knee and hip OA in individuals 45 years and older recruited from Johnston County, North Carolina, USA. The original participants were enrolled between 1990 and 1997[13], with additional participants recruited between 2003 and 2004. Participants were recruited by probability sampling, with oversampling of African Americans, where whites and African Americans represent 68% and 32% of the cohort, respectively. The age of the participants ranged from 45 to 98 years; two-thirds of the participants were women. Additional study details have been previously described[13]. JoCo has been continuously approved by institutional review boards (IRB) at the University of North Carolina at Chapel Hill and the Centers for Disease Control and Prevention, and all participants gave informed consent (IRB approval number, 92-0583). A total of 590 African Americans with radiographic readings for knee OA were genotyped and included in this study.

The OAI is a longitudinal, natural history study of knee OA in middle aged and older individuals who either were at risk for or have symptomatic radiographic knee OA. A total of 4796 subjects aged 45–79 years were enrolled at 4 clinical centers (Baltimore, Maryland; Columbus, Ohio; Pittsburgh, Pennsylvania; and Providence, Rhode Island), received a baseline evaluation between 2004 and 2006, and were invited back to assess incidence or progression of OA annually for up to 8 years. The study was approved by the IRB at each clinical center. All participants provided informed consent. The OAI study and public use of clinical and imaging data used in this study were approved by the committee on Human Research at the University of California, San Francisco (IRB approval no. 10-00532). The current analysis was restricted to 627 African Americans with genotype data and in whom knee radiographic readings, read by consensus, were available from radiographs obtained at the baseline evaluation. Study details and data are publicly available on the OAI Website (oai.epi-ucsf.org/datarelease/docs/StudyDesignProtocol.pdf).

Radiographic knee OA cases were defined similarly in both studies as having definite osteophytes and possible joint space narrowing [Kellgren-Lawrence (KL) grade ≥ 2] or total joint replacement in 1 or both knees. Controls were defined as having in both knees no or doubtful evidence for OA (KL grade = 0 or 1).

Genotyping was performed on the Illumina Infinium 1M-Duo bead array and Illumina Omni-Quad 2.5M array for JoCo and OAI, respectively. Genotypes were called within each study using the Illumina BeadStudio software. Sample level quality control included removal of samples with below-threshold sample call rates (< 0.99 for JoCo and < 0.95 for OAI), samples showing excess evidence for heterozygosity, and samples whose reported gender did not match their sex assignment based on genotype data. SNP with missing call rates > 0.01 were excluded. We additionally eliminated samples showing evidence for cryptic relatedness based on genetic data and SNP showing evidence for extreme deviation from Hardy-Weinberg equilibrium ($p < 1 \times 10^{-6}$).

In JoCo and OAI separately, we imputed SNP dosages in all samples based on the 1000 genomes of the white and African American reference panel (June 2011 release). Imputation for both studies was conducted using Minimac (genome.sph.umich.edu/wiki/Minimac). Following imputation, 8.38 million SNP were available for analysis in JoCo and OAI.

First, we performed a genome-wide association metaanalysis of the combined JoCo and OAI sample to identify novel SNP associated with radiographic knee OA in African Americans. Prior to the genetic association analysis, principal components analysis was performed in each study to assess population substructure. Principal components that were significantly associated with the outcome ($p < 0.05$) were used as covariates in association analyses. We tested each SNP for association with radiographic knee OA within JoCo and OAI separately. We used logistic regression, assuming an additive genetic model, with adjustment for age, sex, and principal components. We additionally adjusted for body mass index (BMI) in secondary analyses. Association analyses for the JoCo and OAI were performed with ProbABEL and PLINK, respectively. Beta estimates were then combined across studies weighting the study-specific estimates by the inverse of their variances using the METAL software program[15]. Based on a combined sample size of 742 cases and 475 controls, we had 80% power to detect OR of 1.51–1.65 for SNP having minor allele frequencies (MAF) ranging from 0.10–0.50 at genome-wide thresholds for statistical significance ($p = 5 \times 10^{-8}$). Heterogeneity between studies was assessed using Cochran's Q statistic. We generated LocusZoom plots to visualize and provide genomic context to top metaanalysis findings ($p < 1 \times 10^{-6}$)[16].

Given the limited power to detect associations at individual SNP, we conducted pathway analyses with MAGENTA (Meta-Analysis Gene-set Enrichment of variant Associations), which can be downloaded from the Broad Institute Website (www.broadinstitute.org/mpg/magenta). Pathway analyses were based on metaanalysis SNP p values and all databases available in MAGENTA, including Gene Ontology, Ingenuity, KEGG, and PANTHER. We set the threshold for significance at false discovery rate (FDR) < 0.05.

Second, we tested whether SNP previously associated with OA in European white populations were also associated with radiographic knee OA in African Americans. We selected for replication 12 SNP associated with knee OA at genome-wide levels of significance or near genome-wide significance in prior genome-wide association studies (GWAS)[8,9,10,11,12]. In addition, we calculated the power to detect the association of each SNP with

radiographic knee OA in our African American sample based on the OR reported from the literature and the allele frequency of that SNP observed in African Americans (Table 1).

RESULTS

Sample characteristics of the 1217 African American subjects included in this analysis (742 cases and 475 controls) are provided in Table 2. Compared to controls, cases were older, had higher BMI, and were more likely to be female. About 50% of JoCo study subjects were cases compared to 72% of OAI study subjects. The larger number of cases than controls in OAI can be attributed to that study's inclusion criteria, which were designed to enrich the cohort with subjects who had symptomatic radiographic knee OA.

We performed a genome-wide association analysis of radiographic knee OA to identify novel associations in African Americans. The genomic inflation factor, λ, was 0.954 for the combined metaanalysis, providing no evidence for inflation of p values. As shown in the metaanalysis GWAS results (Figure 1), 1 locus in *LINC01006*, a long intergenic nonprotein coding RNA on chromosome 7, reached genome-wide significance in the primary metaanalysis (rs7792864, MAF = 12%, OR 2.35, 95% CI 1.77–3.13, $p = 4.11 \times 10^{-9}$). Five other independent loci were associated with knee OA at p values $< 1 \times 10^{-6}$. These loci are located in or near *MAGI1* (rs145965284, MAF = 27%), *ANKRD6* (rs78571182, MAF = 12%), *EPPK1/PLEC* (rs76983122, MAF = 11%), *PAX7/TAS1R2* (rs4920343, MAF = 13%), and *DDX10/C11orf87* (rs9783397, MAF = 29%); OR ranged from 1.83 to 2.08 (Table 3). Regional association plots showed strong supporting signals in high linkage disequilibrium with rs7792864 (*LINC01006*) and rs76983122 (*EPPK1/PLEC*), but not rs78571182 (*ANKRD6*; Figure 2). The reliability of the signal for rs145965284 (*MAGI1*) and rs9783397 (*DDX10/C11orf87*) was unclear owing to lack of linkage disequilibrium data with other SNP. After additional adjustment for BMI, OR were slightly attenuated for associations in *LINC01006, MAGI1, EPPK1/PLEC*, and *PAX7/TAS1R2*, but not *ANKRD6* or *DDX10/C11orf87* (Table 3). P values for heterogeneity ranged from 0.17 to 0.71, providing little evidence that there was significant heterogeneity between studies. In pathway analyses, we identified 2 pathways associated with knee OA that reached statistical significance (FDR < 0.05): dorsal/ventral neural tube patterning, and iron ion transport (Table 4).

Following the genome-wide association analysis, we attempted to replicate 12 SNP previously identified as robustly associated with OA, including 3 SNP associated with knee OA[9,10,11,12] and 9 genome-wide or near genome-wide significant SNP identified by the Arthritis Research Council Osteoarthritis Genetics study, the largest GWAS of OA in European whites to date[8]. Risk allele frequencies were lower in African Americans than European whites for most SNP (chromosome 7q22, *GDF5, MCF2L, GLT8D1, GNL3, KLHDC5/PTHLH*, and *TP63*). We did not test SNP in chromosome 7q22 or *KLHDC5/PTHLH* because of minor allele frequencies < 1%. Of the remaining 10 SNP, none was significantly associated with knee OA in African Americans (Table 1). Power to detect significant associations of the same magnitude as seen in European whites at $p < 0.05$ ranged from 32% to 90%. Power to detect nominal associations was greater than 80% for only 1 locus, *TP63*.

DISCUSSION

Our GWAS metaanalysis is the first genome-wide effort to identify genetic polymorphisms associated with knee OA in

Table 1. Association of knee OA in African Americans with SNP robustly associated with knee OA in prior studies.

SNP	Gene	Chr	Risk/ Other Allele	SNP Effect in European Whites			SNP Effect in African Americans			
				Frequency of Risk Allele	OR	Ref	Frequency of Risk Allele in AA	Power to Detect OR of Magnitude Seen in Whites†	OR (95% CI)‡	P Value from Metaanalysis
rs4730250*	7q22 (*DUS4L*)	7	G / A	0.17	1.17	9, 10	0.01	0.10	NA	NA
rs143383	*GDF5*	20	T / C	0.59–0.68	1.16	11	0.12	0.46	0.92 (0.68–1.24)	0.59
rs11842874	*MCF2L*	13	A / G	0.91–0.94	1.17	12	0.77	0.56	1.00 (0.80–1.26)	0.98
rs6976	*GLT8D1*	3	T / C	0.37	1.12	8	0.15	0.34	0.99 (0.75–1.30)	0.95
rs11177	*GNL3*	3	A / G	0.38	1.12	8	0.17	0.36	0.98 (0.75–1.27)	0.87
rs4836732	*ASTN2*	9	C / T	0.47	1.20	8	0.67	0.79	1.11 (0.90–1.35)	0.33
rs9350591	*FILIP1; SENP6*	6	T / C	0.11	1.18	8	0.12	0.54	0.90 (0.67–1.21)	0.48
rs10492367*	*KLHDC5; PTHLH*	12	T / G	0.19	1.14	8	0.01	0.09	NA	NA
rs835487	*CHST11*	12	G / A	0.34	1.13	8	0.64	0.51	0.93 (0.77–1.15)	0.53
rs12107036	*TP63*	3	G / A	0.52	1.21	8	0.35	0.90	1.12 (0.91–1.38)	0.29
rs8044769	*FTO*	16	C / T	0.50	1.11	8	0.76	0.32	0.94 (0.75–1.17)	0.56
rs10948172	*SUPT3H; CDC5L*	6	C / T	0.29	1.14	8	0.30	0.59	0.95 (0.77–1.16)	0.60

* SNP with a minor allele frequency < 0.05 were excluded from the metaanalysis. † Power based on 742 cases and 475 controls, p = 0.05, and population prevalence of knee OA = 0.35. ‡ OR adjusted for age, sex, and population stratification. OA: osteoarthritis; SNP: single-nucleotide polymorphism; Chr: chromosome; Ref: reference; AA: African Americans; NA: not applicable.

Table 2. Baseline characteristics of JoCo and OAI study participants.

Characteristics	JoCo		OAI		Combined	
	Cases, n = 293	Controls, n = 297	Cases, n = 449	Controls, n = 178	Cases, n = 742	Controls, n = 475
Age, yrs, mean	64.0 (10.8)	58.5 (9.6)	59.6 (8.4)	57.4 (8.3)	61.4 (9.6)	58.1 (9.1)
BMI, kg/m^2	34.7 (8.8)	30.1 (6.3)	31.9 (4.6)	29.0 (4.6)	33.0 (6.7)	29.7 (5.7)
Women, %	68.9	61.9	69.7	61.2	69.4	61.7

JoCo: Johnston County Osteoarthritis Project; OAI: Osteoarthritis Initiative; BMI: body mass index.

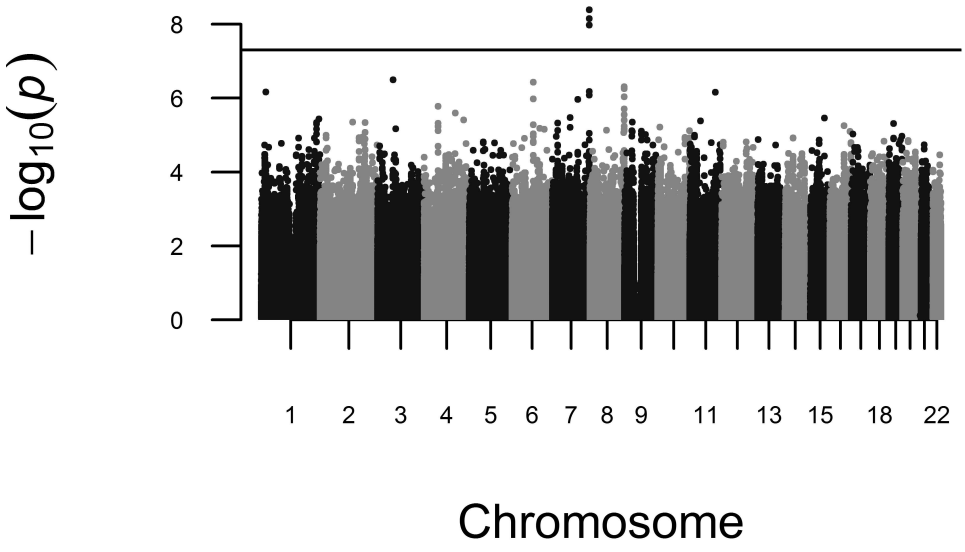

Figure 1. Manhattan plot of the knee OA GWAS metaanalysis in African Americans. The horizontal line represents the threshold for genome-wide significance; p value < 5×10^{-8}. OA: osteoarthritis; GWAS: genome-wide association studies.

Table 3. Associations with knee osteoarthritis in African Americans ($p < 1 \times 10^{-6}$).

Marker	Nearest Gene(s)	Chr	Risk/ Other Allele	Risk Allele Freq	JoCo*		OAI*		Metaanalysis, Adjusted for Age, Sex, and PC		Metaanalysis, Adjusted for Age, Sex, PC, and BMI	
					OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
rs7792864	*LINC01006*	7	C / G	0.88	2.21 (1.43–3.41)	3.56×10^{-4}	2.47 (1.69–3.60)	2.79×10^{-6}	2.35 (1.77–3.13)	4.11×10^{-9}	2.29 (1.69–3.10)	1.02×10^{-7}
rs145965284	*MAGI1*	3	A / T	0.27	1.72 (1.22–2.44)	1.94×10^{-3}	2.27 (1.54–3.33)	2.78×10^{-5}	1.96 (1.51–2.54)	3.18×10^{-7}	1.92 (1.46–2.53)	3.12×10^{-6}
rs78571182	*ANKRD6*	6	T / G	0.88	2.59 (1.70–3.94)	9.69×10^{-6}	1.74 (1.19–2.54)	4.25×10^{-3}	2.08 (1.57–2.75)	3.70×10^{-7}	2.17 (1.61–2.93)	3.62×10^{-7}
rs76983122	*EPPK1/PLEC*	8	T / C	0.11	2.70 (1.75–4.35)	1.00×10^{-5}	1.89 (1.18–3.03)	8.25×10^{-3}	2.31 (1.67–3.20)	4.90×10^{-7}	2.27 (1.60–3.21)	3.76×10^{-6}
rs4920343	*PAX7/TAS1R2*	1	G / A	0.87	1.79 (1.20–2.70)	4.73×10^{-3}	2.17 (1.52–3.13)	3.43×10^{-5}	2.00 (1.52–2.63)	6.82×10^{-7}	2.04 (1.54–2.78)	1.27×10^{-6}
rs9783397	*DDX10/C11orf87*	11	T / G	0.71	2.21 (1.53–3.19)	2.53×10^{-5}	1.59 (1.17–2.18)	3.35×10^{-3}	1.83 (1.44–2.32)	6.99×10^{-7}	1.88 (1.46–2.43)	1.00×10^{-6}

* OR adjusted for age, sex, and population stratification. Chr: chromosome; Freq: frequency; JoCo: Johnston County Osteoarthritis Study; OAI: Osteoarthritis Initiative; PC: principal components; BMI: body mass index.

African Americans, to our knowledge. We identified 1 genome-wide significant locus in *LINC01006* and 5 loci that reached suggestive significance.

Pathway analyses suggested that dorsal/ventral neural tube patterning and iron ion transport pathways may be associated with knee OA in African Americans. However, we found little evidence that previously reported OA susceptibility variants in European whites were associated with knee OA in African Americans. This suggests that the genetic architecture of knee OA in African Americans may be different from that in European whites, warranting future genetic studies of knee OA in populations with African ancestry.

We identified a novel genome-wide significant locus in *LINC01006*, a long intergenic nonprotein coding RNA located on chromosome 7q36 near *INSIG2, SHH, C70rf13, RNF32*, and *LMBR1*. The function of *LINC01006* is not

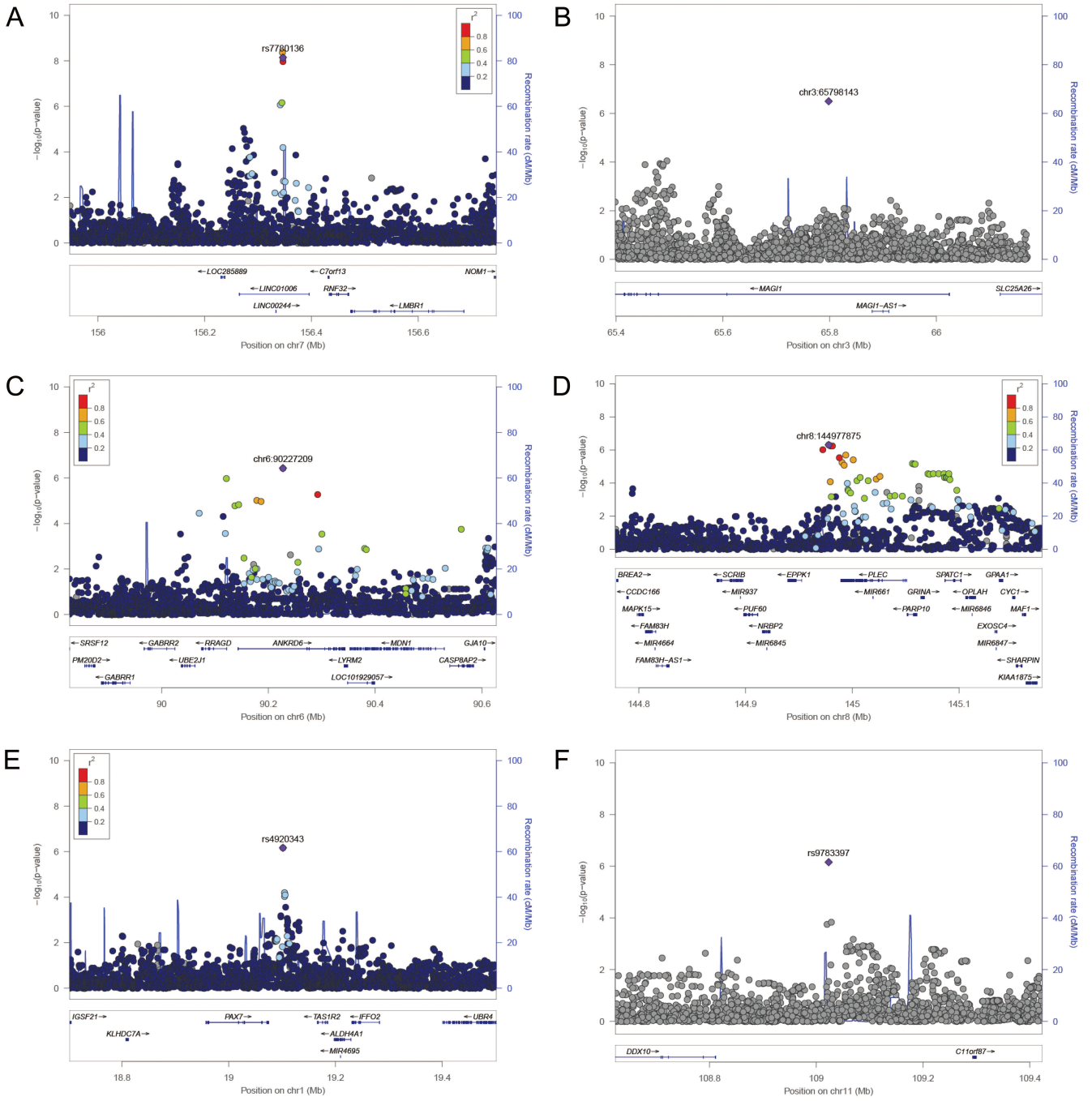

Figure 2. LocusZoom plots for top genetic associations with knee OA. –Log10 of the p values are plotted against the genetic position (hg19) along the chromosome. Colored points represent the degree of linkage disequilibrium (r^2) between the lead SNP (in purple) and all other SNP in the region. Panels A–F are LocusZoom plots for *LINC01006, MAGI1, ANKRD6, EPPK1/PLEC, PAX7/TAS1R2*, and *DDX10/C11orf87*, respectively.

entirely clear, but it is increasingly appreciated that long intergenic nonprotein coding RNA may play key regulatory roles in gene expression, particularly among nearby genes[17]. The locus on chromosome 7q36 has been linked to preaxial polydactyly and other limb disorders, highlighting the possibility that genes and regulatory elements found in this region are related to limb development[18,19,20]. The chromosome 7q36 locus has also been implicated in genetic linkage studies of BMI[21,22]. In this GWAS, adjustment for BMI attenuated the association between *LINC01006* variants and knee OA, suggesting that this locus could act in part through body weight regulation. Because overweight and obesity are highly prevalent in African Americans and also strong risk factors for knee OA[23,24], it is possible that some knee OA loci discovered

Table 4. Pathways that show enrichment of genes by MAGENTA analysis.

Database	Gene Set	Effective Gene Set Size	No. Expected Genes (> 75% cutoff)	No. Observed Genes (> 75% cutoff)	Nominal p	FDR p	Significant Genes*
GOTERM	Dorsal/ventral neural tube patterning	13	3	11	1.00×10^{-5}	5.60×10^{-3}	*PAX7*, *SHH*, *GLI2*, *BMP4*, *PTCH1*, *SMO*, *MNX1*, *PSEN1*, *GSC*, *PSEN2*, *FOXA2*
GOTERM	Iron ion transport	22	6	15	1.00×10^{-4}	1.09×10^{-2}	*STEAP4*, *STEAP3*, *SLC25A28*, *SLC39A14*, *SLC40A1*, *SFXN5*, *FTL*, *TTYH1*, *STEAP2*, *MFI2*, *SFXN1*, *SFXN2*, *SFXN4*, *TF*, *FTH1*

* Enriched genes with scores in the top 25% of all gene scores. Best SNP p values range from 1.68×10^{-3} to 1.27×10^{-6} for the dorsal/ventral neural tube patterning pathway and from 2.62×10^{-3} to 1.18×10^{-4} for the iron ion transport pathway. MAGENTA: Meta-Analysis Gene-set Enrichment of variant Associations; FDR: false discovery rate.

in African Americans may operate through their effects on BMI. After adjusting for BMI, most top loci had attenuated effects and no locus reached genome-wide significance.

None of the candidate SNP that have been robustly associated with OA in prior studies of European white populations was replicated in our study of African Americans. The most likely reason for lack of replication is the relatively low power of our sample — even comprising 742 carefully phenotyped cases — to detect SNP having relatively modest effect sizes (i.e., OR ranging from 1.11 to 1.21). While the small sample size of our study limited ability to detect significant p values, effect size that is independent from sample size may still be a good representation of the magnitude of effect on knee OA. Notably, the 2 loci for which power was sufficient for detecting an association (79% power for the risk allele in *ASTN2* and 90% power for the risk allele in *TP63*), had effect sizes consistent with that found in European whites (OR of 1.11 and 1.12, respectively). The OR for other candidate loci, including *GDF5, MCF2L, GLT8D1, GNL3, FILIP1/SENP6, CHST11, FTO*, and *SUPT3H/CDC5L*, were largely null and inconsistent with effect sizes identified in European whites. The lack of robust replication could be a consequence of low power and/or heterogeneity in the JoCo and OAI populations, or it could indicate a difference in the genetic architecture of OA between African Americans and European whites.

There may be differences in the underlying linkage disequilibrium structure between African and European populations that may alter the degree to which the tested SNP tag the unmeasured pathogenic variant that is responsible for OA. Risk allele frequencies for 10 of 12 OA candidate SNP were noticeably different between ethnic groups, including 7 SNP that had lower frequencies and 3 SNP that had higher frequencies in African Americans compared to whites. The genome-wide significant variant that we identified in *LINC01006* had a minor allele frequency of 12% in African Americans and was much less common in European white populations, where the minor allele frequency was < 3%. Similarly, allele frequencies for other top findings were noticeably different between African Americans and European whites. None of the top African American GWAS loci was associated with knee OA in our previous report of genetic associations in whites[25].

It is also possible that the etiology of OA may be slightly different across ethnic groups. For example, African Americans experience a higher prevalence of knee OA[13], greater lateral tibiofemoral joint space narrowing, greater valgus thrust, and more pain than white Americans, which may be due to either biological or sociocultural differences, or both. However, African Americans are less likely than white Americans to undergo total knee arthroplasty[14].

We had limited power to detect genome-wide significant loci given the small sample size, requiring OR ranging from 1.51 to 1.65 to obtain significant associations in the GWAS; this is a much larger effect size than reported for all prior detected associations in European whites. Effect sizes for all genome-wide significant and suggestive loci in this study were larger than 1.83, exceeding the minimum effect size needed to claim statistical significance with 80% power. This demonstrates an inherent bias in our study. We are more likely to identify variants with large effect sizes than modest effect sizes. It is possible that our top findings may actually have modest effects and by chance have detectable large effects in JoCo and OAI. Because of this, future replication of these associations in other cohorts will be essential. This phenomenon of the "winner's curse" occurs often in GWAS and underscores the need to include even larger studies of knee OA in African Americans to replicate and refine genetic associations.

A strength of our study was the standardized and careful phenotyping of radiographic knee OA used in both JoCo and OAI. However, such assessments are costly and time-consuming to obtain, making it difficult to accrue the very large sample sizes needed for genetic association studies. Despite these difficulties, there is great scientific value to including non-European populations in genetic studies because associations with novel loci not previously detected in Europeans can sometimes be uncovered owing to differ-

ences in allele frequencies between European and non-European populations or to differences in linkage disequilibrium structure. Association testing at established loci in populations representing different ethnic groups may also be useful in efforts to identify the causative variant. Even larger studies of OA genetics in African Americans are needed and have the potential to provide insight into disparities in OA prevalence and etiology. We invite other researchers to contribute additional samples to a larger scale metaanalysis of OA in underrepresented populations.

We conducted a GWAS metaanalysis study of radiographic knee OA in African Americans in 2 large, well-characterized OA cohorts. We identified a genome-wide significant finding in *LINC01006* and significant pathways in dorsal/ventral neural tube patterning and iron ion transport, but did not replicate associations with SNP previously associated with OA in European populations. These results highlight the importance of including non-European ancestry populations in studies of OA genetics.

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