Title: A meta-analysis of the transferability of bone mineral density ge
from European to African ancestry populations

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Abstract

Genetic studies of bone mineral density (BMD) largely have been con
populations. We therefore conducted a meta-analysis of six independ
cohorts to determine whether previously reported BMD loci identified
were transferable to African ancestry populations. We included nearl
both genetic data and assessments of BMD. Genotype imputation wa
1000G reference panel. We assessed SNP associations with femora
BMD in each cohort separately, then combined results in fixed effects
study heterogeneity was high, I^2 index > 60) inverse variance weighte
secondary analyses, we conducted locus-based analyses of rare vari
age ranged from 12 to 68 years. One cohort included only men and a
only women; proportion of women in the other four cohorts ranged fro
BMD loci tested, one locus, 6q25 (*C6orf97*, P-value=8.87×10^{-4}) was a
spine BMD and two loci, 7q21 (*SLC25A13*, P-value=2.84×10^{-4}) and 7
value=2.96×10^{-5}) were associated with femoral neck BMD. Effects w
as previously reported in European ancestry studies and met a Bonfe
threshold, the criteria for transferability to African ancestry populations
associations that met locus-specific Bonferroni-adjusted P-value thres
values<3.33×10^{-4}), 11q14 (*DGKD5*, P-values<5.25×10^{-5}), and 17p13

Keywords: Genetics research, Human association studies, General p

Osteoporosis, DXA. Other keywords: BMD, genetics, African ancestry

Introduction

Osteoporosis is a major public health burden in older adults, a
54% of the US adult population 50 years and older [1]. It is a skeletal
low bone mass and quality that leads to bone fragility and increased s
Assessment of bone mineral density (BMD) utilizing dual-energy X-ra
key to clinical diagnosis of osteoporosis [2] and remains the single bes
Among individuals of European ancestry, women experience about tw
men, but sex differences in fracture rates among African Americans a
American men and women have higher bone mineral density and low
similar aged individuals of European ancestry [5]. In 2005, 12% of all
whites; this is expected to increase to 21% by 2025 [6]. There are eth
osteoporosis diagnosis and treatment that need be better understood
of osteoporotic fractures in older individuals [7].

Genetic factors may contribute to BMD variation within and be
[8]. BMD has a strong genetic component as demonstrated by heritab
50% to 85% [9-13], where estimates tend to be higher in twin and other
16]. Greater African genetic admixture has been associated with highe
biomechanically more favorable hip geometry, but larger decreases in

The majority of genetic studies have been conducted in Europ
and may not reflect the genetic architecture of BMD in African Americ
fraction of BMD loci identified from genetic studies of European popul
(i.e., replicated in non-European populations) [25,26]. For example, a G
American women found that few BMD loci were transferable to Africa
but identified a novel variant in *SVIL* that had not been previously ide
ancestry populations[27]. High transferability of GWAS findings across
reported for other complex traits [24]. Assuming that most underlying c
common and shared across ancestral groups, there still may be differ
architecture and ancestral effects that limit transferability of GWAS fi
ancestry groups [28]. To date, few genetics studies of BMD have been
ancestry populations [29]. Genetic studies in African ancestry populati
whether previously identified BMD risk loci confer the same disease ri
populations and to identify new genetic associations that may have be
based on European populations.

We therefore conducted the largest meta-analysis of selected
independent African ancestry cohorts to determine whether BMD loci
ancestry populations are transferable to African ancestry populations.

femoral neck and/or lumbar spine: the Tobago Bone Health Study (To
Health, Aging and Body Composition Study (Health ABC) (n=1,093),
Neighborhoods of Diversity across the Lifespan (HANDLS) (n=908), W
(WHI) (n=797), Johnston County Osteoarthritis Project (JoCoOA) (n=
Mineral Density in Childhood Study (BMDCS) (n=340).

Tobago: The Tobago Bone Health study is a population-based
Caribbean island of Tobago [30]. Men aged 40 years and older were r
health status except that participants had to be ambulatory, non-instit
terminally ill. Men for this analysis were selected to be of African anc
self-report of 1+ African grandparent; non-African ancestry in Tobago
estimated to be <6% [31]. Lumbar spine and femoral neck BMD were m
QDR4500. The Institutional Review Boards of the University of Pittsbu
Ministry of Health and Social Services approved this study, and all pa
informed consent before data collection.

Health ABC: The Health, Aging and Body Composition study i
men and women aged 70-79 years at the initial visit focused on identi
contribute to functional decline in older persons in relation to changes
age. Participants were recruited from a random sample of white and

age-related health disparities among socioeconomically diverse Africa
in Baltimore [32]. Participants were recruited from 13 contiguous neigh
area probability sampling and randomly selected within strata based o
socioeconomic status. BMD measurements from the first examinatio
analysis. Total body, hip and lumbar spine BMD were measured by L
QDR Discovery-A. Machine type was included as a study-specific co
participants provided written informed consent. The protocol was app
review board at the National Institute of Environmental Health Scienc

WHI: The Women's Health Initiative is a long-term national he
geographically diverse women aged 50-79 years at the time of study
designed to address risk factors for diseases that commonly affect po
including cardiovascular disease, cancer, and osteoporosis [33]. At st
two major components to WHI, an observational study and four clinica
study included women aged 50-79 years in a prospective cohort study
and randomized women aged 50-79 years into one of four placebo-co
post-menopausal hormone therapies, dietary intervention, or calcium
supplementation). Bone mineral density was measured in participant
clinical centers (Pittsburgh, PA; Birmingham, AL; and Tucson/Phoeni

provided written informed consent. Institutional review board approva
participating institutions.

JoCoOA: The Johnston County Osteoarthritis Project is a com
study of white and African American men and women aged 45 years
in North Carolina [38]. The study was designed to determine racial diff
and incidence of risk factors associated with the occurrence and prog
osteoarthritis. Participants were recruited by probability sampling, wit
Americans. Hip and lumbar spine BMD were measured using the Ho
participants provided written informed consent. The study was appro
review boards at the University of North Carolina Schools of Medicine
Centers for Disease and Control Prevention.

BMDCS: The Bone Mineral Density in Childhood Study is a lo
normally developing boys and girls aged 5-20 years old who were rec
2007 from five clinical centers (Los Angeles, CA; Cincinnati, OH; Oma
and New York, NY) [39,40]. Hip and lumbar spine BMD were measured
measurements with either Hologic QDR4500A, QDR4500W, Delphi A
densitometers. Values from the baseline assessment were used. On
at each clinical center. All participants older than 18 years provided v

SNP in each locus (i.e., index SNP) and other haplotype tag SNPs to
in each locus based on the 1000 genomes reference panel (Phase 1)
low call rates (<0.9) and deviation from Hardy-Weinberg equilibrium (
phased haplotypes and imputed SNPs to the 1000 genomes referenc
SHAPEIT [41] and IMPUTE2 [42], respectively. All other cohorts were g
wide arrays and similarly imputed to the same 1000 genomes referen
JoCoOA were genotyped with the Illumina 1M-Duo platform, WHI was
Affymetrix Genome-Wide Human SNP Array 6.0 chip, HANDLS was g
Infinium II platform, and BMDCS was genotyped with the HumanOmn
SNPs with low call rates (<97% for Health ABC, <95% for HANDLS a
WHI, <98% for JoCoOA) and deviation from Hardy-Weinberg equilibri
Health ABC, $<10^{-5}$ for HANDLS, BMDCS, JoCoOA, $<10^{-4}$ for WHI and
prior to imputation.

Association Analyses and Meta-Analyses

We calculated differences in effect allele frequencies between
European and our observed African ancestry populations and compar
blocks between European and African ancestry populations by dividin

association with lumbar spine and femoral neck BMD in each cohort u
Models assumed an additive genetic model and were adjusted for sex
In addition, models were adjusted for study-specific genetic principal c
population stratification [43] and other study-specific covariates such as
different machines were used. Boundaries of the loci were defined by
$_{\text{ancestry (EA)}}\geq 0.8$) furthest up and downstream of the index SNP based on
European ancestry reference panel [44]. Each cohort performed single
autosomal chromosomes and X chromosome using the prepScores a
in the seqMeta R package. We then conducted an inverse-variance w
meta-analysis of lumbar spine and femoral neck BMD associations wi
summary statistics from each cohort. Only SNPs with good imputatio
common SNPs with minor allele frequencies ≥ 0.01 were included. A
value < 0.05 were considered nominally statistically significant. To ac
we used a Bonferroni corrected P-value threshold to account for testi
value=$0.05/56=8.93\times10^{-4}$) if SNPs were in high LD with the index SNP
based on the 1000 genomes African ancestry reference panel. If SNP
($r^2_{AA}<0.8$) with the index SNP, we used a locus-specific P-value thresh
number of SNPs tested in each locus (P-value=0.05/number of tested

To comprehensively assess the entire allele frequency spectru
we also conducted locus-based analyses of less common SNPs using
optimally combines the burden and SKAT tests used in rare variant a
included SNPs with good imputation quality (INFO $\geq$ 0.7) and less co
allele frequencies < 0.01. To account for multiple testing, we used a
value threshold to account for testing 56 independent loci (P-value=0.

Fixed and random effects meta-analyses were implemented w
Wide Association Meta-Analysis) software [46]. SKAT-O analyses wer
seqMeta R package (https://cran.r-project.org/web/packages/seqMeta

Results

We included a total of 4,967 individuals from six African ances
of lumbar spine and/or femoral neck BMD and genotyping data (Table
included only men and another cohort, WHI, included only women. Th
the other four cohorts ranged from 52% to 63%. Mean age ranged fr
weight ranged from 78-86 kg in the adult cohorts. The mean age was
weight was 44 kg in BMDCS, a pediatric cohort.

We tested 56 loci that were originally identified to be genome-

of high LD ($r^2_{AA} \geq 0.8$) around the index SNP. African ancestry LD bloc
to 526 kb (median=16 kb; interquartile range=3 kb to 55 kb) and prop
ancestry LD block sizes ranged from 0% to 775% (median=50%; inte
80%) (Supplementary Table 4). About a third of the loci tested had A
that were 70% smaller than the LD block size in European ancestry p

At least one SNP in high LD ($r^2_{AA} \geq 0.8$) with the index SNP or t
nominal statistical significance (P-value < 0.05) in fixed effects model
lumbar spine BMD in *C6orf97*, *GPATCH1*, *JAG1*, *KLHDC5/PTHLH*, *L*
MAPT, *RSPO3*, *SOX9*, *STARD3NL*, *WLS*, *WNT16*, and *ZBTB40* and
femoral neck BMD in *ARHGAP1*, *C6orf97*, *ERC/WNT5B*, *GPATCH1*,
SLC25A13, *SP7*, *WLS*, *WNT16*, and *ZBTB40* (Table 2). All of these
ERC1/WNT5B had shorter LD blocks in African ancestry populations
populations (Figure 2, Supplementary Figure 1, Supplementary Table
was low to moderate ($I^2<60$) for the majority of nominally significant lo
association with lumbar spine BMD and *ARHGAP1* and *GPATCH1* as
neck BMD (Table 2). In random effect models, only the association b
lumbar spine BMD met nominal significance (P-value < 0.05) but did
threshold after correction for multiple testing (P-value=8.93×10^{-4}) (Sup

removal of BMDCS from the meta-analysis, *C6orf97* remained signific
and *WNT16* remained significant for femoral neck BMD (Supplementa
multiple testing P-value threshold in both fixed and random effects mo
Table 8).

Other SNPs in the locus that were not in LD with the index BM
Consortium (r^2_{EA}<0.8) were tested and were required to meet locus sp
corrected P-value thresholds (Supplementary Table 1). SNPs in *DCD*
wide significance for lumbar spine BMD and SNPs in *C16orf38*, *DCD*
met locus-wide significance for femoral neck BMD (Table 3). Study h
moderate (I^2<60) for the majority of loci except *C16orf38* and *FAM9B*
neck BMD. In random effects models, these associations did not rem
wide threshold (Supplementary Table 9). Only two SNPs, rs978751 a
DCDC5 were previously assessed in GEFOSII (Supplementary Table
analyses, after removal of BMDCS from the meta-analysis, SNPs in *D*
wide significant for lumbar spine BMD and SNPs in *DCDC5* and *LRP5*
significant for femoral neck BMD (Supplementary Table 11).

In secondary gene-based analyses of rare variants (minor alle
associations with lumbar spine BMD in *AKAP11*, *SLC25A13*, *STARD*

tested 56 BMD loci originally identified in the largest GEFOS Consorti
found that only three loci, *C6orf97* (also known as *CCDC170*), *SLC25*
transferable to African ancestry populations. We also found significan
SMG6, and *LRP5* that were not tagged by European ancestry index S
there is between population heterogeneity in tag SNPs for BMD. Furt
evidence that rare genetic variants in *AKAP11*, *MBL2*, *MEPE*, *SLC25*
TNFRSF11A were associated with BMD, though these loci did not me
threshold for significance after correction for multiple testing. Our res
other studies that have shown low transferability of BMD loci between
backgrounds and underscore the need to consider differences in gene
populations when assessing targeted interventions and genetic risk p
Larger genetic studies of BMD in African ancestry populations compa
European ancestry populations will be needed to overcome power lim
study, and to identify other loci that are transferable between populati
population-specific variants.

While only three loci, *C6orf97*, *SLC25A13*, and *WNT16*, reach
transferability, we found 17 other loci that reached a less stringent thr
which all except two loci had effects in the same direction as that repo

our finding that femoral neck BMD had more associations than lumba
direction of effect as European ancestry populations. Our study was
associations at genome-wide significance thresholds for all previously
suggests that with a larger sample size, more loci transferable betwee
ancestry may be identified.

Our findings are consistent with other genetic studies of non-E
Asian populations, at least 16 known loci discovered in European anc
associated with BMD, including *AKAP11*, *C6orf97*, *C17orf53*, *CTNNB*
MEPE, *SLC25A13*, *SPTBN1*, *STARD3NL*, *SOX6*, *TNFRSF11A*, *TNFI*
ZBTB40 [25,26,48]. We identified 20 loci associated with BMD, of which
C6orf97, *SLC25A13*, *STARD3NL*, *WLS*, and *ZBTB40,* were also asso
Asian populations. The three loci that met our criteria for transferabili
and *WNT16*, were also found to be associated with BMD at genome w
ethnic genome-wide association study, though this study only include
African American women [49]. Another study showed that SNPs in *WN*
associated with BMD in premenopausal women, which were replicate
that included a small sample of African American women [29]. On the
has been associated with fracture risk in European populations [19], bu

cortical thickness and increased cortical porosity but does not affect t
Similarly, in humans, genetic variants in *WNT16* are associated with c
Overexpression of *WNT16* in mice increases bone mineral density bu
bone loss [52-54]. The function of *C6orf97* (also referred as *CCDC170*)
implicated in studies of breast cancer. *C6orf97* is located near the ge
receptor 1. Estrogen plays an important role in bone homeostasis an
attenuating bone resorption through estrogen receptor α in osteoclast
WNT16 may play a critical role in acquisition of peak cortical bone ma
at the early stages of puberty, African American children have greater
density, mass and size compared to those of European ancestry [56,57
the possibility that factors related to acquisition and maintenance of c
particularly relevant to African ancestry populations.

We acknowledge that there are limitations to our study. The s
designed to determine genome-wide associations, as the largest cont
limited genotyping of 56 loci selected based on their genome-wide sig
BMD in the previously published, largest GWAS meta-analysis of fem
spine BMD to date [19]. Our original intent was not to discover new loc
approach, but rather to determine whether already-verified European

ancestry populations since these variants may not necessarily confer
which could be attributed to differences in allele frequencies between
ancestry populations and allelic heterogeneity.

Additionally, despite assembling the largest meta-analysis of r
with African ancestry, we still had limited power to detect all previousl
loci, let alone an agnostic GWAS. Due to limited sample size, the inte
for new discovery, but rather to determine racial differences in variant
already been identified. Large GWAS for new discovery in multiple an
direction for the bone field. Interpretation of our findings are also com
tagging SNPs that may not necessarily capture all variation in a locus
causal variants. However, most variants identified by GWAS are com
ancient in origin and shared by different populations [59]. Assuming th
sufficiently tagged by one or more SNPs in the LD block, we were abl
association for several loci since the majority of LD blocks were short
European ancestry populations. Most loci had associations in the sam
previously reported associations and are likely transferable to African
though there may be effect size heterogeneity that impacted our abilit
effects. We cannot exclude the possibility that there may be populatio

adolescence and there is high familial resemblance for most bone trai
Despite these limitations, our study provides the first insights into the
underlying BMD in African ancestry populations. Additionally, the limi
underscores a well-appreciated limitation of the field of human genetic
of populations other than those of European ancestry continue to be l
greater expansion of the field to include large numbers of other ethnic

In summary, we conducted the largest African-ancestry meta-
independent samples, we identified three BMD loci, *C6orf97*, *SLC25A*
transferable to African ancestry populations. Larger genome wide ass
whole genome sequencing studies in African ancestry populations wil
other transferable BMD loci and population-specific variants that may
targeted interventions and genetic risk prediction for osteoporosis in d

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BSZ, SFAG, JMJ, RDJ, MKE, TBH, JMZ, and DPK. Data analysis: M
SKH, LA, AC. Data interpretation: all. Drafting manuscript: MSY. Re
all. Approving final version of manuscript: all. MSY takes responsibili

References

1. Wright NC, Looker AC, Saag KG, Curtis JR, Delzell ES, Rand prevalence of osteoporosis and low bone mass in the United S mineral density at the femoral neck or lumbar spine. J Bone M 2014;29(11):2520-6. Epub 2014/04/29.
2. Kanis JA. Diagnosis of osteoporosis and assessment of fractu 2002;359(9321):1929-36. Epub 2002/06/12.
3. Johnell O, Kanis JA, Oden A, Johansson H, De Laet C, Delma of BMD for hip and other fractures. J Bone Miner Res. Jul 200 2005/06/09.
4. Cummings SR, Melton LJ. Epidemiology and outcomes of ost Lancet. May 18 2002;359(9319):1761-7. Epub 2002/06/07.
5. Cauley JA. Defining ethnic and racial differences in osteoporo Clin Orthop Relat Res. Jul 2011;469(7):1891-9. Epub 2011/03
6. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, and economic burden of osteoporosis-related fractures in the J Bone Miner Res. Mar 2007;22(3):465-75. Epub 2006/12/06.
7. Cauley JA. Public health impact of osteoporosis. J Gerontol A 2013;68(10):1243-51. Epub 2013/08/02.
8. Ferrari S, Rizzoli R, Slosman D, Bonjour JP. Familial resembla mass is expressed before puberty. J Clin Endocrinol Metab. F Epub 1998/02/19.
9. Ralston SH, Uitterlinden AG. Genetics of osteoporosis. Endoc 62. Epub 2010/05/01.
10. Slemenda CW, Turner CH, Peacock M, Christian JC, Sorbel J genetics of proximal femur geometry, distribution of bone mas density. Osteoporos Int. 1996;6(2):178-82. Epub 1996/01/01.
11. Smith DM, Nance WE, Kang KW, Christian JC, Johnston CC, determining bone mass. J Clin Invest. Nov 1973;52(11):2800-
12. Gueguen R, Jouanny P, Guillemin F, Kuntz C, Pourel J, Siest and variance components analysis of bone mineral density in Miner Res. Dec 1995;10(12):2017-22. Epub 1995/12/01.
13. Krall EA, Dawson-Hughes B. Heritable and life-style determina density. J Bone Miner Res. Jan 1993;8(1):1-9. Epub 1993/01/
14. Slemenda CW, Christian JC, Williams CJ, Norton JA, Johnsto

19. Estrada K, Styrkarsdottir U, Evangelou E, Hsu YH, Duncan EL
Genome-wide meta-analysis identifies 56 bone mineral densit
associated with risk of fracture. Nat Genet. May 2012;44(5):49
20. Morris JA, Kemp JP, Youlten SE, Laurent L, Logan JG, Chai R
genetic influences on osteoporosis in humans and mice. Nat G
2019;51(2):258-66. Epub 2019/01/02.
21. Kim SK. Identification of 613 new loci associated with heel bon
polygenic risk score for bone mineral density, osteoporosis an
2018;13(7):e0200785. Epub 2018/07/27.
22. Medina-Gomez C, Chesi A, Heppe DH, Zemel BS, Yin JL, Kal
Contribute to Ethnic and Developmental Differences in Skeleta
Populations: Assessment of Evolutionary Selection Pressures
2015;32(11):2961-72. Epub 2015/08/01.
23. Adeyemo A, Rotimi C. Genetic variants associated with compl
wide variation across multiple populations. Public Health Geno
Epub 2009/05/15.
24. Marigorta UM, Navarro A. High trans-ethnic replicability of GW
common causal variants. PLoS Genet. Jun 2013;9(6):e100356
25. Styrkarsdottir U, Halldorsson BV, Gudbjartsson DF, Tang NL,
European bone mineral density loci are also associated with B
populations. PLoS One. Oct 7 2010;5(10):e13217. Epub 2010
26. Liu JM, Zhang MJ, Zhao L, Cui B, Li ZB, Zhao HY, et al. Analy
osteoporosis susceptibility genes in Han Chinese women. J C
2010;95(9):E112-20. Epub 2010/06/18.
27. Taylor KC, Evans DS, Edwards DRV, Edwards TL, Sofer T, Li
association study meta-analysis of clinical fracture in 10,012 A
Bone Rep. Dec 2016;5:233-42. Epub 2017/06/06.
28. Ntzani EE, Liberopoulos G, Manolio TA, Ioannidis JP. Consist
associations across major ancestral groups. Hum Genet. Jul 2
2011/12/21.
29. Koller DL, Ichikawa S, Lai D, Padgett LR, Doheny KF, Pugh E
association study of bone mineral density in premenopausal E
and replication in African-American women. J Clin Endocrinol
2010;95(4):1802-9. Epub 2010/02/19.
30. Hill DD, Cauley JA, Sheu Y, Bunker CH, Patrick AL, Baker CE
mineral density in men of African ancestry: the Tobago bone h

35. LaCroix AZ, Beck TJ, Cauley JA, Lewis CE, Bassford T, Jacks geometry and incidence of hip fracture in postmenopausal wo conventional bone mineral density? Osteoporos Int. Jun 2010; 2009/09/17.
36. Chen Z, Maricic M, Pettinger M, Ritenbaugh C, Lopez AM, Ba Osteoporosis and rate of bone loss among postmenopausal s Cancer. Oct 1 2005;104(7):1520-30. Epub 2005/08/20.
37. Chen Z, Arendell L, Aickin M, Cauley J, Lewis CE, Chlebowsk predicts breast cancer risk independently of Gail score: results Initiative. Cancer. Sep 1 2008;113(5):907-15. Epub 2008/07/3
38. Jordan JM, Helmick CG, Renner JB, Luta G, Dragomir AD, W of knee symptoms and radiographic and symptomatic knee os Americans and Caucasians: the Johnston County Osteoarthrit rheumatology. Jan 2007;34(1):172-80.
39. Kalkwarf HJ, Zemel BS, Gilsanz V, Lappe JM, Horlick M, Ober mineral density in childhood study: bone mineral content and d sex, and race. J Clin Endocrinol Metab. Jun 2007;92(6):2087-
40. Zemel BS, Kalkwarf HJ, Gilsanz V, Lappe JM, Oberfield S, Sh reference curves for bone mineral content and areal bone min age and sex for black and non-black children: results of the bo childhood study. J Clin Endocrinol Metab. Oct 2011;96(10):31
41. Delaneau O, Marchini J, Zagury JF. A linear complexity phasi of genomes. Nature methods. Feb 2012;9(2):179-81.
42. Howie BN, Donnelly P, Marchini J. A flexible and accurate ge for the next generation of genome-wide association studies. P 2009;5(6):e1000529.
43. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick N components analysis corrects for stratification in genome-wide Genet. Aug 2006;38(8):904-9. Epub 2006/07/25.
44. Genomes Project C, Auton A, Brooks LD, Durbin RM, Garriso global reference for human genetic variation. Nature. Oct 1 20 2015/10/04.
45. Lee S, Emond MJ, Bamshad MJ, Barnes KC, Rieder MJ, Nick unified approach for rare-variant association testing with appli case-control whole-exome sequencing studies. Am J Hum Ge 2012;91(2):224-37.

51. Zheng HF, Tobias JH, Duncan E, Evans DM, Eriksson J, Pate
influences bone mineral density, cortical bone thickness, bone
osteoporotic fracture risk. PLoS Genet. Jul 2012;8(7):e100274
52. Alam I, Alkhouli M, Gerard-O'Riley RL, Wright WB, Acton D, G
Specific Overexpression of Human WNT16 Increases Both Co
Bone Mass and Structure in Mice. Endocrinology. Feb 2016;15
2015/11/20.
53. Ohlsson C, Nilsson KH, Henning P, Wu J, Gustafsson KL, Pou
overexpression partly protects against glucocorticoid-induced
Endocrinol Metab. Jun 1 2018;314(6):E597-E604. Epub 2018/
54. Alam I, Oakes DK, Reilly AM, Billingsley C, Sbeta S, Gerard-O
Overexpression of WNT16 Does Not Prevent Cortical Bone Lo
Treatment in Mice. JBMR Plus. Apr 2019;3(4):e10084. Epub 2
55. Nakamura T, Imai Y, Matsumoto T, Sato S, Takeuchi K, Igaras
prevents bone loss via estrogen receptor alpha and induction
osteoclasts. Cell. Sep 7 2007;130(5):811-23. Epub 2007/09/07
56. Leonard MB, Elmi A, Mostoufi-Moab S, Shults J, Burnham JM
sex, race, and puberty on cortical bone and the functional mus
adolescents, and young adults. J Clin Endocrinol Metab. Apr 2
2010/02/17.
57. Warden SJ, Hill KM, Ferira AJ, Laing EM, Martin BR, Hausma
differences in cortical bone and their relationship to biochemic
White children in the early stages of puberty. Osteoporos Int. J
Epub 2012/10/25.
58. Popejoy AB, Fullerton SM. Genomics is failing on diversity. Na
2016;538(7624):161-4. Epub 2016/10/14.
59. Fu J, Festen EA, Wijmenga C. Multi-ethnic studies in complex
Oct 15 2011;20(R2):R206-13. Epub 2011/09/06.
60. Mitchell JA, Chesi A, Elci O, McCormack SE, Roy SM, Kalkwa
Scores Implicated in Adult Bone Fragility Associate With Pedia
Miner Res. Apr 2016;31(4):789-95. Epub 2015/11/18.

Table 1. African-ancestry cohort characteristics

	Tobago	HABC	HANDLS	WHI
N	1,414	1,093	908	797
% Female	0	57.4	55.2	100
Age in years (SD)	58.8 (10.4)	73.4 (2.9)	48.7 (8.9)	68 (7.1
Weight in kg (SD)	84.5 (15.9)	77.8 (19.0)	83.6 (19.5)	82.8 (18

HABC=Health, Aging, and Body Composition; HANDLS=Healthy Aging in
across the Life Span Study; WHI=Women's Health Initiative; JoCoOA=Jo
Project; BMDCS=Bone Mineral Density in Childhood Study

Table 2. Lead SNP associations in BMD loci (P-value < 0.05 in fixed effects models)

							Lumbar Spine	
Locus	Lead SNP	Closest Gene(s)	A1	A2	Freq1 in EA	Freq1 in AFR	Beta	P-value
1p31.3	rs36100617	*WLS*	g	-	0.63	0.76	**0.01**	**2.74×10^{-2}**
1p36.12	rs10493013	*ZBTB40*	c	t	0.17	0.28	**0.01**	**3.15×10^{-2}**
3q25.31	rs344081	*LEKR1* [a,c]	t	c	0.88	0.47	**0.01**	**1.48×10^{-2}**
4p16.3	rs56079856	*IDUA*	t	g	0.17	0.11	**-0.01**	**2.46×10^{-1}**
6q22.32	rs13204965	*RSPO3* [a]	a	c	0.76	0.95	-0.02	7.49×10^{-3}
6q25.1	rs4869745	*C6orf97* [b]	t	c	0.29	0.69	**-0.01**	**8.87×10^{-4}**
7p14.1	rs6959212	*STARD3NL* [a]	t	c	0.36	0.35	**-0.01**	**2.23×10^{-3}**
7q21.3	rs4342521	*SLC25A13*	g	t	0.64	0.81	**0.01**	**1.16×10^{-1}**
7q31.31	rs10242100	*WNT16* [b]	a	g	0.74	0.63	**-0.02**	**1.88×10^{-6}**
11p11.2	rs10769205	*ARHGAP1* [d]	g	a	0.29	0.82	**0.01**	**2.56×10^{-1}**
11p14.1	rs11030048	*LIN7C*	t	c	0.48	0.86	0.01	2.23×10^{-2}
12p11.22	rs7953528	*KLHDC5/PTHLH* [a, c]	a	t	0.16	0.05	**-0.02**	**3.39×10^{-2}**
12p13.33	rs35223785	*ERC1/WNT5B* [b]	a	g	0.73	0.81	**-0.01**	**5.21×10^{-2}**
12q13.13	rs10783573	*SP7* [b]	a	g	0.67	0.41	**-0.01**	**5.28×10^{-2}**
14q32.32	rs7145113	*MARK3* [b]	g	a	0.36	0.17	**-0.01**	**2.03×10^{-2}**
16p13.11	rs4985155	*NTAN1* [a]	a	g	0.67	0.66	**-0.00**	**1.76×10^{-1}**

Table 3. Locus-wide significant SNPs not in LD with the GEFOS Consortium index SNP in fixed eff

								Lumba	
Locus	SNP	Closest Gene(s)	r^2 in EA [a]	r^2 in AA [a]	A1	A2	Freq1	Beta	P
11p14.1	rs7950105	*DCDC5*	0.62	0.14	t	c	0.81	0.02	5.
11p14.1	rs2145795	*DCDC5*	0.60	0.01	a	g	0.67	0.01	8.
11p14.1	rs650489	*DCDC5*	0.61	0.13	a	g	0.18	-0.02	1.
11p14.1	rs36122686	*DCDC5*	0.63	0.15	a	at	0.82	0.02	1.
11p14.1	rs67243215	*DCDC5*	0.63	0.15	c	t	0.82	0.02	2.
11p14.1	rs978751	*DCDC5*	0.62	0.10	g	a	0.55	0.01	3.
17p13.3	rs79682102	*SMG6*	0.00	0.00	g	a	0.96	-0.04	2.
16p13.3	rs66725354	*C16orf38* [b]	0.36	0.02	g	a	0.88	0.01	1.
Xp22.31	rs5934498	*FAM9B*	0.13	0.20	t	c	0.37	0.02	7.
Xp22.31	rs12863157	*FAM9B* [b]	0.15	0.19	g	t	0.36	0.02	7.
Xp22.31	rs1919627	*FAM9B* [b]	0.13	0.24	a	g	0.36	0.02	1.
Xp22.31	rs5978281	*FAM9B*	0.13	0.21	a	g	0.39	0.01	3.
11q13.2	rs111507948	*LRP5*	0.03	0.00	c	g	0.88	0.01	5.
11q13.2	rs12793818	*LRP5*	0.03	0.00	c	t	0.88	0.01	5.
11q13.2	rs12793822	*LRP5*	0.03	0.00	c	t	0.88	0.01	5.

Table 4. SKAT-O rare variant associations in BMD loci (P-values < 0.

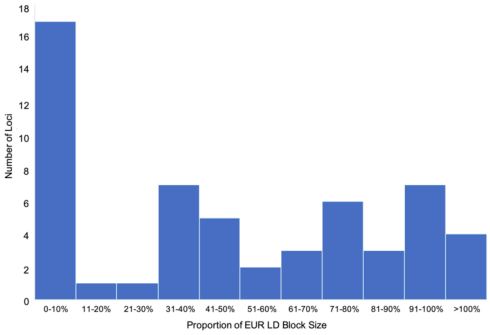
	Gene	P-value	Number of SNPs*
Lumbar spine BMD	*AKAP11*	2.32×10^{-2}	2,228
	SLC25A13	3.03×10^{-2}	1,396
	STARD3NL	3.35×10^{-2}	1,684
	TNFRSF11A	4.71×10^{-2}	1,018
Femoral neck BMD	*MBL2*	4.09×10^{-2}	506
	MEPE	3.15×10^{-2}	1,897
	TNFRSF11A	3.18×10^{-3}	1,018

*SNPs included have minor allele frequencies<0.01

Figure Legends

Figure 1. Distribution of African ancestry linkage disequilibrium block s
We identified linkage disequilibrium (LD) blocks around index BMD SI
and European ancestry ($r^2_{EA} \geq 0.8$) populations. A proportion was deriv
ancestry LD block size by the European ancestry LD block size. A sm
that the African ancestry LD block is much smaller than the LD block i
populations, while a larger proportion indicates that the African ances
size to the European ancestry block size.

Figure 2. African-ancestry meta-analysis narrows *WNT16* locus from
Linkage disequilibrium (LD) blocks represent correlations between SN
the red intensity represents strength of the r^2 value calculated from 10
A. SNPs in high LD ($r^2_{EA} \geq 0.8$) with the *WNT16* index SNP in Europea
values in African ancestry populations for the same set of SNPs prese
asterisks (*) represent the lead SNP identified in the African ancestry
hyphens (-) represent the index SNP identified by the GEFOS Consor
as the lead SNP; a black box is drawn around SNPs in high LD with t



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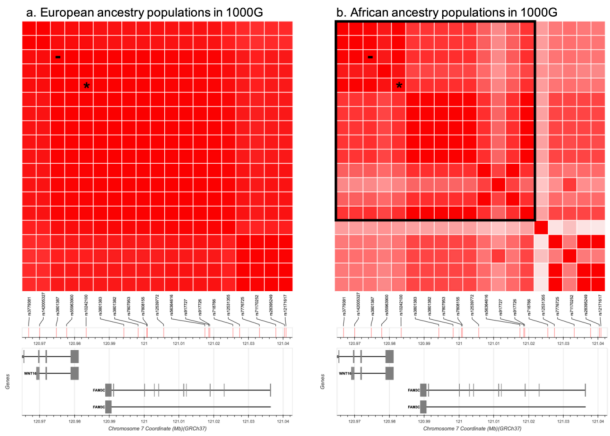

JBMR_4220_Fig2.tif