Bone Reports 5 (2016) 233–242

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr

A genome-wide association study meta-analysis of clinical fracture in 10,012 African American women

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ARTICLE INFO

Article history:
Received 18 August 2016
Accepted 25 August 2016
Available online 27 August 2016

Keywords:
Fracture
Osteoporosis
Genome-wide association study (GWAS)
Meta-analysis

ABSTRACT

Background: Osteoporosis is a major public health problem associated with excess disability and mortality. It is estimated that 50–70% of the variation in osteoporotic fracture risk is attributable to genetic factors. The purpose of this hypothesis-generating study was to identify possible genetic determinants of fracture among African American (AA) women in a GWAS meta-analysis.

Methods: Data on clinical fractures (all fractures except fingers, toes, face, skull or sternum) were analyzed among AA female participants in the Women's Health Initiative (WHI) (N = 8155), Cardiovascular Health Study (CHS) (N = 504), BioVU (N = 704), Health ABC (N = 651), and the Johnston County Osteoarthritis Project (JoCoOA) (N = 291). Affymetrix (WHI) and Illumina (Health ABC, JoCoOA, BioVU, CHS) GWAS panels were used for genotyping, and a 1:1 ratio of YRI:CEU HapMap haplotypes was used as an imputation reference panel. We used Cox proportional hazard models or logistic regression to evaluate the association of ~2.5 million SNPs

Abbreviations: AA, African American; ASW, African ancestry individuals from Southwest USA; BMD, bone mineral density; BMI, body mass index; BMP, bone morphogenetic protein; CES-D, Center for Epidemiological Studies-Depression scale; CEU, CEPH-Utah (Utah residents with ancestors from central and western Europe); CHS, Cardiovascular Health Study; DNA, deoxyribonucleic acid; EAF, effect allele frequency; GEFOS, Genetic Factors of Osteoporosis; GPGE, genetically predicted gene expression; GTEx Project, Genotype-Tissue Expression project; GWAS, genome-wide association study; JoCoOA, Johnston County Osteoarthritis Project; MAC, minor allele count; MAF, minor allele frequency; OF, osteoporotic fracture; RNA, ribonucleic acid; SD, standard deviation; SHARe, SNP Health Association Resource; SNP, single nucleotide polymorphism; WHI, Women's Health Initiative; YRI, Yoruban (Nigeria).

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http://dx.doi.org/10.1016/j.bonr.2016.08.005

African American
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with fracture risk, adjusting for ancestry, age, and geographic region where applicable. We conducted a fixed-effects, inverse variance-weighted meta-analysis. Genome-wide significance was set at $P < 5 \times 10^{-8}$.
Results: One SNP, rs12775980 in an intron of *SVIL* on chromosome 10p11.2, reached genome-wide significance ($P = 4.0 \times 10^{-8}$). Although this SNP has a low minor allele frequency (0.03), there was no evidence for heterogeneity of effects across the studies ($I^2 = 0$). This locus was not reported in any previous osteoporosis-related GWA studies. We also interrogated previously reported GWA-significant loci associated with fracture or bone mineral density in our data. One locus (*SMOC1*) generalized, but overall there was not substantial evidence of generalization. Possible reasons for the lack of generalization are discussed.
Conclusion: This GWAS meta-analysis of fractures in African American women identified a potentially novel locus in the supervillin gene, which encodes a platelet-associated factor and was previously associated with platelet thrombus formation in African Americans. If validated in other populations of African descent, these findings suggest potential new mechanisms involved in fracture that may be particularly important among African Americans.

1. Introduction

Osteoporosis is a major public health problem that over a lifetime results in fractures in 40% of aging women (Melton et al., 1992). Although the lifetime risk of fractures is slightly lower in nonwhite women, the absolute risk is still substantial and may be rising (Farmer et al., 1984; Baron et al., 1994; Baron et al., 1996). By 2025, 21% of all fractures in the United States will occur in nonwhite women (Burge et al., 2007). Importantly, the consequences of fractures may be greater among nonwhite women. For example, African-American women who suffer a hip fracture have longer hospitalization stays and are more likely to be nonambulatory compared with European-American women (Furstenberg and Mezey, 1987). Furthermore, mortality after a hip fracture is higher among African-American than European-American women, pointing to disparities in access to health care or differences in comorbidities (Jacobsen et al., 1992). The Surgeon General's Report on Bone Health and Osteoporosis noted the lack of information on ethnic and racial minorities as a priority (United States Public Health Service Office of the Surgeon General, 2004).

Osteoporosis has a strong genetic component, with 25–85% of the variation in osteoporosis-related traits (such as bone mineral density) being attributable to genetic factors (Ralston, 2002; Ferrari, 2008). The heritability of osteoporotic fracture (OF) has been estimated to be 0.5–0.7 (Deng et al., 2002; Michaelsson et al., 2005). Genetic interactions with both ethnicity and sex may be an important source of heterogeneity (Johnson et al., 2009). To date, genome-wide association scans have focused on bone mineral density (BMD) and osteoporosis in populations of primarily European or Asian descent. The largest relevant genome-wide association study (GWAS) to date is a meta-analysis conducted by the Genetic Factors of Osteoporosis (GEFOS) consortium, which included individuals of European and East Asian descent, and identified 56 BMD-associated loci (Estrada et al., 2012). Fourteen of these loci were also associated with fracture (any type) at a Bonferroni-corrected level of significance. Richards et al. identified an additional gene that increased risk of fracture independent of bone mineral density in a European sample (Richards et al., 2008). Two other GWAS (Xiong et al., 2009; Guo et al., 2010a) and two genome-wide copy number variation studies (Oei et al., 2014; Yang et al., 2008) in have identified a few other putative fracture loci in Chinese and European samples. In one published GWAS that used radiographic vertebral fractures as the primary outcome of interest, one genome-wide significant locus was identified in the discovery sample, but did not replicate (Oei et al., 2013).

Although some progress has been made, genes identified to this point only explain a small portion of the total heritability of osteoporosis-related traits, and it remains to be determined how these genes and others affect risk of fracture in populations of African ancestry. Moreover, it has been argued that more genome-wide association studies should focus on fracture (the most severe osteoporosis-related-phenotype) rather than BMD or other intermediate endpoints (Liu et al., 2014).

Here, we meta-analyze GWAS data from 5 studies examining clinical fracture in African-American women in an effort to identify potentially novel genome-wide significant loci. Because there is not a replication sample within this study, the results are viewed as hypothesis-generating. We also examine the generalizability of previously discovered osteoporosis-related loci to this population of African-American women.

2. Methods

2.1. Subjects

Subjects for this study were African-American women from five studies with information on clinical fracture: the Women's Health Initiative (WHI) (N = 8155) (Design of the Women's Health Initiative clinical trial and observational study, 1998); the Cardiovascular Health Study (CHS) (N = 504) (Fried et al., 1991); BioVU (N = 704) (Roden et al., 2008); the Health ABC study (N = 651) (Newman et al., 2003); and the Johnston County Osteoarthritis Project (JoCoOA, N = 291) (Jordan et al., 2007). Women included in this study were over 50 years of age (for WHI, CHS, BioVU, and Health ABC), or over 45 (for JoCoOA). Women from the WHI were part of the WHI-SHARe (SNP Health Association Resource) project, which included randomly selected African-American and Hispanic-American women who consented to genetic research from both the observational study and the clinical trial arms of the WHI. See Supplementary materials (Cohort Descriptions) for additional descriptive information regarding each study. All studies were cohort studies except BioVU, which defined cases and controls for fracture by linking a DNA repository to electronic medical records.

2.2. Fracture phenotype

All studies measured fractures, excluding fingers, toes, face, skull, or sternum. Radiographic vertebral fractures were not included. Fractures were incident after age 45 (for JoCoOA) or age 50 (WHI, CHS, BioVU, and Health ABC). Fractures included in this analysis were adjudicated in WHI, BioVU, and Health ABC, and self-reported in CHS and JoCoOA. For WHI, hip fractures were centrally adjudicated. All other fractures were centrally adjudicated for women in the clinical trial and for women in the observational study enrolled at three BMD sites (Pittsburgh, Birmingham, Tucson/Phoenix). For Health ABC, Fractures were adjudicated at the clinical centers based on radiograph confirmation. For BioVU, fracture phenotype was determined from medical records in the BioVU database. For the other two studies (JoCoOA and CHS), self-reported fractures were used. However, good reliability has been found between self-reported fracture and adjudicated fracture (Chen et al., 2004). More information about the ascertainment of fracture in