Association of DXA-derived Bone Mineral Density and Fat Mass With African Ancestry

Heather M. Ochs-Balcom, Leah Preus, Jean Wactawski-Wende, Jing Nie, Nicholas A. Johnson, Fouad Zakharia, Hua Tang, Chris Carlson, Cara Carty, Zhao Chen, Thomas Hoffman, Carolyn M. Hutter, Rebecca D. Jackson, Robert C. Kaplan, Li Li, Song Liu, Marian L. Neuhouser, Ulrike Peters, John Robbins, Michael F. Seldin, Timothy A. Thornton, Cheryl L. Thompson, Charles Kooperberg, and Lara E. Sucheston*

Context: Both genes and environment have been implicated in determining the complex body composition phenotypes in individuals of European ancestry; however, few studies have been conducted in other race/ethnic groups.

Objective: We conducted a genome-wide admixture mapping study in an attempt to localize novel genomic regions associated with genetic ancestry.

Setting/Participants: We selected a sample of 842 African-American women from the Women's Health Initiative single nucleotide polymorphism (SNP) Health Association Resource for whom several dual-energy X-ray absorptiometry (DXA)-derived bone mineral density (BMD) and fat mass phenotypes were available.

Methods: We derived both global and local ancestry estimates for each individual from Affymetrix 6.0 data and analyzed the correlation of DXA phenotypes with global African ancestry. For each phenotype, we examined the association of local genetic ancestry (number of African ancestral alleles at each marker) and each DXA phenotype at 570 282 markers across the genome in additive models with adjustment for important covariates.

Results: We identified statistically significant correlations of whole-body fat mass, trunk fat mass, and all 6 measures of BMD with a proportion of African ancestry. Genome-wide (admixture) significance for femoral neck BMD was achieved across 2 regions ~3.7 MB and 0.3 MB on chromosome 19q13; similarly, total hip and intertrochanter BMD were associated with local ancestry in these regions. Trunk fat was the most significant fat mass phenotype showing strong, but not genomewide significant associations on chromosome Xp22.

Conclusions: Our results suggest that genomic regions in postmenopausal African-American women contribute to variance in BMD and fat mass existence and warrant further study. **(*J Clin Endocrinol Metab* 98: E713–E717, 2013)**

Admixture mapping allows for the identification of chromosomal regions that influence complex phenotypes with variable incidence in different racial/ethnic groups (1). In the United States, African-Americans (AAs) are particularly suited for admixture mapping because they comprise a diverse population who have admixed ancestry to varying degrees with other populations, including European-Americans.

Body composition phenotypes are particularly appealing for admixture mapping, given the well-established differences in bone mineral density (BMD) (2) and fat mass phenotypes (2) between AAs and European-Americans. This disparity coupled with literature showing correlations between global ancestry and body composition phenotypes (3, 4) lends support for a search for novel chro-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received November 15, 2012. Accepted January 28, 2013.
First Published Online February 22, 2013

* Author affiliations are shown at the bottom of the next page.

Abbreviations: AA, African-American; BMD, bone mineral density; CEU, Northern and Western European ancestry; DXA, dual-energy X-ray absorptiometry; GWAS, genome-wide association study; MAF, minor allele frequency; MET, metabolic equivalents; SHARe, SNP Health Association Resource; SNP, single nucleotide polymorphism; WHI, Women's Health Initiative; YRI, Yoruban in Ibadan, Nigeria.

mosomal regions/genes using an admixture mapping approach.

We hypothesized that BMD and fat mass phenotypes are associated with both global and local African ancestry proportions in AA women. To test these hypotheses, we performed an admixture mapping study in the Women's Health Initiative (WHI) single nucleotide polymorphism (SNP) Health Association Resource (SHARe).

Materials and Methods

WHI

The WHI SHARe has extensive phenotypic and genome-wide data on 8515 self-identifying AA postmenopausal women between 50 and 79 years of age at baseline randomly selected from 12 151 AA participants. Study protocols and consent forms were approved by the Institutional Review Boards at all participating institutions.

Genotyping

Genotyping was performed at Affymetrix Inc (Affymetrix, Santa Clara, California; www.affymetrix.com) using the Genome-Wide Human SNP Array 6.0 on DNA extracted from blood at the Fred Hutchinson Cancer Research Center. We removed SNPs that failed genotyping (<0.001%), call rates <95%, concordance rates <98%, and with minor allele frequency (MAF) <1%, leaving 855 034 SNPs for analysis.

Global ancestry estimation

Frappe (5) estimates of each individual's global ancestry were generated using 656 852 autosomal markers on 475 samples from the Human Genome Diversity project (6) representing African (Yoruban, YRI), Northern and Western European (CEU), East Asian (Han Chinese and Japanese from Tokyo), and Native American ancestry.

Local ancestry estimation

For each individual, we estimated locus-specific ancestry at 570 282 SNPs on the autosomal chromosomes applying an extension of the model in SABER software (7, 8); we used phased haplotype data from the HapMap3 CEU and YRI individuals as reference panels. We statistically replicated SABER estimates using approaches implemented in HAPMIX (9) and LAMP (10). For the X chromosome, we derived HAPMIX-only estimates and considered LAMP estimates for statistical replication.

Imputation

Imputation was performed using MACH (11) with reference panels from HapMap 2, release 22. The starting proportion of CEU and YRI assumed was 20% and 80%, respectively. For 2 190 779 SNPs we obtained imputations with MAF >1% and estimated $r^2 > 0.3$. Imputation quality was measured on 2% of genotyped SNPs (selected randomly) using allelic discordance and r^2, which varied between 0.9%–2.0% and 0.90–0.95, respectively.

Dual-energy X-ray absorptiometry (DXA) measures

Whole-body DXA scans were performed using the Hologic QDR scanners (QDR 2000, 2000+, or 4500W; Hologic, Waltham, Massachusetts). Scans were rigorously monitored at 3 participating sites for quality.

BMD phenotypes include total body, total hip, trochanter, femoral neck, intertrochanter, and L2-L4 spine (g/cm^2). Fat mass phenotypes include whole-body, trunk fat mass (measured in grams), whole-body percentage fat mass, and ratio of trunk-to-whole-body fat mass.

The DXA admixture study sample

In 842 of 8515 AA women, a DXA scan was performed at WHI baseline. Women were then excluded on the basis of estimated relatedness (n = 12) and <15% estimated AA ancestry (n = 12). For analyses of whole-body BMD we excluded those with hip or other replacements (n = 20) and ever broken spine or hip (n = 8), yielding n = 774. Due to missingness, femoral neck BMD sample size was 802 and L2-L4 spine sample included 782 women. The sample size for all fat mass analyses was 802.

Descriptive analyses

We estimated numerous descriptive statistics for relevant variables and Pearson correlation coefficients between all DXA phenotypes and global African ancestry adjusted for age and geographic region. We selected WHI covariates for final models using univariate regression models and *t* tests. Covariates in final fat mass models include age at menopause, metabolic equivalents (MET)-hours per week of exercise from walking, hormone therapy use, ever smoker, height, weight, study site, and global ancestry. BMD models include age, study site, age at menopause, lifetime hormone therapy duration, log-transformed body mass index, height, MET-hours per week due to moderate exercise and global ancestry. Models assessing L2-L4 spine BMD variation also included fracture at age 55 or older.

Admixture mapping analyses

We regressed each DXA phenotype (separately) on locus-specific ancestry estimates adjusting for covariates described above. We define statistically significant admixture associations according to the literature ($P < 1.5 \times 10^{-5}$) (12).

Department of Social and Preventive Medicine (H.M.O.-B., L.P., J.W.-W., J.N.), University at Buffalo, Buffalo, New York 14214-8001; Department of Cancer Prevention and Control (L.P., L.E.S.), Roswell Park Cancer Institute, Buffalo, New York 14263; Department of Statistics (N.A.J.), Stanford University, Stanford, California 94305; Department of Genetics (F.Z., H.T.), Stanford University, Stanford, California 94305; Public Health Sciences Division (C.Carl., C.Cart., C.M.H., M.L.N., U.P., C.K.), Fred Hutchinson Cancer Research Center, Seattle, Washington 98109; College of Public Health (Z.C.), University of Arizona, Tucson, Arizona 85724; Department of Epidemiology and Biostatistics (T.H.), University of California, San Francisco, San Francisco, California 94107; Institute for Human Genetics (T.H.), University of California, San Francisco, San Francisco, California 94143; Division of Endocrinology, Diabetes, and Metabolism (R.D.J.), Ohio State University, Columbus, Ohio 43210; Department of Epidemiology and Population Health (R.C.K.), Albert Einstein College of Medicine, Bronx, New York 10461; Case Comprehensive Cancer Center (L.L., C.L.T.), University Hospitals Case Medical Center, Case Western Reserve University, Cleveland, Ohio 44106; Department of Biostatistics (S.L.), University at Buffalo, Buffalo, New York 14214; Department of Epidemiology (U.P.), University of Washington, Seattle, Washington 98195; Department of Biochemistry (J.R., M.F.S.) and Molecular Medicine, University of California, Davis, Davis, California 95616; and Department of Biostatistics (T.A.T.), University of Washington, Seattle, Washington 98195

Table 1. Characteristics of WHI SHARe DXA Admixture Study Participants by Study Site

Characteristics	Northeast (n = 125)	Southeast (n = 649)	Southwest (n = 33)
Age at WHI baseline (y)	63.9 (7.4)[a]	61.1 (7.2)[a, b]	64.8 (6.9)[b]
Age at menopause (y)	47.3 (6.6)[a]	45.3 (7.8)[a]	46.4 (6.0)
Pack-years of smoking	7.1 (12.3)	5.8 (13.8)	6.9 (9.7)
Body mass index (kg/m^2)	29.6 (5.7)[a]	31.3 (6.4)[a]	30.0 (6.6)
Waist circumference (cm)	89.3 (12.8)[a]	91.9 (12.7)[a]	87.2 (14.2)[a]
Oral contraceptive use ever (%)	40.8[a]	43.1[a]	18.2[a]
Lifetime hormone therapy use (y)	1.9 (4.2)[a]	3.3 (6.2)[b]	8.0 (11.1)[a, b]
DXA fat mass variables			
Whole body fat mass (g)	32 998.1 (11282.7)[a]	38 336.2 (12 777.4)[a]	33 036.6 (10 981.7)
Trunk fat mass (g)	14 656.8 (5553.1)[a]	17 414.4 (6417.8)[a]	14 881.7 (6036.1)
Trunk: whole body fat mass ratio	0.44 (0.06)	0.45 (0.06)	0.44 (0.07)
Whole body percentage fat (%)	42.6 (6.3)[a]	45.6 (7.0)[a, b]	42.4 (6.5)[b]
DXA bone mineral density variables			
Whole body BMD (g/cm^2)	1.06 (0.11)[a]	1.05 (0.11)[b]	1.11 (0.12)[a, b]
L2-L4 spine BMD (g/cm^2)	1.02 (0.16)	1.05 (0.17)	1.09 (0.17)
Total hip BMD (g/cm^2)	0.91 (0.14)[a]	0.95 (0.15)[a]	0.96 (0.15)
Hip intertrochanter BMD (g/cm^2)	1.07 (0.18)	1.11 (0.17)	1.14 (0.17)
Hip trochanter BMD (g/cm^2)	0.68 (0.11)	0.70 (0.12)	0.72 (0.12)
Femoral neck BMD (g/cm^2)	0.80 (0.13)	0.83 (0.14)	0.82 (0.14)
Global ancestry proportions			
European (CEU)	0.25 (0.15)[a]	0.16 (0.11)[a]	0.20 (0.11)
Yoruban	0.72 (0.15)[a]	0.81 (0.11)[a]	0.77 (0.11)
Native American	0.01 (0.01)	0.01 (0.01)	0.01 (0.01)
East Asian	0.02 (0.01)	0.02 (0.02)	0.02 (0.01)

Values shown are mean (SD) for continuous variables and percentages for categorical variables. Comparisons of means among different study sites were computed by ANOVA; comparisons of categories were analyzed using χ^2 tests. Those with same letter are significantly different at $P < .05$.

Fine mapping

We performed genetic association testing for regions identified via admixture mapping using genotypes from the Affymetrix 6.0 array and imputed data. For genotyped SNPs we used linear regression models adjusted for the same covariates used for admixture mapping. For analyses of imputed SNPs, dosage data were used to account for uncertainty.

Results

Several characteristics differ by site according to the covariates analyzed, including proportion of global ancestry (Table 1). All hip BMD measures (total, femoral neck, trochanter, and intertrochanter) were highly correlated (0.81–0.88), as were measures of hip with L2-L4 BMD (0.67–0.68). There are statistically significant positive correlations between global African ancestry and all BMD phenotypes $r > 0.10$, all $P < .012$. Similarly, whole-body and trunk fat mass were positively correlated with global African ancestry ($0.06 < r < 0.12$; all $P < .04$).

BMD admixture mapping

Correlations between SABER, LAMP, and HAPMAX were excellent ($r > 0.98$); we therefore report on results of SABER only for autosomal chromosomes and HAPMIX for chromosome X. Femoral neck BMD was the only phenotype that reached genome-wide (admixture) significance ($P < 1.5 \times 10^{-5}$) (Table 2). Although we identified 2 regions on chromosome 19 (45599248–49306048 bp and 51106133–51435085 bp) associated with femoral neck, given their extensive linkage disequilibrium we cannot rule out that these signals represent one large region; not surprisingly, other highly correlated hip measures showed similar magnitude of association at these loci but were not genome-wide significant. β Coefficients indicate that with increasing copies of European alleles, femoral neck BMD decreases. Another admixture signal of interest was identified on chromosome 13 for BMD of L2-L4 vertebrae spanning 60627830–68949981 bp ($P = 3.2 \times 10^{-5}$).

BMD fine mapping

Our 3 most significant genotype associations with femoral neck BMD are rs7250326 ($P = 3.6 \times 10^{-6}$), rs2293166 ($P = 3.7 \times 10^{-6}$), and rs13343790 ($P = 5.8 \times 10^{-6}$) located on 19q13 at 49700082 bp, 49696663 bp, and 45013678 bp, respectively. The rs7250326 SNP was genotyped, whereas the latter 2 SNPs were imputed (r^2 for imputation quality was 0.92). For all 3 genetic associations, we found that as the number of minor alleles increases femoral neck BMD increases by approximately 0.03 g/cm^2. On average, the reference allele frequency for these 3 SNPs differs between YRI and CEU by 25%. The strongest L2-L4 BMD-genetic association on chromosome 13 ($P = 1.5 \times 10^{-5}$) was rs4884565 at 63724687 bp; the MAF at this SNP differs by >40% between YRI and CEU.

Fat mass admixture mapping and fine mapping

No fat mass phenotypes reached genome-wide significance. The most significant signals identified were that of

Table 2. Top Admixture Results for DXA-derived Measures of BMD and Fat Mass, WHI SHARe African Americans

Phenotype	Chromosome	Significant Region[a]	Most Significant SNP in Region		
			SNP	β (per copy of European allele)	*P* Value
Regions statistically significant at $P < 1.5 \times 10^{-5}$					
Femoral neck BMD	19q13	45599248–49306048	rs4099161	−0.04	6.10×10^{-6}
Femoral neck BMD	19q13	51106133–51435085	rs10424322	−0.04	1.06×10^{-5}
Regions borderline statistically significant at $P < 1.5 \times 10^{-4}$					
Trunk fat mass	Xp22	2716944–2832253	rs311187	−4.24	2.64×10^{-5}
L2-L4 spine BMD	13q21	60627830–68949981	rs12859844	0.05	3.21×10^{-5}
Total hip BMD	19q13	48854901–49306048	rs10410645	−0.04	3.30×10^{-5}
Total hip BMD	19q13	51106133–51479323	rs10424322	−0.03	6.85×10^{-5}
Trunk fat mass, South only	Xp22	2716944–2904827	rs311187	−3.99	7.50×10^{-5}
Percentage fat mass, diabetics removed	2q14	121700491–121708437	rs1078442	−1.37	7.93×10^{-5}
Intertrochanter BMD	19q13	48879346–48926544	rs10410645	−0.04	8.25×10^{-5}
Percentage fat mass	2q14	118846592–118970033	rs4073566	−1.27	8.61×10^{-5}
Trunk: whole body fat mass, South only	12p12	24104553–24186023	rs11830218	0.02	1.73×10^{-4}

[a] Region boundaries based on *P* value thresholds ($P < 1.5 \times 10^{-5}$ or 1.5×10^{-4}), National Center for Biotechnology Information (NCBI) Build 36.

trunk fat mass and a region on chromosome X, as well as percentage fat mass and 2 nonoverlapping regions on chromosome 2. For all regions, as the number of European alleles increase, percentage fat mass decreases (Table 2). Our most significant fine mapping association with fat mass (rs5939379) was observed on chromosome X at 2793776 bp ($P < 3 \times 10^{-4}$). The MAF at this SNP differs by >80% between YRI and CEU.

Discussion

Previous studies demonstrated a relationship of global ancestry with DXA-derived phenotypes; however, to our knowledge, we have completed the only genome-wide admixture scan of DXA-derived phenotypes in an AA sample. Our findings suggest higher femoral neck BMD is associated with higher levels of African ancestry in a region on chromosome 19 and potentially chromosome 13. Suggestive associations for fat mass were identified on chromosomes X and 12.

To date, linkage and association studies have included primarily individuals of European ancestry. One linkage study showed significant evidence for cosegregation in our chromosome 19 region with osteoarthritis (13) and a recent genome-wide association study (GWAS) meta-analysis identified a novel signal for lumbar spine BMD (and a lesser association with femoral neck BMD) near the boundary of our 19q region (14). Although the association of African ancestry and L2-L4 spine BMD on 13q21 did not meet strict genome-wide significance, genetic association with femoral neck BMD was reported in this region (15).

The rs2293166 BMD SNP is an expression quantitative trait locus (eQTL) for *ZNF180* (16), which is expressed in bone (17). Several transcription factors in different cell lines and multiple histone marks overlap the region containing rs2293166, and this SNP is contained within a deoxyribonuclease I (DNaseI) hypersensitivity site. The rs7250326 SNP also sits on a histone mark (H3K27AC) and is an open chromatin region, implying potential for this SNP to serve a regulatory role (18). Given the genetic features associated with these SNPs, it is possible that they affect transcription factor binding in this area.

Our fat mass associations were not significant genome-wide but we present the 12p12 findings in light of 2 obesity GWAS that identified a SNP (rs718314) approximately 2 MB from our ratio of trunk:whole-body fat mass peak (19, 20). Another GWAS meta-analysis reported an association of rs6487924 in *IPO8* with abdominal obesity phenotypes at 12p11.21 (21).

Admixture mapping using a dense panel of markers in AAs is known to require fewer samples and the conduct of fewer independent tests relative to GWAS (22). Despite our relatively modest sample size, the admixture mapping approach and the distribution of our quantitative phenotype in the two populations offered our study 80% power to detect variants contributing as little as 2.5% to phenotypic variation. We were able to identify a statistically significant association of femoral neck BMD and African ancestry on chromosome 19q13. The overlap of significant regions and genetic variants from published studies to date on top of our results provide further impetus for more fine mapping and replication studies. The primary strengths of our study are the unique WHI SHARe population with detailed epidemi-

ologic and demographic information on a group of well-characterized AA women coupled with the availability of a large number of markers for admixture mapping.

In summary, using a genome-wide admixture approach in 842 AA women from WHI SHARe, we detected 2 novel regions on chromosome 19 associated with femoral neck BMD and near significant associations with fat mass. The new information coming from our study suggests that ancestry may be an important modifier of the genetic associations with complex phenotypes associated with this genomic region and should be carefully studied further with regard to pleiotropic effects that may exist.

Acknowledgments

We gratefully acknowledge the dedicated efforts of investigators and staff at the 40 Women's Health Initiative (WHI) clinical centers, the WHI Clinical Coordinating Center, and the National Heart, Lung, and Blood Institute program office (listing available at http://www.whi.org). Most importantly, we recognize the WHI participants for their extraordinary commitment to the WHI program.

Address all correspondence and requests for reprints to: Heather Ochs-Balcom, PhD, Department of Social and Preventive Medicine, 270 Farber Hall, University at Buffalo, Buffalo, New York 14214-8001. E-mail: hmochs2@buffalo.edu; or Lara E. Sucheston, PhD, Roswell Park Cancer Institute, Department of Cancer Prevention and Control, Elm and Carlton Streets, Buffalo, New York 14263. E-mail: lara.sucheston@roswellpark.org.

This work was supported in part by the National Cancer Institute (5K07CA136969 to H.O.-B.), the Stanford Genome Training Program (T32 HG000044 to N.J.), a Ric Weiland fellowship (to N.J.), the National Institute of Aging (R01AG031890 to R.K.), and NHLBI BAA Contract Number HHSN268200764319C (to M.S.). The WHI program is funded by the National Heart Lung and Blood Institute, National Institutes of Health, United States Department of Health and Human Services through Contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN 268201100004C, and HHSN271201100004C. Funding for WHI SHARe genotyping was provided by National Heart Lung and Blood Institute Contract N02-HL-64278.

This manuscript was prepared in collaboration with investigators and has been reviewed and approved by the WHI.

The data sets used for the analyses described in this manuscript were obtained from dbGaP at http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap through dbGaP Accession Number phs000200.v5.p2.

Disclosure Summary: The authors have nothing to disclose.

References

1. **Winkler CA, Nelson GW, Smith MW.** Admixture mapping comes of age. *Ann Rev Genomics Hum Genet*. 2010;11:65–89.
2. **Wagner DR, Heyward VH.** Measures of body composition in blacks and whites: a comparative review. *Am J Clin Nutr*. 2000;71:1392–1402.
3. **Nassir R, Qi L, Kosoy R, et al.** Relationship between adiposity and admixture in African-American and Hispanic-American women. *Int J Obes*. 2011;36:304–313.
4. **Chen Z, Qi L, Beck TJ, et al.** Stronger bone correlates with African admixture in African-American women. *J Bone Miner Res*. 2011; 26:2307–2316.
5. **Tang H, Peng J, Wang P, Risch NJ.** Estimation of individual admixture: analytical and study design considerations. *Genet Epidemiol*. 2005;28:289–301.
6. **Cann HM, de Toma C, Cazes L, et al.** A human genome diversity cell line panel. *Science*. 2002;296:261–262.
7. **Tang H, Coram M, Wang P, Zhu X, Risch N.** Reconstructing genetic ancestry blocks in admixed individuals. *Am J Hum Genet*. 2006; 79:1–12.
8. **Tang H, Siegmund DO, Johnson NA, Romieu I, London SJ.** Joint testing of genotype and ancestry association in admixed families. *Genet Epidemiol*. 2010;34:783–791.
9. **Price AL, Tandon A, Patterson N, et al.** Sensitive detection of chromosomal segments of distinct ancestry in admixed populations. *PLoS Genet*. 2009;5:e1000519.
10. **Sankararaman S, Sridhar S, Kimmel G, Halperin, E.** Estimating local ancestry in admixed populations. *Am J Hum Genet*. 2008;82:290–303.
11. **Li Y, Willer CJ, Ding J, Scheet P, Abecasis GR.** MaCH: using sequence and genotype data to estimate haplotypes and unobserved genotypes. *Genet Epidemiol*. 2010;34:816–834.
12. **Carty CL, Johnson NA, Hutter CM, et al.** Genome-wide association study of body height in African Americans: the Women's Health Initiative SNP Health Association Resource (SHARe). *Hum Mol Genet*. 2012;21:711–720.
13. **Demissie S, Cupples LA, Myers R, Aliabadi P, Levy D, Felson, DT.** Genome scan for quantity of hand osteoarthritis: the Framingham Study. *Arthritis Rheum*. 2002;46:946–952.
14. **Estrada K, Styrkarsdottir U, Evangelou E, et al.** Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture. *Nat Genet*. 2012;44:491–501.
15. **Kiel DP, Demissie S, Dupuis J, Lunetta KL, Murabito JM, Karasik D.** Genome-wide association with bone mass and geometry in the Framingham Heart Study. *BMC Med Genet 8 Suppl*. 2007;1:S14.
16. **Gamazon ER, Huang RS, Dolan ME, Cox NJ.** Copy number polymorphisms and anticancer pharmacogenomics. *Genome Biol*. 2011;12:R46.
17. **Kalogeropoulos M, Varanasi SS, Olstad OK, et al.** Zic1 transcription factor in bone: neural developmental protein regulates mechanotransduction in osteocytes. *FASEB J*. 2010;24:2893–2903.
18. **Boyle AP, Hong EL, Hariharan M, et al.** Annotation of functional variation in personal genomes using RegulomeDB. *Genome Res*. 2012;22:1790–1797.
19. **Heid IM, Jackson AU, Randall JC, et al.** Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. *Nat Genet*. 2010;42:949–960.
20. **Fox CS, Liu Y, White CC, et al.** Genome-wide association for abdominal subcutaneous and visceral adipose reveals a novel locus for visceral fat in women. *PLoS Genet*. 2012;8:e1002695.
21. **Lindgren CM, Heid IM, Randall JC, et al.** Genome-wide association scan meta-analysis identifies three Loci influencing adiposity and fat distribution. *PLoS Genet*. 2009;5:e1000508.
22. **Patterson N, Hattangadi N, Lane B, et al.** Methods for high-density admixture mapping of disease genes. *Am J Hum Genet*. 2004;74: 979–1000.