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Allele Frequencies of the Single Nucleotide Polymorphisms Related to the Body Burden of Heavy Metals in the Korean Population and Their Ethnic Differences

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This study was performed to select single nucleotide polymorphisms (SNPs) related to the body burden of heavy metals in Koreans, to provide Korean allele frequencies of selected SNPs, and to assess the difference in allele frequencies with other ethnicities. The candidate-gene approach method and genome-wide association screening were used to select SNPs related to the body burden of heavy metals. Genotyping analysis of the final 192 SNPs selected was performed on 1,483 subjects using the VeraCode Goldengate assay. Allele frequencies differences and genetic differentiations between the Korean population and Chinese (CHB), Japanese (JPT), Caucasian (CEU), and African (YIR) populations were tested by Fisher's exact test and fixation index (F_{ST}), respectively. The Korean population was genetically similar to the CHB and JPT populations ($F_{ST} < 0.05$, for all SNPs in both populations). However, a significant difference in the allele frequencies between the Korean and CEU and YIR populations were observed in 99 SNPs (60.7%) and 120 SNPs (73.6%), respectively. Ten (6.1%) and 26 (16.0%) SNPs had genetic differentiation ($F_{ST} > 0.05$) among the Korean-CEU and Korean-YIR comparisons, respectively. The SNP with the largest F_{ST} value between the Korean and African populations was *cystathionine-β-synthase* rs234709 (F_{ST}: KOR-YIR, 0.309; KOR-CEU, 0.064). Our study suggests that interethnic differences exist in SNPs associated with heavy metals of Koreans, and it should be considered in future studies that address ethnic differences in heavy-metal concentrations in the body and genetic susceptibility to the body burden of heavy metals.

***Key words*:** Genetic diversity, Single nucleotide polymorphism, Gene frequency, Metals

INTRODUCTION

It is well known that heavy metals induce adverse health effects in humans, including kidney damage, bone loss, neurological disorders, developmental abnormalities, vascular diseases, and cancer (1,2). Even the general population that does not have occupational exposure is chronically exposed to a low concentration of heavy metals because heavy metals are widely distributed in the environment (1,3). Heavy-metal concentration in the body is affected by various factors such as age, sex, smoking, diet, and nutritional status, and the environmental exposure level is a critical factor in determining the body burden of heavy metal (1,3,4). However, heavy metals go through the processes of absorption, distribution, metabolism, and excretion, in which a number of genetic factors are involved directly or indirectly. Therefore, in addition to environmental factors, genetic factors and their interactions may also play important roles in determining heavy-metal concentrations in the body (5). Previous studies reported that single nucleotide polymorphisms (SNPs) of a gene involved in iron metabolism were associated with not only the iron level but also with the lead and cadmium levels (6,7). Furthermore, in a twin study, the

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blood cadmium concentration was more strongly affected by genetics than by environmental factors (8). Therefore, genetic predisposition can play an important role in the body burden of heavy metals.

The blood cadmium and mercury levels in the general Korean population are approximately 2~4 times higher than the levels in the American population (9). Although consuming grains and shellfish was predicted to be a major factor in the heavy-metal high exposure levels of Korean populations (10), the general Korean population's estimated total dietary intake of cadmium was not high compared to that of other nations and was considerably lower (about 30%) than the provisional tolerable weekly intake (11). This mismatch between external exposure and internal concentration indicates that there is the possibility that Koreans have a genetic predisposition associated with high absorption, low excretion, and high accumulation rates of heavy metals. Therefore, the goal of this study was to select SNPs related to the body burden of heavy metals, such as lead, mercury, cadmium, and arsenic, provide Korean allele frequencies of selected SNPs, and assess the difference in allele frequencies with other ethnicities.

MATERIALS AND METHODS

Study subjects. This study was based on a cohort established by the Korean Research Project on Integrated Exposure Assessment to Hazardous Materials for Food Safety (KRIEFS). The characteristics of this KRIEFS cohort and the method used to select the study subjects were described in detail in previous studies (12). Out of the 2,118 adults who enrolled in a KRIEFS cohort, 1,558 consented to participating in the genetic study. Among them, 71 subjects were excluded for the following reasons: incomplete data on heavy-metal exposure ($n = 48$) and insufficient blood sample ($n = 23$). Ultimately, 1,487 subjects were selected as study subjects. This study was approved by the Institutional Review Board of Dankook University Hospital, Republic of Korea (IRB No. 2013-03-008), and informed consent was obtained from all individual participants included in the study.

Selection of SNPs-related body burden of heavy metals in the Korean population and genotyping analysis. The candidate-gene approach method and genome-wide association screening using an exome chip were performed to select SNPs related to the body burden of heavy metals in the Korean population.

Candidate-gene approach: The genes involved in absorption, distribution, metabolism, and excretion of heavy metals were selected as candidate genes through a literature review, and databases search, such as Catalog of Published GWAS (13) and HuGE Navigator (14). SNPs located in the transcription regulatory region (promoter region or start codon) and the coding region (splice site, exon, or stop codon) of the selected candidate genes were selected as candidate SNPs using the Functional Element SNPs Database II (15). We searched the International HapMap Project database (HapMap Data Rel 27, population CHB and JPT/*R*-square cutoff 0.9, minor allele frequency cutoff 0.05) for the haplotype tagging SNP of each candidate gene and selected the candidate SNPs from this source.

Genome-wide association screening: After randomly selecting 500 people from the study subjects, genome-wide association screening was conducted using a Human Exome chipv1.2 (Illumina, San Diego, USA) in which 244,770 SNPs could be simultaneously analyzed. There were 783 SNPs not in Hardy-Weinberg equilibrium (HWE) ($p < 0.001$), and 309 SNPs had call rates of less than 95%. The average call rate of all samples was greater than 99.9%, with a minimum value of 99.4%. As a result of conducting a blind replication test on 20 randomly selected samples, the error rate of all samples was less than 0.05%, and the average concordance rate was 99.96%. For the SNPs located on autosomal chromosomes that satisfied the call rate (> 95%) and were in HWE ($p > 0.001$), the association with the marker of heavy-metal body burden (blood lead, blood cadmium, blood mercury, urinary cadmium and total arsenic) was evaluated by multiple regression analysis using the program PLINK, and 81 significant SNPs ($p < 1.0 \times 10^{-4}$) were selected.

Genotyping analysis: Ultimately, 192 SNPs were selected based on the candidate-gene approach method and genome-wide association screening. Genotyping analysis was performed on the selected 192 SNPs using the VeraCode Goldengate assay (Illumina, San Diego, CA, USA). An analysis was performed on 1,483 subjects who passed the DNA quality control (QC). The average call rate of the samples was 99.41%, and the average call rate of the SNPs was 99.38%. From 15 of the 192 total SNPs that were not in HWE, six SNPs with call rates less than 95% and two samples with call rates less than 95% were excluded from the final analysis. As a result of conducting a blind replication test on 19 randomly selected samples, high reproducibility was confirmed with an average concordance rate of 99.5%.

SNP frequencies in other ethnic populations. The frequencies of the selected SNPs in other ethnic populations were investigated using the Database of Single Nucleotide Polymorphisms (dbSNP build 142) and International HapMap DB (HapMap Data Rel #27 Phases I, II, and III). In this study, the gene frequencies in the Korean population were compared to those in four ethnic populations: Han Chinese individuals from Beijing, China (CHB), Japanese individuals from Tokyo, Japan (JTP), Caucasian individuals from Utah, USA of Northern and Western European ancestry from the Centre de'Etude du Polymorphism Humain-collection (CEU), and African Yoruba individuals in Ibadan, Nigeria (YRI).

Statistical analysis. HWE and allele frequency, as determined by the program PLINK, were used to analyze the data for 192 SNPs in the Korean individuals in this study. Based on the minor allele in the Korean population, the allele frequencies in each ethnic group were calculated. For the 163 SNPs that passed SNP QC, the difference in SNP frequencies between the Korean populations and other ethnic groups was compared using Fisher's exact test. For each of the SNPs, we used Bonferroni correction for multiple tests and set the statistical significance threshold to p-value $< 3.1 \times 10^{-4}$ ($0.05/163$ SNPs $= 3.1 \times 10^{-4}$). Genetic differentiation among four ethnicities was measured by the Fixation index (F_{ST}), which describes the degree of population differentiation based on genetic polymorphisms (16). F_{ST} among a pairwise comparison between different ethnic groups was schematized with a Manhattan plot. F_{ST} at 0.05 to 0.15 was interpreted as moderate genetic differentiation, 0.15 to 0.25 was high genetic differentiation, and above 0.25 was very high genetic differentiation.

RESULTS

The study was conducted on 1,487 Korean subjects to calculate the allele frequencies of SNPs involved in the body burden of heavy metals, and their demographic characteristics and the level of heavy metals in subjects are presented in Table 1. The mean age of study subjects was 45.5 ± 14.5 years, 56.8% of all subjects was females. The

Table 1. General characteristics of study subjects

		N (%)
Total subjects		1,487
Gender	Males	643 (43.2)
	Females	844 (56.8)
Age, mean ± std.		45.5 ± 14.5
Age groups	-29	255 (17.2)
	30~39	266 (17.9)
	40~49	341 (22.9)
	50~59	334 (22.5)
	60+	291 (19.6)
Smoking history	Never smokers	966 (65.0)
	Ex-smokers	243 (16.3)
	Current smokers	278 (18.7)
Alcohol use	Non-drinkers	362 (24.3)
	Drinkers	1125 (75.7)
Heavy metal levels*		
Blood lead, unit: μg/dL		2.21 (2.17, 2.26)
Blood mercury, unit: μg/L		4.05 (3.91, 4.19)
Blood cadmium, unit: μg/L		1.06 (1.03, 1.09)
Urinary cadmium, unit: μg/g creatinine		1.09 (1.05, 1.13)
Urinary total arsenic, unit: μg/g creatinine		102.7 (98.03, 107.60)

*Presented as geometric mean and 95% confidence intervals.

Table 2. Information about the 192 SNPs and allele frequencies tested in this study

rs ID	Chr.	Gene	Location	Minor allele	MAF	Selection rationale	Related heavy metals
rs1948368	1	*S1PR1/OLFM3*	Intergenic	A	0.003	Exome chip based	Cd
rs714282	1	*GPR177*	Intron	A	0.419	Exome chip based	Cd
rs3736930	1	*ATP6V1G3*	Complex	T	0.057	Candidate gene approached	Cd
rs2666839	1	*CENPF*	Coding	T	0.163	Exome chip based	Cd
rs34545462	1	*SLC2A7*	Coding	T	0.050	Exome chip based	Hg
rs11265263	1	*DUSP23/CRP*	Intergenic	A	0.170	Exome chip based	Cd
rs13306731	1	*SOAT1*	Coding	G	0.380	Candidate gene approached	Cd, Hg
rs11118075	1	*RRP15*	Coding	C	0.070	Exome chip based	Hg
rs11805194	1	*NUP133*	Coding	C	0.140	Exome chip based	Cd
rs2479409	1	*BSND/PCSK9*	Intergenic	A	0.366	Exome chip based	Cd
rs35351292	1	*LAPTM5*	Coding	A	0.065	Exome chip based	Cd
rs41268474	1	*C1orf68*	Coding	A	0.068	Exome chip based	Pb
rs1284852	1	*FLVCR1/VASH2*	Intergenic	G	0.446	Candidate gene approached	Cd
rs58275168	1	*SLC35F3*	Intron	A	0.282	Exome chip based	Cd
rs1476413	1	*MTHFR*	Intron	A	0.176	Candidate gene approached	As
rs4845625	1	*IL6R*	Intron	T	0.443	Exome chip based	Pb
rs267733	1	*ANXA9*	Coding	G	0.077	Exome chip based	Pb
rs2698530	2	*PELI1/HSPC159*	Intergenic	A	0.350	Candidate gene approached	Cd, Pb
rs1457451	2	*LOC729348/LOC100131818*	Intergenic	A	0.172	Candidate gene approached	Cd
rs4664325	2	*RBMS1*	Intron	G	0.315	Exome chip based	Cd
rs12623234	2	*MRPS9/GPR45*	Intergenic	G	0.476	Exome chip based	Cd
rs1130609	2	*RRM2*	UTR	G	0.338	Candidate gene approached	Pb
rs2165738	2	*NCOA1/ITSN2*	Intergenic	G	0.387	Exome chip based	Hg
rs61197218	2	*LOC100128572/IQCA1*	Intergenic	A	0.271	Exome chip based	Hg
rs2287059	2	*NOL10*	Coding	T	0.114	Exome chip based	Hg

Table 2. Continued

rs ID	Chr.	Gene	Location	Minor allele	MAF	Selection rationale	Related heavy metals
rs10455	2	*CYBRD1*	UTR	A	0.331	Candidate gene approached	Pb
rs3747673	3	*TNK2*	Coding	T	0.111	Exome chip based	Cd
rs2293232	3	*MUC4*	Coding	T	0.219	Exome chip based	Cd
rs3817672	3	*TFRC*	Coding	A	0.175	Candidate gene approached	Cd
rs72953098	3	*C3orf30*	UTR	G	0.067	Exome chip based	Hg
rs7640978	3	*CMTM6*	Intron	T	0.057	Exome chip based	Cd
rs832038	3	*GABRR3*	Intron	G	0.452	Candidate gene approached	Pb, Cd
rs6799969	3	*RAD18/OXTR*	Intergenic	G	0.358	Exome chip based	Cd
rs1799852	3	*TF*	Coding	T	0.218	Candidate gene approached	Cd, Pb
rs3804141	3	*TFRC*	Intron	A	0.212	Candidate gene approached	Cd
rs2718812	3	*TOPBP1/TF*	Intergenic	A	0.490	Candidate gene approached	Cd
rs1830084	3	*TF/SRPRB*	Intergenic	A	0.472	Candidate gene approached	Cd, Pb
rs75123867	3	*CCDC50*	Coding	T	0.048	Exome chip based	Cd
rs3811647	3	*TF*	Intron	A	0.419	Candidate gene approached	Cd
rs1561072	3	*SOX2OT/ATP11B*	Intergenic	C	0.180	Exome chip based	Hg
rs2276790	3	*MFI2*	Coding	T	0.061	Candidate gene approached	Cd
rs1049296	3	*TF*	Coding	T	0.266	Candidate gene approached	Cd
rs34193982	4	*NEIL3*	Coding	G	0.118	Exome chip based	Hg
rs74511500	4	*FAT1*	Coding	A	0.091	Exome chip based	Hg
rs11556167	4	*PET112L*	Coding	A	0.059	Exome chip based	Cd
rs4073	4	*RASSF6/IL8*	Intergenic	A	0.367	Candidate gene approached	As
rs2725264	4	*ABCG2*	Intron	G	0.219	Candidate gene approached	Hg
rs17208187	5	*TMCO6*	Coding	G	0.258	Exome chip based	Hg
rs7579	5	*SEPP1*	UTR	A	0.329	Candidate gene approached	Hg
rs3822751	5	*GLRX*	Intron	C	0.294	Candidate gene approached	As
rs2052550	5	*ARSB*	Intron	G	0.452	Candidate gene approached	Cd, Pb
rs3877899	5	*SEPP1*	Coding	-	0.000	Candidate gene approached	Hg
rs13188386	5	*GHR/LOC100129630*	Intergenic	-	0.000	Candidate gene approached	Cd, Pb
rs2354124	5	*MRPL36/LOC728613*	Intergenic	G	0.255	Exome chip based	Cd
rs1130435	5	*FABP6*	Complex	T	0.456	Exome chip based	Cd
rs3749779	5	*SLC25A2*	Coding	G	0.095	Exome chip based	Hg
rs1801394	5	*MTRR*	Complex	G	0.283	Candidate gene approached	Cd
rs3765467	6	*GLP1R*	Coding	T	0.252	Exome chip based	Hg
rs2301227	6	*HLA-DPA1*	Intron	C	0.073	Exome chip based	Cd, Hg
rs3129953	6	*C6orf10/BTNL2*	Intergenic	T	0.083	Exome chip based	Cd
rs76100089	6	*LOC729792*	Coding	T	0.203	Exome chip based	Hg
rs1800629	6	*TNF/LTA*	Intergenic	A	0.068	Candidate gene approached	Cd
rs17270561	6	*SLC17A1*	Intron	A	0.145	Candidate gene approached	Pb, Cd
rs13194984	6	*BTN1A1/BTN2A1*	Intergenic	T	0.007	Candidate gene approached	Cd, Pb
rs17342717	6	*SLC17A1*	Intron	T	0.008	Candidate gene approached	Cd, Pb
rs2071593	6	*ATP6V1G2*	UTR	T	0.084	Candidate gene approached	Hg
rs3957356	6	*GSTA1/GSTA5*	Intergenic	T	0.156	Candidate gene approached	Hg
rs932316	6	*SCGN/LRRC16A*	Intergenic	C	0.136	Candidate gene approached	Cd, Pb
rs12216125	6	*HIST1H1A/TRIM38*	Intergenic	T	0.122	Candidate gene approached	Cd, Hg
rs1799945	6	*HFE*	Complex	G	0.048	Candidate gene approached	Cd, Pb
rs9357283	6	*DNAH8*	Coding	A	0.314	Candidate gene approached	Cd
rs4516970	6	*WTAP/SOD2*	Intergenic	-	0.000	Candidate gene approached	Cd, Pb
rs2274089	6	*LRRC16A*	Intron	A	0.031	Candidate gene approached	Cd, Pb
rs1183201	6	*SLC17A1*	Intron	A	0.143	Candidate gene approached	Hg
rs17883901	6	*GCLC/KLHL31*	Intergenic	T	0.115	Candidate gene approached	Hg
rs2858881	6	*HLA-DQB1/HLA-DQA2*	Intergenic	G	0.048	Exome chip based	Hg
rs3736781	6	*BTN1A1*	Coding	G	0.314	Candidate gene approached	Hg
rs2142672	6	*MYLIP/GMPR*	Intergenic	C	0.264	Exome chip based	Pb
rs972275	6	*LOC728666/RSPO3*	Intergenic	G	0.458	Candidate gene approached	Cd, Pb
rs35868297	7	*GALNTL5*	Coding	C	0.196	Exome chip based	Cd
rs194524	7	*STEAP2*	Complex	A	0.213	Candidate gene approached	Pb

Table 2. Continued

rs ID	Chr.	Gene	Location	Minor allele	MAF	Selection rationale	Related heavy metals
rs2718021	7	*SEPT7/EEPD1*	Intergenic	T	0.480	Exome chip based	Cd
rs13225097	7	*LOC100288724/GIMAP4*	Intergenic	G	0.188	Exome chip based	Cd
rs4722266	7	*STK31*	Complex	A	0.260	Exome chip based	Pb
rs13306698	7	*PON1*	Coding	G	0.086	Candidate gene approached	Cd
rs29880	7	*INHBA/C7orf10*	Intergenic	G	0.144	Candidate gene approached	Cd, Pb
rs662	7	*PON1*	Coding	A	0.355	Candidate gene approached	Pb
rs6971925	7	*DGKB*	Intron	T	0.078	Exome chip based	Cd
rs1106634	8	*ATP6V1B2*	Intron	A	0.211	Candidate gene approached	Hg
rs8191664	8	*NEIL2*	Complex	T	0.193	Exome chip based	Cd
rs11544484	8	*TOP1MT*	Coding	A	0.063	Exome chip based	Hg
rs4732748	8	*ESCO2*	Coding	T	0.200	Exome chip based	Cd, Hg
rs74846385	8	*C8orf86*	Coding	C	0.106	Exome chip based	Cd
rs17058207	8	*SCARA5*	Coding	G	0.320	Candidate gene approached	Pb, Cd
rs4872511	8	*PPP3CC/SORBS3*	Intergenic	T	0.084	Exome chip based	Pb
rs1800435	9	*ALAD*	Coding	C	0.073	Candidate gene approached	Pb
rs10818708	9	*OR1N1*	Coding	G	0.099	Exome chip based	Cd
rs3740393	10	*AS3MT*	Intron	C	0.253	Candidate gene approached	As
rs743572	10	*CYP17A1*	UTR	G	0.496	Candidate gene approached	As
rs1046778	10	*AS3MT*	UTR	C	0.385	Candidate gene approached	As
rs10749138	10	*NRAP*	Coding	T	0.419	Exome chip based	Hg
rs4462262	10	*IPMK/ZWINT*	Intergenic	T	0.078	Exome chip based	Hg
rs717620	10	*ABCC2*	UTR	A	0.222	Candidate gene approached	Hg
rs11191439	10	*AS3MT*	Coding	C	0.014	Candidate gene approached	As
rs10748835	10	*AS3MT*	Intron	A	0.491	Candidate gene approached	As
rs156697	10	*GSTO2*	Coding	C	0.259	Candidate gene approached	Cd
rs11191453	10	*AS3MT*	Intron	C	0.250	Candidate gene approached	As
rs7085104	10	*C10orf32/AS3MT*	Intergenic	G	0.435	Candidate gene approached	As
rs2297235	10	*GSTO2*	UTR	G	0.149	Candidate gene approached	As
rs4925	10	*GSTO1*	Coding	A	0.150	Candidate gene approached	As
rs2273697	10	*ABCC2*	Coding	A	0.080	Candidate gene approached	Cd
rs3740066	10	*ABCC2*	Coding	A	0.245	Candidate gene approached	Hg
rs3740390	10	*AS3MT*	Intron	A	0.250	Candidate gene approached	As
rs10891692	11	*FAM55A*	Coding	C	0.382	Exome chip based	Cd
rs1695	11	*GSTP1*	Coding	G	0.176	Candidate gene approached	Cd, Hg
rs4149182	11	*SLC22A8*	Intron	C	0.316	Candidate gene approached	Hg
rs11568496	11	*SLC22A8*	Coding	-	0.000	Candidate gene approached	Hg
rs45566039	11	*SLC22A8*	Coding	-	0.000	Candidate gene approached	Hg
rs77030286	11	*SNHG1/SNORD28*	Intergenic	-	0.000	Candidate gene approached	Hg
rs10047462	11	*KIAA0999*	Intron	G	0.499	Candidate gene approached	Cd, Pb
rs12362209	11	*CCDC83*	Coding	G	0.082	Exome chip based	Hg
rs236918	11	*PCSK7*	Intron	C	0.444	Candidate gene approached	Cd, Hg
rs4752805	11	*PTPRJ*	Intron	G	0.211	Exome chip based	Cd
rs4149170	11	*SLC22A6*	UTR	A	0.278	Candidate gene approached	Hg
rs1965	12	*LOC341378/CKAP4*	Intergenic	G	0.345	Candidate gene approached	Hg
rs12229654	12	*LOC100131138/CUX2*	Intergenic	G	0.139	Exome chip based	Pb
rs11111245	12	*NAV3/SYT1*	Intergenic	C	0.080	Exome chip based	Cd
rs2291075	12	*SLCO1B1*	Coding	T	0.422	Candidate gene approached	As
rs7975232	12	*VDR*	Intron	A	0.249	Candidate gene approached	Pb
rs2464196	12	*HNF1A*	Coding	C	0.454	Candidate gene approached	Pb
rs11066280	12	*LOC100287871*	Intron	A	0.178	Exome chip based	Pb
rs4304840	12	*CLEC4D*	Coding	G	0.160	Exome chip based	Hg
rs885389	12	*GPR133*	Intron	G	0.423	Exome chip based	Pb
rs1564370	12	*SLCO1B1*	Intron	C	0.259	Candidate gene approached	As
rs10842971	12	*PZP*	Coding	T	0.063	Exome chip based	Hg
rs17124715	12	*LARP4*	Complex	C	0.079	Exome chip based	Cd, Hg
rs757343	12	*VDR*	Intron	A	0.190	Candidate gene approached	Pb

Table 2. Continued

rs ID	Chr.	Gene	Location	Minor allele	MAF	Selection rationale	Related heavy metals
rs1800802	12	*ERP27/MGP*	Intergenic	C	0.340	Candidate gene approached	Pb
rs671	12	*ALDH2*	Coding	A	0.158	Exome chip based	Pb
rs1544410	12	*VDR*	Intron	A	0.051	Candidate gene approached	Pb
rs60683621	12	*OR6C70*	Coding	G	0.489	Exome chip based	Hg
rs17278868	13	*LATS2/SAP18*	Intergenic	C	0.366	Exome chip based	Hg
rs636437	13	*RFC3/NBEA*	Intergenic	G	0.132	Exome chip based	Cd, Hg
rs973968	14	*FLJ43390/KCNH5*	Intergenic	G	0.059	Candidate gene approached	Cd
rs12879346	14	*SLC7A8*	UTR	T	0.486	Candidate gene approached	Hg
rs12588118	14	*SLC7A8*	Intron	G	0.096	Candidate gene approached	Hg
rs34691153	14	*SLC7A8*	Coding	-	0.000	Candidate gene approached	Hg
rs1130650	14	*NP*	Coding	T	0.227	Candidate gene approached	As
rs8005905	14	*HSP90AA1*	Coding	T	0.223	Candidate gene approached	Hg
rs2234636	14	*SLC39A2*	Coding	C	0.424	Candidate gene approached	As
rs11549465	14	*HIF1A*	Coding	T	0.053	Candidate gene approached	Cd, Hg
rs4984390	15	*MCTP2*	Intron	A	0.318	Exome chip based	Hg
rs55799438	15	*C15orf56*	Coding	G	0.047	Exome chip based	Cd
rs13180	15	*IREB2*	Coding	T	0.465	Candidate gene approached	Cd
rs11643815	16	*MT4*	Coding	A	0.004	Candidate gene approached	Hg
rs28366003	16	*MT2A*	UTR	G	0.127	Candidate gene approached	Cd
rs9936741	16	*MT1M*	UTR	C	0.069	Candidate gene approached	Hg
rs12919719	16	*CDH1*	Intron	G	0.164	Candidate gene approached	As
rs11076161	16	*MT1A*	Intron	A	0.292	Candidate gene approached	Cd
rs4148356	16	*ABCC1*	Coding	A	0.069	Candidate gene approached	Pb
rs35529209	16	*ABCC1*	Coding	-	0.000	Candidate gene approached	Hg
rs41395947	16	*ABCC1*	Coding	-	0.000	Candidate gene approached	Hg
rs33916661	16	*SLC7A5/CA5A*	Intergenic	G	0.119	Candidate gene approached	Hg
rs11075290	16	*ABCC1*	Intron	T	0.379	Candidate gene approached	Hg
rs10636	16	*MT2A*	UTR	C	0.266	Candidate gene approached	Cd
rs3785879	17	*LOC100130148/MAPT*	Intergenic	A	0.388	Candidate gene approached	Hg
rs78388447	17	*EFCAB3*	Complex	G	0.102	Exome chip based	Cd
rs242557	17	*MAPT/LOC100130148*	Intergenic	G	0.471	Exome chip based	Cd
rs542939	17	*ABHD15*	Coding	T	0.070	Exome chip based	Cd
rs7216284	17	*GGT6*	Coding	A	0.146	Candidate gene approached	Cd
rs312893	17	*SEPT9*	Intron	T	0.163	Exome chip based	Cd
rs3744807	17	*PYCR1*	UTR	T	0.048	Exome chip based	Hg
rs2660917	18	*SOCS6/CBLN2*	Intergenic	C	0.057	Candidate gene approached	Cd
rs2276199	18	*PSTPIP2*	Coding	G	0.439	Exome chip based	Pb
rs11555891	19	*IRGC*	Coding	A	0.132	Exome chip based	Hg
rs3745262	19	*RAVER1*	Coding	C	0.080	Exome chip based	Cd
rs10427027	19	*PRDX2*	Intron	C	0.077	Candidate gene approached	As
rs1644731	19	*RDH8*	Coding	A	0.439	Exome chip based	Cd
rs4452075	19	*ZNF527*	Coding	G	0.315	Exome chip based	Hg
rs1043673	19	*NLRP2*	Coding	A	0.225	Candidate gene approached	Cd
rs3761144	20	*GSS/MYH7B*	Intergenic	C	0.463	Candidate gene approached	Hg
rs1056720	20	*CDC25B*	Complex	T	0.331	Candidate gene approached	Cd
rs2762934	20	*CYP24A1*	UTR	A	0.114	Exome chip based	Cd
rs4925386	20	*LAMA5*	Intron	T	0.225	Exome chip based	Cd
rs62200482	20	*FERMT1*	Coding	A	0.071	Exome chip based	Cd
rs6126559	20	*VSTM2L*	Intron	A	0.472	Exome chip based	Pb
rs4920037	21	*CBS*	Intron	A	0.026	Candidate gene approached	As
rs234709	21	*CBS*	Intron	T	0.091	Candidate gene approached	As
rs855791	22	*TMPRSS6*	Coding	C	0.106	Candidate gene approached	Cd, Pb
rs987710	22	*PRAMEL/VPREB1*	Intergenic	G	0.310	Candidate gene approached	Cd, Pb
rs4820268	22	*TMPRSS6*	Coding	G	0.490	Candidate gene approached	Cd, Pb
rs2430212	X	*KLHL13*	Intron	C	0.299	Candidate gene approached	Cd, Pb

Chr.: chromosome, MAF: minor allele frequency, UTR: untranslated region.

geometric means of blood lead, mercury, cadmium levels in all subjects were 2.21 μg/dL, 4.05 μg/L and 1.06 μg/L, respectively. The geometric mean concentrations of cadmium and total arsenic in urine were 1.06, 102.7 μg/g creatinine, respectively.

Table 2 shows the annotation information, minor allele frequency and selection rationale for the 192 selected SNPs. For the 163 SNPs that passed SNP QC, the allele frequency of minor (variant) alleles in the Korean population and the allele frequencies in CHB, JPT, CEU, and YIR were compared by pairwise comparison; the results are presented in Supplemental Table 1. Six SNPs (3.7%) showed a statistically significant difference in allele frequency between the Korean and CHB populations, and eight SNPs (4.9%) dif-

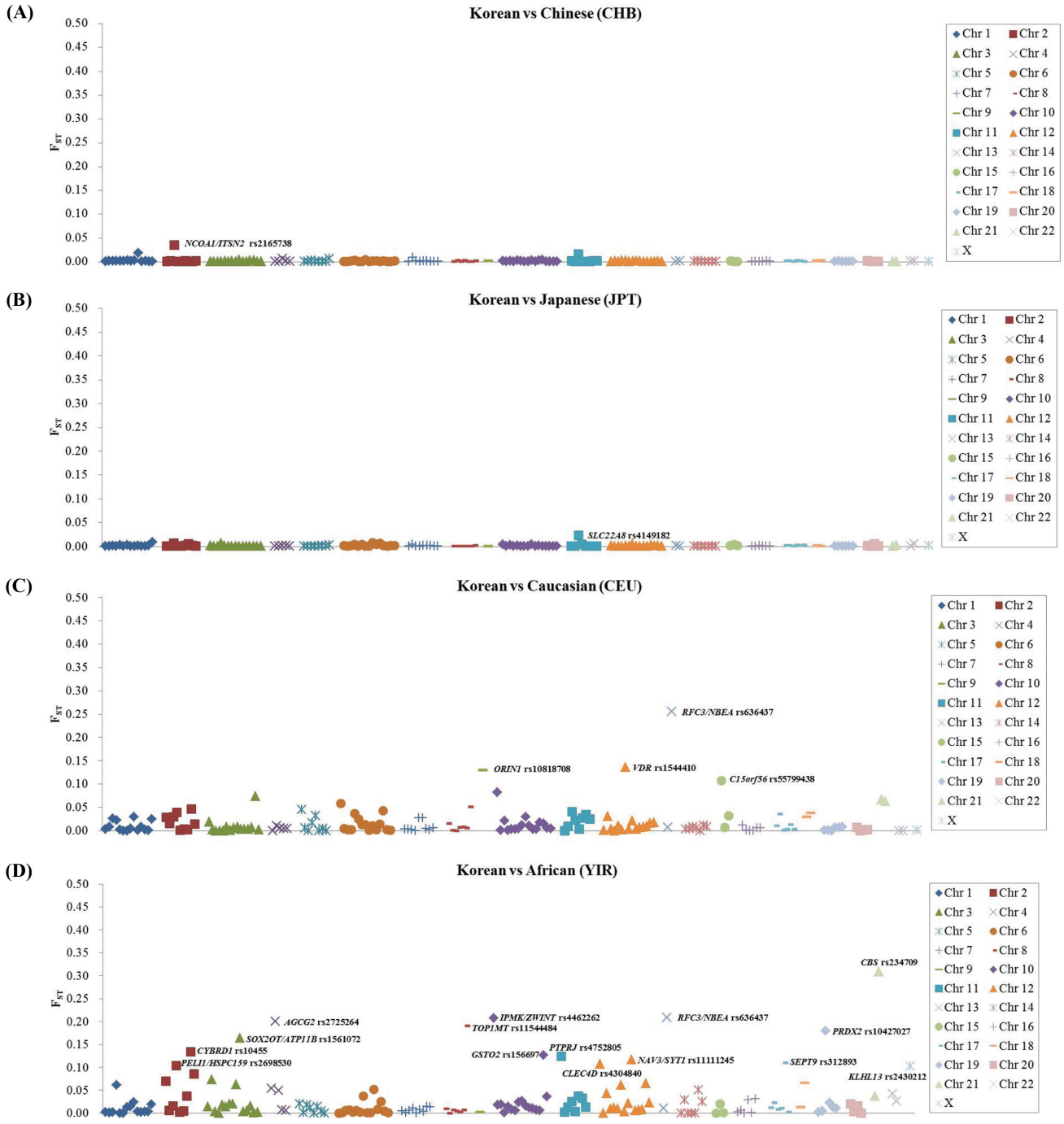

Fig. 1. Genetic differentiation between Korean and other ethnic populations. A: Korean versus Chinese (CHB). B: Korean versus Japanese (JPT). C: Korean versus Caucasian (CEU). D: Korean versus African (YIR).

Table 3. Allele frequencies and fixation index (F_{ST}) among different ethnics for selected 31 SNPs

SNP ID	Gene symbol	Chr.	Referent/ variant allele*	Variant allele* frequency					KOR versus CHB		KOR versus JPT		KOR versus CEU		KOR versus YIR	
				KOR	CHB	JPT	CEU	YIR	$P^{\dagger}$	F_{ST}	$P^{\dagger}$	F_{ST}	$P^{\dagger}$	F_{ST}	$P^{\dagger}$	F_{ST}
rs2479409	*BSND/PCSK9*	1	T/C	0.37	0.32	0.39	0.65	0.79	0.115	0.0008	0.518	0.0002	8.1×10^{-17}	0.0225	5.9×10^{-46}	0.0620
rs10455	*CYBRD1*	2	G/A	0.33	0.33	0.40	0.73	0.96	1.000	0.0001	0.047	0.0014	1.0×10^{-32}	0.0467	4.2×10^{-105}	0.1343
rs1130609	*RRM2*	2	A/G	0.34	0.37	0.35	0.74	0.98	0.573	0.0001	0.819	0.0001	1.5×10^{-19}	0.0283	1.1×10^{-52}	0.0695
rs2698530	*PELI1/HSPC159*	2	T/C	0.35	0.37	0.36	0.72	0.90	0.467	0.0002	0.718	0.0001	8.7×10^{-28}	0.0388	8.9×10^{-79}	0.1035
rs61197218	*LOC100128572/IQCA1*	2	T/G	0.27	0.32	0.28	0.04	0.86	0.114	0.0008	0.931	0.0000	2.1×10^{-15}	0.0148	6.8×10^{-56}	0.0860
rs1561072	*SOX2OT/ATP11B*	3	G/A	0.18	0.19	0.15	0.10	0.78	0.565	0.0003	0.368	0.0004	0.001	0.0033	1.6×10^{-97}	0.1643
rs1830084	*TF/SRPRB*	3	G/A	0.47	0.58	0.50	0.65	0.91	3.9×10^{-4}	0.0039	0.447	0.0002	4.0×10^{-7}	0.0080	9.2×10^{-53}	0.0626
rs3817672	*TFRC*	3	T/C	0.18	0.15	0.19	0.60	0.14	0.451	0.0002	0.651	0.0001	3.7×10^{-42}	0.0736	0.166	0.0006
rs7640978	*CMTM6*	3	T/C	0.06	0.05	0.05	0.10	0.31	0.785	0.0003	0.764	0.0004	0.012	0.0026	5.4×10^{-36}	0.0736
rs2725264	*ABCG2*	4	T/A	0.22	0.23	0.19	0.05	0.92	0.760	0.0000	0.357	0.0002	3.6×10^{-11}	0.0109	1.7×10^{-132}	0.2004
rs4073	*RASSF6/IL8*	4	T/C	0.37	0.41	0.33	0.39	0.86	0.283	0.0004	0.297	0.0004	0.513	0.0001	7.3×10^{-40}	0.0546
rs2142672	*MYLIP/GMPR*	6	T/C	0.26	0.29	0.20	0.69	0.26	0.392	0.0003	0.033	0.0015	3.7×10^{-38}	0.0587	0.835	0.0001
rs2858881	*HLA-DQB1/HLA-DQA2*	6	T/C	0.05	0.05	0.12	0.01	0.24	0.767	0.0000	3.8×10^{-5}	0.0063	0.003	0.0019	4.2×10^{-26}	0.0516
rs11544484	*TOP1MT*	8	G/A	0.06	0.08	0.05	0.30	0.53	0.198	0.0009	0.773	0.0005	6.4×10^{-25}	0.0513	1.4×10^{-86}	0.1900
rs10818708	*OR1N1*	9	T/C	0.10	0.13	0.09	0.58	0.15	0.141	0.0009	0.727	0.0002	1.1×10^{-61}	0.1300	0.015	0.0021
rs156697	*GSTO2*	10	C/A	0.26	0.27	0.29	0.39	0.83	0.719	0.0001	0.307	0.0005	8.9×10^{-5}	0.0054	8.8×10^{-85}	0.1262
rs4462262	*IPMK/ZWINT*	10	A/G	0.08	0.05	0.03	0.42	0.61	0.190	0.0009	0.002	0.0029	7.8×10^{-39}	0.0820	6.4×10^{-98}	0.2073
rs4752805	*PTPRJ*	11	A/G	0.21	0.28	0.19	0.16	0.98	0.112	0.0008	0.791	0.0000	0.187	0.0005	8.5×10^{-75}	0.1245
rs11111245	*NAV3/SYT1*	12	G/T	0.08	0.09	0.09	0.00	0.46	0.487	0.0000	0.612	0.0000	5.5×10^{-5}	0.0032	2.2×10^{-57}	0.1166
rs1544410	*VDR*	12	G/A	0.05	0.04	0.11	0.44	0.27	0.383	0.0012	0.001	0.0046	5.7×10^{-56}	0.1364	4.7×10^{-30}	0.0611
rs2464196	*HNF1A*	12	T/A	0.45	0.52	0.38	0.70	0.90	0.031	0.0015	0.037	0.0014	6.6×10^{-13}	0.0160	8.9×10^{-54}	0.0652
rs4304840	*CLEC4D*	12	A/G	0.16	0.15	0.12	0.22	0.62	0.730	0.0000	0.072	0.0008	0.032	0.0013	1.1×10^{-61}	0.1070
rs636437	*RFC3/NBEA*	13	C/T	0.13	0.17	0.14	0.90	0.76	0.097	0.0010	0.608	0.0003	2.4×10^{-133}	0.2552	5.4×10^{-113}	0.2089
rs973968	*FLJ43390/KCNH5*	14	A/G	0.06	0.04	0.08	0.17	0.27	0.345	0.0000	0.313	0.0000	4.2×10^{-8}	0.0119	1.3×10^{-26}	0.0508
rs55799438	*C15orf56*	15	G/A	0.05	0.06	0.02	0.41	0.05	0.298	0.0008	0.062	0.0016	8.6×10^{-41}	0.1078	1.000	0.0005
rs312893	*SEPT9*	17	A/G	0.16	0.21	0.19	0.00	0.63	0.062	0.0012	0.226	0.0005	1.6×10^{-15}	0.0129	1.8×10^{-63}	0.1099
rs2660917	*SOCS6/CBLN2*	18	C/A	0.06	0.10	0.05	0.25	0.30	0.015	0.0023	0.764	0.0003	6.5×10^{-19}	0.0376	6.4×10^{-33}	0.0667
rs10427027	*PRDX2*	19	G/A	0.08	0.07	0.08	0.10	0.56	0.553	0.0002	0.699	0.0001	0.304	0.0005	2.6×10^{-85}	0.1802
rs234709	*CBS*	21	G/A	0.09	0.12	0.15	0.44	0.93	0.159	0.0004	0.012	0.0020	2.8×10^{-30}	0.0637	1.3×10^{-135}	0.3093
rs4920037	*CBS*	21	C/T	0.03	0.01	0.03	0.23	0.16	0.315	0.0004	0.666	0.0000	2.5×10^{-27}	0.0673	1.4×10^{-18}	0.0379
rs2430212	*KLHL13*	X	A/G	0.30	0.36	0.39	0.24	0.91	0.279	0.0005	0.105	0.0010	0.186	0.0007	5.3×10^{-72}	0.1028

Chr.: chromosome, KOR: Koreans in this study, CHB: Han Chinese in Beijing, China, JTP: Japanese in Tokyo, Japan, CEU: Utah residents with Northern and Western European ancestry from the CEPH collection, YRI: Yoruba in Ibadan, Nigeria.

*Variant allele defined as the minor allele in the Korean population. †*P* value calculated by Fisher's exact test.

fered between the Korean and JPT populations. However, there was no genetic differentiation among populations because F_{ST} was less than 0.05 in all SNPs. In the allele frequency comparison between the Korean and CEU populations, significant differences were found in 99 SNPs (60.7%), and F_{ST} was above 0.05 in 10 SNPs (6.1%). In comparison between the Korean and YIR populations, 120 SNPs (73.6%) showed a significant difference in the allele frequency, and F_{ST} was above 0.05 in 26 SNPs (16.0%). Therefore, the biggest genetic divergence was observed between the Korean and YIR populations (Fig. 1).

Table 3 shows that 31 SNPs had F_{ST} above 0.05 at least once in a pairwise comparison between ethnic groups. The SNP with the largest F_{ST} value between the Korean and CEU populations was rs636437, which is located in the intergenic region between *replication factor C subunit 3* (*RFC3*) and *neurobeachin* (*NBEA*) (F_{ST}: KOR-CEU, 0.255; KOR-YIR, 0.209). The SNP with the largest F_{ST} value between the Korean and African populations was *cystathionine-β-synthase* (*CBS*) rs234709 (F_{ST}: KOR-YIR, 0.309; KOR-CEU, 0.064). The three SNPs had F_{ST} above 0.05 both in pairwise comparison between the Korean and CEU populations and between the Korean and YIR populations [*vitamin D receptor* (*VDR*) rs1544410 (F_{ST}: KOR-CEU, 0.136; KOR-YIR, 0.061), *inositol polyphosphate multikinase/ZW10 interacting kinetochore protein* (*IPMK/ZWINT*) rs4462262 (F_{ST}: KOR-CEU, 0.082; KOR-YIR, 0.207), and *mitochondrial topoisomerase I* (*TOP1MT*) rs11544484 (F_{ST}: KOR-CEU, 0.051; KOR-YIR, 0.190)].

DISCUSSION

Our interethnic comparison study for SNPs related to the body burden of heavy metals revealed that Koreans were genetically very similar to other East Asians, including Chinese and Japanese individuals but considerably different from Caucasian and African individuals. This result was consistent with the ethnic differences in previous studies on SNPs associated with asthma (17), pharmacogenesis (18), and autoimmunity (19), although direct comparison is impossible because the studied SNPs differed. The ethnic differences in SNPs are affected by genetic drift, migration, and natural selection, and verifying these differences will help us better understand the ethnic variations in disease susceptibility and phenotypes as well as complex genetic-environment interactions (20).

There are several studies reported that the body concentration of heavy metals differs across ethnicity (21,22). The U.S. National Health and Nutrition Examination Survey (NHANES) report shows that the body concentration of heavy metals in Asians was higher than in all other ethnic populations, especially for cadmium, mercury, and arsenic (23). Blood cadmium, mercury and the urinary total arsenic levels in our cohort subjects were about two, five and ten times greater than those in the U.S. population, respectively (23). Until now, it mainly focused on the ethnic differences in environmental factors including dietary habit to explain for this variation. However, our study is the first to verify the ethnic divergence in SNPs that may be related to heavy metal body burden in Koreans.

In this study, *CBS* rs234709 showed the highest F_{ST} value compared between Korean and African individuals (F_{ST} = 0.309), and moderate genetic differentiation was observed for both *CBS* rs234709 and rs4920037 in the comparison between Korean and Caucasian individuals. *CBS* gene wasselected as a candidate gene because of the association with arsenic metabolism (24). *CBS* enzyme catalyzes the synthesis of cystathionine from homocysteine. A decrease in CBS activity is associated with the increases in homocysteine concentration in the body. Elevated homocysteine can deplete S-adenosylmethionine which is a methyl donor. Therefore, a modulation in CBS activity by genetic variation might affect methylation capacity in human (24-26). Recently, the evidence for this mechanism has been reported that *CBS* rs234709 or rs4920037 variant allele were associated with an increased in monomethylarsonous acid (a less-methylated form of arsenic metabolites), while with a decrease in dimethylarsinic acid (a more-methylated form) (25,26). That is, interethnic genetic variations in enzymes involved in arsenic metabolism can affect interethnic differences in methylation capacity, which results in ethnic differences in urine arsenic methylated metabolite compositions (26,27).

In this study, there was a genetic variation between Korean and CEU populations in *Transferrin receptor 1* (*TFRC*) rs3817672 (F_{ST} = 0.0736), which is involved in iron absorption, and *VDR* rs1544410 (F_{ST} = 0.1364), which is involved in calcium absorption. Because heavy metals such as cadmium and lead are not metabolized in the body, interactions with various essential minerals during absorption and excretion processes can act as an important factor that affects body burden. Deficiency of essential metals such as iron, calcium, and zinc in the body increases absorption of heavy metals such as cadmium and lead (4). Genetic factors associated with iron homeostasis were identified by several GWAS studies (28), and the association between SNPs associated with iron homeostasis and urine cadmium concentration in non-smoking women was reported (7).

Comparison between Korean and CEU populations and between Korean and YIR populations revealed intergenic SNPs, including *RFC3/NBEA* rs636437 and *IPMK/ZWINT* rs4462262, with F_{ST} values that indicated moderate genetic differentiation. No studies on these two SNPs and body burden of heavy metals have been conducted to date, and the functions of these SNPs have not been identified. Only the association of *IPMK/ZWINT* rs4462262 with diabetes retinopathy was reported by a Taiwanese GWAS study (29).

To our knowledge, this is the first report on ethnic differ-

ences in SNPs associated with the body burden of heavy metals. In this study, we presented the Koreans allele frequencies of SNPs highly associated with the body burden of heavy metals, which were selected using a candidate-gene approach and GWAS in Korean individuals, and compared the allele frequencies with those of Caucasian, African, and other ethnic Asian populations. Compared with other ethnic Asian populations such as Chinese and Japanese people, Korean individuals were not genetically different ($F_{ST} < 0.05$). However, compared to the Caucasian and African populations, significant differences in allele frequencies were confirmed in more than 60% of the SNPs analyzed in this study, and high genetic divergence ($F_{ST} > 0.05$) was observed in ten (6.1%) and 26 (16.0%) SNPs, respectively. Because there have not been many studies on the genetic effects of the body burden of heavy metals to date, ethnic differences in SNPs associated with heavy metals confirmed in this study should be considered in future studies that address ethnic differences in heavy-metal concentrations in the body and genetic susceptibility to the body burden of heavy metals.

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