

# 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 ( $F_{\rm ST} < 0.05$ , 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- $\beta$ -synthase rs234709 (F<sub>ST</sub>: 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 Hap-Map 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 pvalue  $< 3.1 \times 10^{-4}$  (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).  $F_{\rm ST}$  among a pairwise comparison between different ethnic groups was schematized with a Manhattan plot.  $F_{\rm ST}$  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  $45.5 \pm 14.5$  years, 56.8% of all subjects was females. The

		N (%)					
Total subjects		1.487					
Total Subjects		1,107					
Gender	Males	643 (43.2)					
	Females	844 (56.8)					
Age, mean $\pm$ std.		$45.5\pm14.5$					
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)					
Smaking history	Novor amolyona	066 (65 0)					
Smoking history	The set of	900 (03.0)					
	Ex-smokers	243 (16.3)					
	Current smokers	2/8 (18./)					
Alcohol use	Non-drinkers	362 (24.3)					
	Drinkers	1125 (75.7)					
*							
Heavy metal levels							
Blood lead, unit: µg/c	L	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, un	it: µg/g creatinine	1.09 (1.05, 1.13)					
Urinary total arsenic,	unit: µg/g creatinine	102.7 (98.03, 107.60)					

Table 1. General characteristics of study subjects

<sup>\*</sup>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	А	0.003	Exome chip based	Cd
rs714282	1	GPR177	Intron	А	0.419	Exome chip based	Cd
rs3736930	1	ATP6V1G3	Complex	Т	0.057	Candidate gene approached	Cd
rs2666839	1	CENPF	Coding	Т	0.163	Exome chip based	Cd
rs34545462	1	SLC2A7	Coding	Т	0.050	Exome chip based	Hg
rs11265263	1	DUSP23/CRP	Intergenic	А	0.170	Exome chip based	Cd
rs13306731	1	SOAT1	Coding	G	0.380	Candidate gene approached	Cd, Hg
rs11118075	1	RRP15	Coding	С	0.070	Exome chip based	Hg
rs11805194	1	NUP133	Coding	С	0.140	Exome chip based	Cd
rs2479409	1	BSND/PCSK9	Intergenic	А	0.366	Exome chip based	Cd
rs35351292	1	LAPTM5	Coding	А	0.065	Exome chip based	Cd
rs41268474	1	Clorf68	Coding	А	0.068	Exome chip based	Pb
rs1284852	1	FLVCR1/VASH2	Intergenic	G	0.446	Candidate gene approached	Cd
rs58275168	1	SLC35F3	Intron	А	0.282	Exome chip based	Cd
rs1476413	1	MTHFR	Intron	А	0.176	Candidate gene approached	As
rs4845625	1	IL6R	Intron	Т	0.443	Exome chip based	Pb
rs267733	1	ANXA9	Coding	G	0.077	Exome chip based	Pb
rs2698530	2	PELI1/HSPC159	Intergenic	А	0.350	Candidate gene approached	Cd, Pb
rs1457451	2	LOC729348/LOC100131818	Intergenic	А	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	А	0.271	Exome chip based	Hg
rs2287059	2	NOL10	Coding	Т	0.114	Exome chip based	Hg

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able 2. Cor	ntinued	Gene	Location	Minor allele	MAF	Selection rationale	Related heavy me
rs10455	2	CYBRD1	LITR		0.331	Candidate gene approached	Ph
rs3747673	3	TNK?	Coding	л Т	0.331	Exome chin based	Cd
rs2293232	3	MUC4	Coding	T 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	Но
rs7640978	3	CMTM6	Intron	T	0.007	Exome chip based	Cd
rs832038	3	GABRR3	Intron	G	0.452	Candidate gene approached	Ph. 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	Т	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	MF12	Coding	Т	0.061	Candidate gene approached	Cď
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	С	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	Т	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	Cď
rs3765467	6	GLP1R	Coding	Т	0.252	Exome chip based	Hg
rs2301227	6	HLA-DPA1	Intron	С	0.073	Exome chip based	Cd, Hg
rs3129953	6	C6orf10/BTNL2	Intergenic	Т	0.083	Exome chip based	Cd
rs76100089	6	LOC729792	Coding	Т	0.203	Exome chip based	Hg
rs1800629	6	TNF/LTA	Intergenic	А	0.068	Candidate gene approached	Cd
rs17270561	6	SLC17A1	Intron	А	0.145	Candidate gene approached	Pb, Cd
rs13194984	6	BTN1A1/BTN2A1	Intergenic	Т	0.007	Candidate gene approached	Cd, Pb
rs17342717	6	SLC17A1	Intron	Т	0.008	Candidate gene approached	Cd, Pb
rs2071593	6	ATP6V1G2	UTR	Т	0.084	Candidate gene approached	Hg
rs3957356	6	GSTA1/GSTA5	Intergenic	Т	0.156	Candidate gene approached	Hg
rs932316	6	SCGN/LRRC16A	Intergenic	С	0.136	Candidate gene approached	Cd, Pb
rs12216125	6	HIST1H1A/TRIM38	Intergenic	Т	0.122	Candidate gene approached	Cd, Hg
rs1799945	6	HFE	Complex	G	0.048	Candidate gene approached	Cd, Pb
rs9357283	6	DNAH8	Coding	А	0.314	Candidate gene approached	Cd
rs4516970	6	WTAP/SOD2	Intergenic	-	0.000	Candidate gene approached	Cd, Pb
rs2274089	6	LRRC16A	Intron	А	0.031	Candidate gene approached	Cd, Pb
rs1183201	6	SLC17A1	Intron	А	0.143	Candidate gene approached	Hg
rs17883901	6	GCLC/KLHL31	Intergenic	Т	0.115	Candidate gene approached	Hg
rs2858881	6	HLA-DQB1/HLA-DQA2	Intergenic	G	0.048	Exome chip based	Hg
rs3736781	6	BTNIAI	Coding	G	0.314	Candidate gene approached	Hg
rs2142672	6	MYLIP/GMPR	Intergenic	С	0.264	Exome chip based	Pb
rs972275	6	LOC728666/RSPO3	Intergenic	G	0.458	Candidate gene approached	Cd, Pb
rs35868297	7	GALNTL5	Coding	С	0.196	Exome chip based	Cd
rs194524	7	STEAP2	Complex	А	0.213	Candidate gene approached	Pb

ref18001   7   SET / 2007	rs ID	Chr.	Gene	Location	Minor allele	MAF	Selection rationale	Related heavy metals	
sh122297   7   LOCI00288724/GLMLP4   Integenic   G   0.138   Exome chip based   Cd     sh130668   7   PONI   Complex   0.006   Candidate gene approached   Cd     sh230669   7   PONI   Complex   0.018   Exome chip based   Cd     reg87   7   PONI   Coling   A   0.025   Candidate gene approached   Hg     reg971025   7   POKB   Intron   A   0.211   Candidate gene approached   Hg     rs1916644   8   ALL2   Complex   1   0.030   Exome chip based   Cd     rs1154448   8   SCO2   Coding   C   0.106   Exome chip based   Cd     rs1762807   8   CAR45   Coding   G   0.020   Exome chip based   Pb     rs1763807   8   CAR45   Coding   G   0.020   Candidate gene approached   As     rs1763707   10   ASTMT   Intro   C   0.232   Candidate g	rs2718021	7	SEPT7/EEPD1	Intergenic	Т	0.480	Exome chip based	Cd	
sr472266   7   STS31   Comips   A   0.260   Exome chip based   Pb     sr330608   7   PVBLB4CTor/ID   Integanic   G   0.0144   Candidate gene approached   Cd, Pb     sr360102   7   DGKD   Intron   T   0.078   Fxome chip based   Cd     sr310664   8   ATEV/1B2   Intron   A   0.010   Exome chip based   Cd     sr310643   8   AVEL2   Complex   1   0.100   Exome chip based   Cd, Hg     sr3105643   8   NEL2   Coding   C   0.000   Exome chip based   Cd, Hg     sr3105850   8   SCARJ5   Coding   G   0.030   Candidate gene approached   Pb     sr3005871   8   SCARJ5   Coding   G   0.079   Exome chip based   Cd   Cd     sr3005871   8   SCARJ5   Coding   G   0.079   Exome chip based   Hg     sr3005781   0   ASMT   Interganic	rs13225097	7	LOC100288724/GIMAP4	Intergenic	G	0.188	Exome chip based	Cd	
n13306087POVICodingG0.0066Candidate gene approachedCdne6627POVIIntronN0.355Candidate gene approachedCdns69719257DCKBIntronN0.218Exome clip basedCdns1166648ATP6/11B2IntronN0.018Exome clip basedCdns11944848TOP1ATCodingA0.061Exome clip basedCdns174484356CodingC0.108Exome clip basedCdns17458478CSO/2CodingC0.016Exome clip basedCdns17458478CSA/45CodingC0.020Exome clip basedPbns17585778SCARA5CodingC0.073Candidate gene approachedPbns17585789ALADCodingC0.023Candidate gene approachedAsns17685789ORIN1CodingC0.023Candidate gene approachedAsns176857810ASMTUTRC0.326Candidate gene approachedAsns176857810ASMTUTRC0.326Candidate gene approachedAsns176857910ASMTUTRC0.326Candidate gene approachedAsns176857910ASMTCodingC0.275Candidate gene approachedAsns176857910ASSMTCodingC0.220C	rs4722266	7	STK31	Complex	А	0.260	Exome chip based	Pb	
rs2880   7   NIBACConf.0   Integrine   G   0.14   Candidate gene approached   PK     rs697   PON   Coding   A   0.35   Candidate gene approached   Hg     rs110643   8   ATPVHZ2   Complex   T   0.19   Exome chip based   Cd     rs1154444   8   CAPLAT   Coding   T   0.00   Exome chip based   Cd, Hg     rs7480458   8   CARLS   Coding   T   0.00   Exome chip based   Cd, Hg     rs7484585   8   CARLS   Coding   G   0.30   Candidate gene approached   Pb     rs8100453   9   ALLD   Coding   G   0.00   Candidate gene approached   Pb     rs8100453   9   ALLD   Coding   C   0.03   Candidate gene approached   As     rs8100453   9   ALLD   Coding   C   0.03   Candidate gene approached   As     rs810471   UTR   Cadinge   0.049   Scandidate gene approa	rs13306698	7	PON1	Coding	G	0.086	Candidate gene approached	Cd	
ref62   7   PONI   Coding   A   0.355   Candidate gene approached   Pb     rsP110634   8   ATPWTB2   Intron   A   0.211   Candidate gene approached   Hig     rs8191664   8   NELL2   Complex   T   0.193   Exome chip based   Hig     rs4752148   8   ESCO2   Coding   A   0.201   Exome chip based   Cd     rs4752148   8   CSO/66   Coding   G   0.103   Candidate gene approached   Pb     rs475318   8   CSULALS   Coding   G   0.073   Candidate gene approached   Pb     rs18184781   8   STAT   Intragenic   G   0.073   Candidate gene approached   Ps     rs18184781   9   OLV1/1   Coding   G   0.076   Cadidate gene approached   As     rs1047978   10   ASMT   Intragenic   T   0.78   Candidate gene approached   As     rs10749138   10   ASMT   Intragen	rs29880	7	INHBA/C7orf10	Intergenic	G	0.144	Candidate gene approached	Cd, Pb	
rs6971925   7   DCKB   Intron   T   0.078   Exome chip based   Cd     s110664   8   MF2H/2   Intron   A   0.211   Candidate gene approached   Hg     s1154444   8   DFP/MT   Coding   T   0.003   Exome chip based   Cd, Hg     s7434635   8   CSC/2   Coding   G   0.200   Exome chip based   Cd, Hg     s7457274   8   SC/LA/5   Coding   G   0.020   Candidate gene approached   Pb     s7457521   8   C/LA/5   Coding   G   0.079   Exome chip based   Cd     s745752   10   C/P/T/A1   Coding   G   0.079   Exome chip based   As     s743572   10   A/SMT   UTR   G   0.485   Exome chip based   As     s714572   10   A/SMT   UTR   G   0.479   Exome chip based   As     s1046778   10   A/SMT   Intro   C   0.233 <td< td=""><td>rs662</td><td>7</td><td>PONI</td><td>Coding</td><td>А</td><td>0.355</td><td>Candidate gene approached</td><td>Pb</td></td<>	rs662	7	PONI	Coding	А	0.355	Candidate gene approached	Pb	
rs1106648.MTMV1B2IntronA0.211Candidate gene approachedHgrs1154648.NELL2Complex0.003Exome chip basedCdHgrs1734488.NELL2CodingC0.100Exome chip basedCdHgrs17547488.SC02CodingC0.100Exome chip basedCdCdrs17058778.SC02CodingC0.100Exome chip basedPhrs17058778.PPPSCCSORBESIntregenicT0.004Exome chip basedPhrs180187089.ORIMICodingG0.073Galidate gene approachedAsrs104577510JEADCodingG0.073Galidate gene approachedAsrs10477810SISMITIntroC0.233Candidate gene approachedAsrs104781810NRAPCodingT0.419Exome chip basedHgrs104781810NRAPCodingC0.141Exome chip basedHgrs104781810NRAPCodingC0.141Cadidate gene approachedAsrs104781810ASSMITIntregenic0.0419Cadidate gene approachedAsrs10488510ASSMITIntregenic0.049Cadidate gene approachedAsrs104818510ASSMITIntregenic0.049Cadidate gene approachedAsrs1044223510ASSMITI	rs6971925	7	DGKB	Intron	Т	0.078	Exome chip based	Cd	
rsN19648NUL2ConglexT0.133Fxome chip basedCdrs11544488ZDP/MTCodingT0.063Exome chip basedCd, Hgrs74840858CSO766CodingG0.010Exome chip basedCdrs74840858CSUR45CodingG0.020Candidate gene approachedPhrs8475118PPPSCCSORBSIntegerieC0.073Candidate gene approachedPhrs8476739ALADCodingG0.099Exome chip basedCdrs74877810ASMTCodingG0.093Candidate gene approachedAsrs74877710ASMTCodingT0.419Candidate gene approachedAsrs74878710ASMTUTRC0.383Candidate gene approachedAsrs104787810ASMTIntegerieT0.078Exome chip basedHgrs14478410NR4/ZPINTIntegerieT0.078Candidate gene approachedAsrs104783510ASMTCodingC0.235Candidate gene approachedAsrs104783510ASMTIntergerieC0.235Candidate gene approachedAsrs104837510ASMTIntergerieG0.435Candidate gene approachedAsrs104837510ASMTIntergerieG0.435Candidate gene approachedAsrs10483510 <td>rs1106634</td> <td>8</td> <td>ATP6V1B2</td> <td>Intron</td> <td>А</td> <td>0.211</td> <td>Candidate gene approached</td> <td>Hg</td>	rs1106634	8	ATP6V1B2	Intron	А	0.211	Candidate gene approached	Hg	
rs1154444   8 <i>TOPINT</i> Coding   A   0.063   Exome chip based   Cd, Hg     rs4732748   8 <i>ESCO2</i> Coding   C   0.106   Exome chip based   Cd     rs17055207   8 <i>SCMRA5</i> Coding   G   0.320   Candidate gene approached   Pb     rs18015708   9 <i>JLD</i> Coding   G   0.073   Candidate gene approached   Pb     rs18018708   9 <i>RIN1</i> Coding   G   0.073   Candidate gene approached   As     rs10147018   10 <i>ASSMT</i> Introp   C   0.235   Candidate gene approached   As     rs1047718   10 <i>ASSMT</i> UTIR   G   0.496   Candidate gene approached   As     rs1047813   10 <i>MAP</i> Coding   T   0.479   Exome chip based   Hg     rs110439   0 <i>ASSMT</i> Intergenic   Coding   Candidate gene approached   As     rs104622   10 <i>MACC2</i> UTIR	rs8191664	8	NEIL2	Complex	Т	0.193	Exome chip based	Cď	
sr432348   8   ESC02   Coding rs74846385   T   0.200   Exome chip based Cd   Call From thip based Pb   Call Cd     sr17085207   8   SCLRJ5   Coding SCORPS   C   0.030   Candidas gene approached Pb   Pc     sr802357   9   ALAD   Coding SCORPS   C   0.032   Candidate gene approached Pb   Pc     sr803757   9   ALAD   Coding SCORPS   C   0.073   Candidate gene approached As   As     sr1045778   10   CYP1741   UTR   C   0.335   Candidate gene approached As   As     sr1047918   10   XSMT   Intron   C   0.353   Candidate gene approached As   As     sr1047918   10   ASMT   Intron   A   0.479   Candidate gene approached As   As     sr1047918   10   ASMT   Intron   A   0.491   Candidate gene approached As   As     sr1047843   10   ASMT   Intron   C   0.259   Candidate gene approached As   As	rs11544484	8	TOP1MT	Coding	А	0.063	Exome chip based	Hg	
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rs17058207 8 SC/A45 Coding G 0.32 Candidate gene approached Pb   rs4872511 8 PPP3CC/SORBS3 Intergenic T 0.084 Exome chip based Pb   rs1081708 9 <i>ALLD</i> Coding G 0.093 Candidate gene approached As   rs740373 10 <i>ASIMT</i> Intron C 0.325 Candidate gene approached As   rs104572 10 <i>ASIMT</i> UTIR G 0.496 Candidate gene approached As   rs1049178 10 <i>ASIMT</i> UTIR C 0.385 Candidate gene approached As   rs10749135 10 <i>ASIMT</i> Coding C 0.014 Candidate gene approached As   rs11049135 0 <i>ASIMT</i> Introgenic 0.0250 Candidate gene approached As   rs10788104 0.435MT Introgenic 0.0250 Candidate gene approached As   rs10494835 10 <i>ASIMT</i> Introgenic 0.0250 Candidate gene approached As   rs104966 10	rs74846385	8	C8orf86	Coding	С	0.106	Exome chip based	Cd	
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	rs1800435	9	ALAD	Coding	С	0.073	Candidate gene approached	Pb	
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rs74357210CYPTA1UTRG0.4496Candidate gene approachedAsrs10477810AS3MTUTRC0.385Candidate gene approachedAsrs104791310NRAPCodingT0.419Exome chip basedHgrs71762010ABCC2UTRA0.222Candidate gene approachedHgrs71762010ABCC2UTRA0.221Candidate gene approachedAsrs104833510AS3MTIntronA0.491Candidate gene approachedAsrs167883510AS3MTIntronC0.250Candidate gene approachedAsrs1784357210GSTO2CodingC0.250Candidate gene approachedAsrs29725510GSTO1CodingA0.150Candidate gene approachedAsrs29725510GSTO1CodingA0.150Candidate gene approachedAsrs27766710ABCC2CodingA0.245Candidate gene approachedAsrs1698011SLC2248IntronA0.245Candidate gene approachedAsrs1699113SLC2248Coding-0.000Candidate gene approachedHgrs1698113SLC2248Coding-0.000Candidate gene approachedHgrs1698115SLC2248Coding-0.000Candidate gene approachedHgrs16981 <td< td=""><td>rs3740393</td><td>10</td><td>AS3MT</td><td>Intron</td><td>Č</td><td>0.253</td><td>Candidate gene approached</td><td>As</td></td<>	rs3740393	10	AS3MT	Intron	Č	0.253	Candidate gene approached	As	
	rs743572	10	CYP17A1	UTR	G	0.496	Candidate gene approached	As	
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$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	rs10749138	10	NRAP	Coding	Т	0.419	Exome chip based	На	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	rs4462262	10	IPMK/ZWINT	Intergenic	Т	0.412	Exome chip based	Hα	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	rs717620	10	ABCC2	LITR	Δ	0.272	Candidate gene approached	Hα	
	rs11101/20	10	ADCC2	Coding	A C	0.222	Candidate gene approached	Λg	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	rs10748835	10	ASSMI	Intron	۲ ۵	0.014	Candidate gene approached	As	
$      In 10007  10  OS102 \qquad Coding  C \qquad 0.2.9  Candidate gene approached  As \\      rs 10191453  10  C100rf32/AS3MT \qquad Intergenic  G \qquad 0.435  Candidate gene approached  As \\      rs 227367  10  GST01 \qquad Coding  A \qquad 0.149  Candidate gene approached  As \\      rs 2273697  10  ABCC2 \qquad Coding  A \qquad 0.080  Candidate gene approached  As \\      rs 3740066  10  ABCC2 \qquad Coding  A \qquad 0.045  Candidate gene approached  As \\      rs 3740390  10  AS3MT \qquad Intron  A \qquad 0.245  Candidate gene approached  As \\      rs 3740390  10  AS3MT \qquad Intron  A \qquad 0.250  Candidate gene approached  As \\      rs 3740390  10  AS3MT \qquad Intron  A \qquad 0.250  Candidate gene approached  As \\      rs 3740390  10  AS3MT \qquad Intron  C \qquad 0.316  Candidate gene approached  Ag \\      rs 10891692  11  FAM55A \qquad Coding  C \qquad 0.316  Candidate gene approached  Hg \\      rs 4149182  11  SLC22A8 \qquad Coding  - \qquad 0.000  Candidate gene approached  Hg \\      rs 45566039  11  SLC22A8 \qquad Coding  - \qquad 0.000  Candidate gene approached  Hg \\      rs 4752605  11  SLC22A8 \qquad Coding  - \qquad 0.000  Candidate gene approached  Hg \\      rs 4752605  11  SLC4A8 \qquad Coding  - \qquad 0.000  Candidate gene approached  Hg \\      rs 4752605  11  SLC4A8 \qquad Coding  - \qquad 0.000  Candidate gene approached  Hg \\      rs 4752605  11  SLC4A8 \qquad Coding  - \qquad 0.000  Candidate gene approached  Hg \\      rs 236918  11  SLC4A8 \qquad Coding  G  0.082  Exome chip based \qquad Cd \\      rs 4752805  11  PTPM \qquad Intron  G  0.241  Exome chip based \qquad Cd \\      rs 4149170  11  SLC2A6 \qquad UTR  A  0.278  Candidate gene approached  Hg \\      rs 12291075  12  SLC01B1 \qquad Introm  A  0.278  Candidate gene approached  Hg \\      rs 12291075  12  SLC01B1 \qquad Introm  A  0.249  Candidate gene approached  Hg \\      rs 1111245  12  NA473SYTT \qquad Intergenic  G  0.345  Candidate gene approached  Hg \\      rs 1111245  12  NA73SYTT \qquad Intergenic  G  0.345  Candidate gene approached  Hg \\      rs 1111245  12  NA73SYTT \qquad Introm  A  0.278  Candidate $	1510/46655	10	ASSW1 CSTO2	Coding	A C	0.491	Candidate gene approached	AS	
$      Introp 14.53  10 \qquad ASSM1 \qquad Introp C \qquad 0.250  Caldidate gene approached As       sr2085104  10 \qquad C100rf32/ASSMT \qquad Intergenic G \qquad 0.435  Candidate gene approached As       rs2297235  10 \qquad GSTO2 \qquad UTR \qquad G \qquad 0.149  Candidate gene approached As       rs2273697  10 \qquad ABCC2 \qquad Coding A \qquad 0.080  Candidate gene approached As       rs2740066  10 \qquad ABCC2 \qquad Coding A \qquad 0.245  Candidate gene approached Hg       rs37400360  10 \qquad ASSMT \qquad Intron A \qquad 0.250  Candidate gene approached As       rs10891692  11 \qquad FAM55A \qquad Coding C \qquad 0.382  Exome chip based \qquad Cd       rs10891692  11 \qquad FAM55A \qquad Coding G \qquad 0.176  Candidate gene approached As       rs10891692  11 \qquad SLC22A8 \qquad Intron C \qquad 0.316  Candidate gene approached Hg       rs4149182  11 \qquad SLC22A8 \qquad Coding - \qquad 0.000  Candidate gene approached Hg       rs41568496  11 \qquad SLC22A8 \qquad Coding - \qquad 0.000  Candidate gene approached Hg       rs45566039  11 \qquad SLC22A8 \qquad Coding - \qquad 0.000  Candidate gene approached Hg       rs45566039  11 \qquad SLC22A8 \qquad Coding - \qquad 0.000  Candidate gene approached Hg       rs4526209  11 \qquad SLC22A8 \qquad Coding G \qquad 0.0499  Candidate gene approached Hg       rs1047462  11 \qquad KLA00999 \qquad Intron G \qquad 0.444  Candidate gene approached Hg       rs1236209  11 \qquad CCDC83 \qquad Coding G \qquad 0.082  Exome chip based \qquad Hg       rs455805  11 \qquad PTPRJ \qquad Intron C \qquad 0.444  Candidate gene approached Hg       rs4752805  11 \qquad PTPRJ \qquad Intron G \qquad 0.211  Exome chip based \qquad Hg       rs122654  12  LOC341378/CKAP4 \qquad Intergenic G \qquad 0.345  Candidate gene approached Hg       rs122654  12  LOC341378/CKAP4 \qquad Intergenic G \qquad 0.345  Candidate gene approached Hg       rs122654  12  LOC100137138/CVL2 \qquad Intergenic G \qquad 0.345  Candidate gene approached Hg       rs122654  12  LOC100137138/CVL2 \qquad Intergenic G \qquad 0.345  Candidate gene approached Hg       rs122664  12  HNF1A \qquad Coding \ C \qquad 0.454  Candidate gene approached Hg       rs1264196  12  HNF1A \qquad Coding \ C \qquad 0.454  Candidate gene approached Hg       rs264196  12  HNF1A \qquad Coding \ C \qquad 0.4$	15130097	10	452102 4521/T	Lintron	C	0.259	Candidate gene approached	Cu A a	
	rs11191455	10	A55MI	Intron	C	0.250	Candidate gene approached	AS	
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	rs3/40390	10	AS3MI	Intron	A	0.250	Candidate gene approached	As	
	rs10891692	11	FAM35A	Coding	C	0.382	Exome chip based		
rs414918211SLC22A8IntronC0.316Candidate gene approachedHgrs1156849611SLC22A8Coding-0.000Candidate gene approachedHgrs4556603911SLC22A8Coding-0.000Candidate gene approachedHgrs7703028611SLC22A8Coding-0.000Candidate gene approachedHgrs1004746211KLA40999IntronG0.499Candidate gene approachedHgrs23691811PCSK7IntronC0.444Candidate gene approachedHgrs415017011SLC22A6UTRA0.278Candidate gene approachedHgrs414917011SLC22A6UTRA0.278Candidate gene approachedHgrs1222965412LOC10131138/CUX2IntergenicG0.345Candidate gene approachedHgrs1111124512NAV3/SYT1IntergenicC0.080Exome chip basedCdrs29107512SLC01B1CodingT0.422Candidate gene approachedPbrs1106628012LOC100287871IntronA0.249Candidate gene approachedPbrs435419612SLC01B1CodingG0.160Exome chip basedPbrs430484012CLC4DCodingG0.259Candidate gene approachedAsrs1106628012LOC100287871IntronG0.259Candi	rs1695	11	GSIPI	Coding	G	0.1/6	Candidate gene approached	Ca, Hg	
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rs246419612HNF1ACodingC0.454Candidate gene approachedPbrs1106628012LOC100287871IntronA0.178Exome chip basedPbrs430484012CLEC4DCodingG0.160Exome chip basedHgrs88538912GPR133IntronG0.423Exome chip basedPbrs156437012SLCO1B1IntronC0.259Candidate gene approachedAsrs1084297112PZPCodingT0.063Exome chip basedHgrs1712471512LARP4ComplexC0.079Exome chip basedCd, Hgrs75734312VDRIntronA0.190Candidate gene approachedPb	rs7975232	12	VDR	Intron	А	0.249	Candidate gene approached	Pb	
rs1106628012LOC100287871IntronA0.178Exome chip basedPbrs430484012CLEC4DCodingG0.160Exome chip basedHgrs88538912GPR133IntronG0.423Exome chip basedPbrs156437012SLCO1B1IntronC0.259Candidate gene approachedAsrs1084297112PZPCodingT0.063Exome chip basedHgrs1712471512LARP4ComplexC0.079Exome chip basedCd, Hgrs75734312VDRIntronA0.190Candidate gene approachedPb	rs2464196	12	HNF1A	Coding	С	0.454	Candidate gene approached	Pb	
rs430484012CLEC4DCodingG0.160Exome chip basedHgrs88538912GPR133IntronG0.423Exome chip basedPbrs156437012SLCO1B1IntronC0.259Candidate gene approachedAsrs1084297112PZPCodingT0.063Exome chip basedHgrs1712471512LARP4ComplexC0.079Exome chip basedCd, Hgrs75734312VDRIntronA0.190Candidate gene approachedPb	rs11066280	12	LOC100287871	Intron	А	0.178	Exome chip based	Pb	
rs88538912GPR133IntronG0.423Exome chip basedPbrs156437012SLC01B1IntronC0.259Candidate gene approachedAsrs1084297112PZPCodingT0.063Exome chip basedHgrs1712471512LARP4ComplexC0.079Exome chip basedCd, Hgrs75734312VDRIntronA0.190Candidate gene approachedPb	rs4304840	12	CLEC4D	Coding	G	0.160	Exome chip based	Hg	
rs156437012SLCO1B1IntronC0.259Candidate gene approachedAsrs1084297112PZPCodingT0.063Exome chip basedHgrs1712471512LARP4ComplexC0.079Exome chip basedCd, Hgrs75734312VDRIntronA0.190Candidate gene approachedPb	rs885389	12	GPR133	Intron	G	0.423	Exome chip based	Pb	
rs1084297112PZPCodingT0.063Exome chip basedHgrs1712471512LARP4ComplexC0.079Exome chip basedCd, Hgrs75734312VDRIntronA0.190Candidate gene approachedPb	rs1564370	12	SLCO1B1	Intron	С	0.259	Candidate gene approached	As	
rs1712471512LARP4ComplexC0.079Exome chip basedCd, Hgrs75734312VDRIntronA0.190Candidate gene approachedPb	rs10842971	12	PZP	Coding	Т	0.063	Exome chip based	Hg	
rs757343 12 VDR Intron A 0.190 Candidate gene approached Pb	rs17124715	12	LARP4	Complex	С	0.079	Exome chip based	Cd, Hg	
	rs757343	12	VDR	Intron	А	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	С	0.340	Candidate gene approached	Ph
rs671	12	ALDH2	Coding	A	0.158	Exome chip based	Ph
rs1544410	12	VDR	Intron	A	0.051	Candidate gene approached	Ph
rs60683621	12	OR6C70	Coding	G	0.031	Exome chip based	Ησ
rs17278868	12	$I \Delta T S^2/S \Delta P 18$	Intergenic	C	0.165	Exome chip based	На
rs636437	13	REC3/NRE4	Intergenic	G	0.132	Exome chip based	Cd Ha
r:073068	13	EL 1/3200/KCNH5	Intergenic	G	0.152	Condidate gene approached	Cd, Hg
139/3900	14	SLC749	LITD	U T	0.039	Candidate gene approached	Cu Ua
18120/9340	14	SLC7A0	UIK	I C	0.460	Candidate gene approached	пg Ца
ro24601152	14	SLC740	Coding	U	0.090	Candidate gene approached	пg Ца
1834091133	14	SLC/A0	Coding	- T	0.000	Candidate gene approached	ng A -
rs1130050	14		Coding	I T	0.227	Candidate gene approached	AS
rs8005905	14	HSP90AA1	Coding	I C	0.223	Candidate gene approached	Hg
rs2234636	14	SLC39A2	Coding	C	0.424	Candidate gene approached	As
rs11549465	14	HIFIA	Coding	1	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	Т	0.465	Candidate gene approached	Cd
rs11643815	16	MT4	Coding	А	0.004	Candidate gene approached	Hg
rs28366003	16	MT2A	UTR	G	0.127	Candidate gene approached	Cd
rs9936741	16	MT1M	UTR	С	0.069	Candidate gene approached	Hg
rs12919719	16	CDH1	Intron	G	0.164	Candidate gene approached	As
rs11076161	16	MT1A	Intron	А	0.292	Candidate gene approached	Cd
rs4148356	16	ABCC1	Coding	А	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	Т	0.379	Candidate gene approached	Hg
rs10636	16	MT2A	UTR	С	0.266	Candidate gene approached	Cd
rs3785879	17	LOC100130148/MAPT	Intergenic	А	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	Т	0.070	Exome chip based	Cd
rs7216284	17	GGT6	Coding	А	0.146	Candidate gene approached	Cd
rs312893	17	SEPT9	Intron	Т	0.163	Exome chip based	Cd
rs3744807	17	PYCR1	UTR	Т	0.048	Exome chip based	Hg
rs2660917	18	SOCS6/CBLN2	Intergenic	С	0.057	Candidate gene approached	Cď
rs2276199	18	PSTPIP2	Coding	G	0.439	Exome chip based	Pb
rs11555891	19	IRGC	Coding	A	0.132	Exome chip based	Но
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	Hσ
rs1043673	19	NI RP2	Coding	Δ	0.225	Candidate gene approached	Cd
rs3761144	20	GSS/MYH7B	Intergenic	C	0.223	Candidate gene approached	Cu Hα
rs1056720	20	CDC25R	Compley	т	0.331	Candidate gene approached	Cd
rs2762034	20	CVP2441		1	0.331	Exome chin based	Cd
182/02934	20		UIN	A T	0.114	Exome chip based	Cd
184925560	20	LAMAJ EEDMTI	Cadina	1	0.223	Exome chip based	
1802200482	20		Luture	A	0.071	Exome chip based	
rs01200027	20	V ST MIZL	Intron	A	0.4/2	Exome chip based	ru
rs492003/	21		Intron	A	0.026	Candidate gene approached	AS
rs234709	21		Intron	I	0.091	Candidate gene approached	AS
rs855791	22	IMPROSO	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	Х	KLHL13	Intron	С	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  $2.21 \,\mu\text{g/dL}$ ,  $4.05 \,\mu\text{g/L}$  and  $1.06 \,\mu\text{g/L}$ , respectively. The geometric mean concentrations of cadmium and total arsenic in urine were 1.06,  $102.7 \,\mu\text{g/g}$  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).

SNIP ID Gono gumbal		Cha	Referent/	Variant allele <sup>*</sup> frequency				KOR versus CHB		KOR versus JPT		KOR versus CEU		KOR versus YIR		
SNP ID	Gene symbol	Chir.	variant allele*	KOR	CHB	JPT	CEU	YIR	$P^{\dagger}$	$F_{\rm ST}$	$P^{\dagger}$	$F_{\rm ST}$	$P^{\dagger}$	$F_{\rm ST}$	$P^{\dagger}$	$F_{\rm ST}$
rs2479409	BSND/PCSK9	1	T/C	0.37	0.32	0.39	0.65	0.79	0.115	0.0008	0.518	0.0002	$8.1 \times 10^{-17}$	0.0225	$5.9 \times 10^{-46}$	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	$1.0 \times 10^{-32}$	0.0467	$4.2 \times 10^{-105}$	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	$1.5 \times 10^{-19}$	0.0283	$1.1 \times 10^{-52}$	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	$8.7  imes 10^{-28}$	0.0388	8.9×10 <sup>-79</sup>	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	$2.1 \times 10^{-15}$	0.0148	$6.8  imes 10^{-56}$	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	$1.6 \times 10^{-97}$	0.1643
rs1830084	TF/SRPRB	3	G/A	0.47	0.58	0.50	0.65	0.91	$3.9 \times 10^{-4}$	0.0039	0.447	0.0002	$4.0 \times 10^{-7}$	0.0080	$9.2 \times 10^{-53}$	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	$3.7 \times 10^{-42}$	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	$5.4 \times 10^{-36}$	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	$3.6 \times 10^{-11}$	0.0109	$1.7 \times 10^{-132}$	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	$7.3  imes 10^{-40}$	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	$3.7 \times 10^{-38}$	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	$3.8 \times 10^{-5}$	0.0063	0.003	0.0019	$4.2 \times 10^{-26}$	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	$6.4 \times 10^{-25}$	0.0513	$1.4  imes 10^{-86}$	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	$1.1 \times 10^{-61}$	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	$8.9 \times 10^{-5}$	0.0054	$8.8 \times 10^{-85}$	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	$7.8  imes 10^{-39}$	0.0820	$6.4  imes 10^{-98}$	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	$8.5 \times 10^{-75}$	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	$5.5 \times 10^{-5}$	0.0032	$2.2 \times 10^{-57}$	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	$5.7 \times 10^{-56}$	0.1364	$4.7 \times 10^{-30}$	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	$6.6 \times 10^{-13}$	0.0160	$8.9 \times 10^{-54}$	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	$1.1 \times 10^{-61}$	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	$2.4 \times 10^{-133}$	0.2552	$5.4 \times 10^{-113}$	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	$4.2 \times 10^{-8}$	0.0119	$1.3 \times 10^{-26}$	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	$8.6 \times 10^{-41}$	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	$1.6 \times 10^{-15}$	0.0129	$1.8 \times 10^{-63}$	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	$6.5  imes 10^{-19}$	0.0376	$6.4 \times 10^{-33}$	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	$2.6 \times 10^{-85}$	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	$2.8 \times 10^{-30}$	0.0637	$1.3 \times 10^{-135}$	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	$2.5 \times 10^{-27}$	0.0673	$1.4  imes 10^{-18}$	0.0379
rs2430212	KLHL13	Х	A/G	0.30	0.36	0.39	0.24	0.91	0.279	0.0005	0.105	0.0010	0.186	0.0007	$5.3 \times 10^{-72}$	0.1028

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

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.

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fered between the Korean and JPT populations. However, there was no genetic differentiation among populations because  $F_{\rm ST}$  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  $F_{\rm ST}$  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  $F_{\rm ST}$  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  $F_{\rm ST}$  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<sub>ST</sub>: KOR-CEU, 0.255; KOR-YIR, 0.209). The SNP with the largest  $F_{\rm ST}$  value between the Korean and African populations was cystathionine- $\beta$ -synthase (CBS) rs234709 ( $F_{ST}$ : KOR-YIR, 0.309; KOR-CEU, 0.064). The three SNPs had  $F_{\rm ST}$  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<sub>ST</sub>: KOR-CEU, 0.136; KOR-YIR, 0.061), inositol polyphosphate multikinase/ZW10 interacting kinetochore protein (IPMK/ZWINT) rs4462262 (F<sub>ST</sub>: 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 geneticenvironment 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  $F_{\rm ST}$  value compared between Korean and African individuals ( $F_{\rm ST}$  = 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 lessmethylated 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 ( $F_{\rm ST}$  < 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 ( $F_{\rm ST} > 0.05$ ) 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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