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Preliminary study of genome-wide association identifies novel susceptibility genes for serum mineral elements in the Chinese Han population

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Abstract

Mineral elements (copper (Cu), zinc (Zn), calcium (Ca), magnesium (Mg), iron (Fe)) play important biological roles in enzymes, hormones, vitamins, and normal metabolism. The deficiency of mineral elements can lead to abnormal physiological functions. And some elements (such as lead (Pb)) are harmful to the body. We aim to identify genetic loci which can influence the serum levels of mineral elements (Cu, Zn, Ca, Mg, Fe, and Pb). Genotyping was performed using Applied Biosystems Axiom™ PMDA in 587 individuals, and 6,423,076 single-nucleotide polymorphisms (SNPs) were available for the genome-wide association study (GWAS) analysis. The association between genotype and phenotype was analyzed using mixed linear regression (additive genetic model) adjusting by age and gender combined with identical by descent (IBD) matrix. Genetic loci in *BCHE-LOC105374194*, *DTX2P1-UPK3BP1-PMS2P11*, *VAT1L*, *LINC00908-LINC00683*, *LINC01310-NONE*, and rs6747410 in *VWA3B* were identified to be associated with serum Cu element concentration ($p < 5 \times 10^{-6}$). *ADAMTSL1* rs17229526 ($p = 4.96 \times 10^{-6}$) was significantly associated with serum Zn element levels. Genetic loci in *LRP1B*, *PIGZ-MELTF*, *LINC01365-LINC02502*, and *HAPLN3* were related to serum Ca element levels ($p < 5 \times 1\ 0^{-6}$). Three SNPs in *ALPK1*, *ASAP1-ADCY8* and *IER3IP1-SKOR2* also achieved a significant association with Mg element levels ($p < 5 \times 10^{-6}$). *TACSTD2-MYSM1*, *LRP1B*, and *ASAP1-ADCY8* showed suggestive associations with serum Fe element levels ($p < 5 \times 10^{-6}$). Moreover, the two most significant SNPs associated with Pb were rs304234 in *CADPS-LINC00698* ($p = 2.47 \times 10^{-6}$) and rs12666460 in *LOC101928211-GPR37* ($p = 1.81 \times 10^{-6}$). In summary, we reported 19 suggestive loci associated with serum mineral elements in the Chinese Han population. These findings provided new insights into the potential mechanisms regulating serum mineral elements levels.

Keywords GWAS · Serum mineral elements · Chinese Han population · Applied Biosystem Axiom™ PMDA

Introduction

The metals are essential but very limited in humans. These mineral elements play important biological roles in enzymes, hormones, vitamins, and normal metabolism [1]. The deficiency of these mineral elements can lead to abnormal physiological functions in humans, and ultimately lead to varieties of relevant diseases and disorders. Fortunately, those problems mentioned

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above can be prevented or reversed by appropriate supplementation [2]. Adequate intake of such elements as copper (Cu), zinc (Zn), and iron (Fe) supports Th1/Th2-mediated immune response and produces sufficient proinflammatory cytokines [3]. The concentration of calcium (Ca) is associated with maintaining normal neuromuscular activity [4]. Magnesium (Mg) is a divalent cation that is important for bone and calcium metabolism and the normal secretion of parathyroid hormone [5]. Heavy metal pollutants such as lead (Pb) may also contribute to the genesis of coronary atherosclerosis and hypertension [6]. Serum concentrations of mineral elements have been shown to have a component with heritability [7].

The identification of suggestive loci and genes associated with circulating mineral element concentrations may provide insights into physiologic regulators of mineral element homeostasis. Genome-wide association study (GWAS) has made a major contribution to our understanding of the genetics of complex disorders [8]. At present, it has been reported that some loci are closely related to serum mineral elements levels. Beben Benyamin et al. have identified eleven iron-related significant loci (*HFE*, *TF*, *TFR2*, and *TMPRSS6*) [9]. Previous population-based studies have identified two loci on chromosome 1 (rs1175550 and rs2769264) for Cu and three loci on chromosomes 8, 15, and X (rs1532423, rs2120019, and rs4826508) for Zn [10]. It was found that common loci at six genes (*MUC1*, *TRPM6*, *SHROOM3*, *ATP2B1*, *DCDC5*, and *MDS1*) were contributed to circulate Mg concentrations [7]. Esther Ng et al. reported some novel genetic variants associated with whole blood levels of toxic metals [11]. However, these loci can only be used to explain parts of the heritability of mineral elements, and many loci have not been discovered yet. In addition, previous large-scale studies are focusing on European and American populations, and the genetic contribution to circulating mineral element concentrations in the Chinese population has not been fully understood.

To identify genetic loci which have an influence on the serum levels of mineral elements (Cu, Zn, Ca, Mg, Fe, and Pb), we performed a GWAS using 6,423,076 imputed single-nucleotide polymorphisms (SNPs) in 587 healthy Chinese Han population.

Material and Method

Study Cohorts

A total of 587 individuals (285 females and 302 males) were recruited from the annual checkup of Hainan Affiliated Hospital of Hainan Medical University for GWAS analyses. All participants were healthy Chinese Han population. Subjects with infections and immunological diseases, tumors, or known disease were excluded in this study. Demographic and clinical information was collected from questionnaires and/or medical records. All participating cohorts provided written informed consents. The protocols were approved by the institutional review boards of Hainan Affiliated Hospital of Hainan Medical University, and were in the Declaration of Helsinki.

GWAS Genotyping

Approximately 5 mL peripheral blood samples were collected from each participant in EDTA-coated tubes. Genomic DNA was extracted from the blood samples using a GoldMag DNA isolation Kit (GoldMag Co., Ltd., Xi'an, China). All participants were genotyped using Applied Biosystems Axiom™ Precision Medicine Diversity Array (PMDA) on GeneTitan™ Multi-Channel Instrument (Thermo Fisher, CA, USA). Genotype clustering was analyzed using the Axiom Analysis Suite 6.0 software. Quality control (QC) was performed based on sample calling rate > 0.95, maker calling rate > 0.90, and Hardy-Weinberg equilibrium (HWE) $> 5 \times 10^{-06}$. After removing Indel, copy number variation (CNV), duplication and loci from sex chromosome, and QC, 796,288 SNPs were available for subsequent analyses.

Genotype Imputation

Genome-wide data were imputed to 9336,679 markers from phase 3 of 1000 genome haplotype reference panel using IMPUTE2 software. Taking into account the uncertainty of imputation, Gold Helix SNP & Variation Suite 8.7 software was used for the association analysis. Loci with a minor allele frequency (MAF) < 1% and non bi-allelic were removed. After QC and imputation, 6,423,076 SNPs were available for the final analyses.

Data Analysis

The association between genotype and phenotype (mineral elements) was analyzed using mixed linear regression (additive genetic model) adjusting by age and gender combined with identical by descent (IBD) matrix using the PLINK software. The concentrations of mineral elements were normalized using rank-based inverse normal transformations. Locus regional plots were constructed by the LocusZoom 1.1 software (https://statgen.github.io/localzoom/). Manhattan plots and quantile-quantile (QQ) plots were generated by $-\log_{10}$ (p value) using the R-package. $p < 5 \times 10^{-6}$ means a statistical significance for the GWAS analysis.

Results

Overall, 587 individuals (44.39 ± 9.40 years) were recruited in the study. The characteristics of subjects including mean ages,

gender distributions, body mass index (BMI), and serum levels of mineral elements (Cu, Zn, Ca, Mg, Fe, and Pb) are presented in Table 1. After having stringent QC filters, 6,423,076 imputed SNPs were analyzed to the discovery analyses of loci associated with serum concentrations of mineral elements.

In GWAS, 105 loci in different chromosomal regions with suggestive significance of p values $< 5 \times 10^{-6}$ are shown in Suppl_ Table 1. Manhattan plot (Figure 1) exhibited the chromosome location of suggestive loci for serum levels of Cu (39 loci), Zn (1 locus), Ca (5 loci), Mg (21 loci), Fe (33 loci), and Pb (6 loci). QQ plots for serum levels of mineral elements are displayed in Figure 2. The p value at the point of deviation from the band in the QQ plot was used as the threshold for suggestive associations.

Table 2 presents 19 selected top loci (p-values) of each chromosome for serum mineral elements levels. Regional plots of significant loci associated with serum concentrations of mineral elements are displayed in Suppl_ Figure 1 (Cu), Suppl _Figure 2 (Zn), Suppl_ Figure 3 (Ca), Suppl_ Figure 4 (Mg), Suppl_ Figure 5 (Fe), and Suppl_ Figure 6 (Pb). Six loci were associated with serum Cu element concentration, including rs68128869 in *BCHE-LOC105374194* ($p = 4.47 \times 10^{-06}$), rs12673824 in *DTX2P1-UPK3BP1-PMS2P11* ($p = 3.23 \times 10^{-06}$), rs116919355 in *VAT1L* ($p = 2.02 \times 10^{-06}$), rs186084489 in *LINC00908-LINC00683* ($p = 3.18 \times 10^{-07}$), rs17000827 in L*INC01310-NONE* ($p = 3.75 \times 10^{-06}$), and rs6747410 in *VWA3B* ($p = 4.06 \times 10^{-06}$). Zn element levels were significant associated with rs17229526 on chromosome 9 ($p = 4.96 \times 10^{-06}$) in the intron region of *ADAMTSL1* gene. rs76917806 in *LRP1B* ($p = 5.9 \times 10^{-07}$), rs111232694 in *PIGZ-MELTF* ($p = 3.5 \times 10^{-06}$), rs72684540 in *LINC01365-LINC02502* ($p = 3.4 \times 10^{-06}$), and rs8039131 in *HAPLN3* ($p = 4.4 \times 10^{-06}$) were related to serum Ca element levels. Three SNPs also achieved the significant association with Mg element levels with p values of 4.2×10^{-06}, 1.3×10^{-06}, and 3×10^{-06} for rs2074379 in *ALPK1*, rs72728275 in *ASAP1-ADCY8*, and rs117060920 in *IER3IP1-SKOR2*, respectively. rs232870 in *TACSTD2-MYSM1* ($p = 1.9 \times 10^{-06}$), rs76917806 in *LRP1B* ($p = 5 \times 10^{-06}$), and rs28428945 in *ASAP1-ADCY8* ($p = 1.4 \times 10^{-07}$) showed suggestive associations with serum Fe element levels. Moreover, the two most significant SNPs associated with Pb were rs304234 in *CADPS-LINC00698* ($p = 2.47 \times 10^{-06}$) and rs12666460 in *LOC101928211-GPR37* ($p = 1.81 \times 10^{-06}$).

Table 1 Characteristics of samples used in the GWAS

Characteristics	GWAS
n	587
Age (years, mean ± SD)	44.39 ± 9.40
Female, *n* (%)	285 (48.55%)
BMI (kg/m^2, mean ± SD)	24.39 ± 4.78
Cu (μmol/L, mean ± SD)	19.21 ± 3.78
Zn (μmol/L, mean ± SD)	95.06 ± 11.40
Ca (mmol/L, mean ± SD)	1.33 ± 0.13
Mg (mmol/L, mean ± SD)	1.47 ± 0.15
Fe (mmol/L, mean ± SD)	8.19 ± 0.96
Pb (μg/L, mean ± SD)	22.18 ± 14.96

GWAS, genome-wide association study; *SD*, standard deviation; *BMI*, body mass index

Discussion

In this study, our study identified 19 loci with suggestive significance of p values $< 5 \times 10^{-6}$ related to circulating levels of Cu (6 loci), Zn (1 locus), Ca (4 loci), Mg (3 loci), Fe (3 loci), and Pb (2 loci), which explain a part of the variation in these mineral elements. This is the first GWAS investigating the contribution of genetic loci to normal physiologic variation in serum concentrations of mineral elements in the Chinese Han population.

Cu, a cofactor of many metalloenzymes, plays an important role in the human metabolism. The disturbance of Cu homeostasis cause strong pathological manifestations, such as severe chronic liver diseases including Wilson's disease and idiopathic toxicosis [12]. In our study, six loci (rs68128869 in *BCHE-LOC105374194*, rs12673824 in *DTX2P1-UPK3BP1-PMS2P11*, rs116919355 in *VAT1L*, rs186084489 in *LINC00908-LINC00683*, rs17000827 in L*INC01310-NONE*, and rs6747410 in *VWA3B*) were associated with serum Cu element concentration. *BCHE* gene is located on chromosome 3q26.1. The function of *LOC105374194*, *DTX2P1*, *UPK3BP1*, *PMS2P11*, *LINC00908*, *LINC00683*, *LINC01310*, and *NONE* genes deserve further study. In recent years, some studies have shown that flavanone derivatives complexed to Cu can act as selective cholinesterase inhibitors against butyrylcholinesterase [13]. The details of possible links between *VAT1L* (chromosome 16q23.1) and *VWA3B* (chromosome 2q11.2) genes and circulating Cu concentration are still unknown.

Zinc is a component of most enzymes, and free Zn is an essential intracellular signaling molecule [14, 15]. Zn deficiency has been related to cardiovascular disease, diabetes, immune dysfunction, and infectious diseases [16–18]. Zn element levels were significant associated with rs17229526 on chromosome 9 in the intron region of *ADAMTSL1* gene. ADAMTS1, a secreted protein, is a member of family of ADAMTS proteases, which a disintegrin and metalloprotease with thrombospondin repeats, and the zinc-binding domain may affect the catalytic activity of ADAMTS1 [19]. The contribution of *ADAMTSL1* polymorphisms to Zn concentration needs to be further studied.

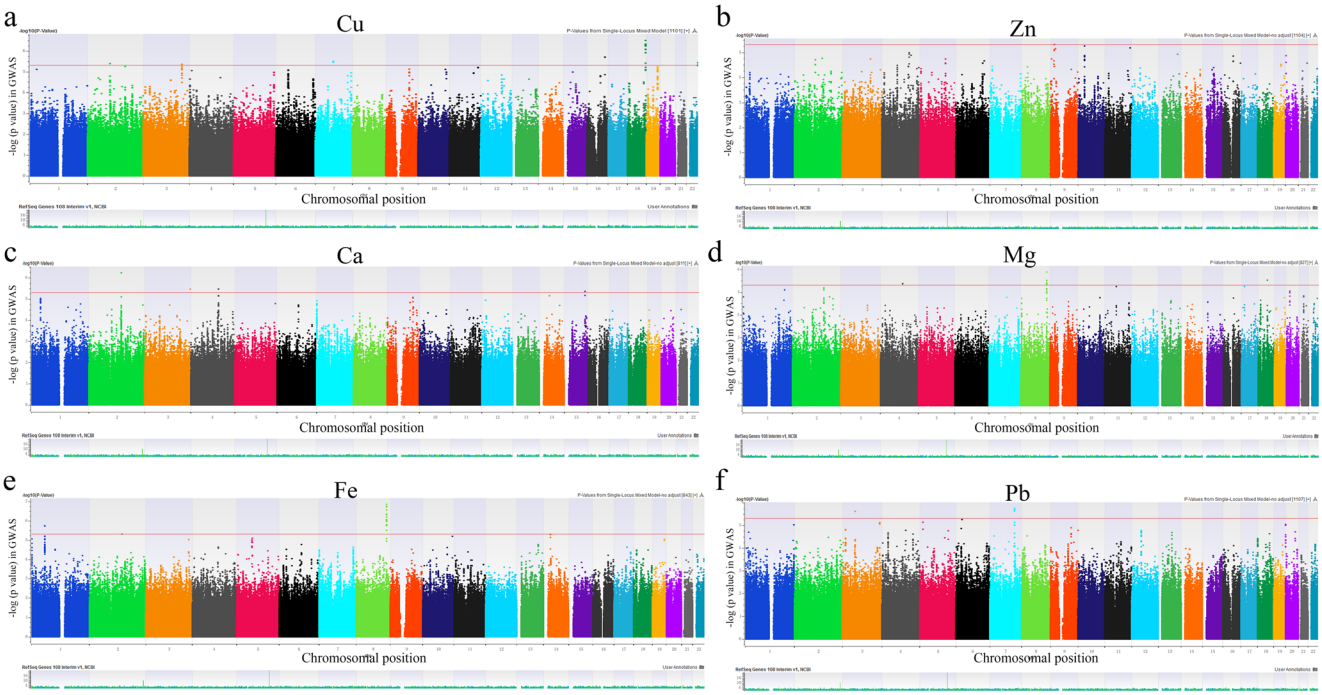

Fig. 1 Manhattan plot for loci associated with serum levels of Cu (**a**), Zn (**b**), Ca (**c**), Mg (**d**), Fe (**e**), and Pb (**f**)

Approximately 99% of Ca is usually contained in the bone; the remainder is present intracellular or circulating. Plasma Ca is mainly influenced by parathyroid hormone [20]. Ca accumulation inside mitochondria contributes to a wide range of

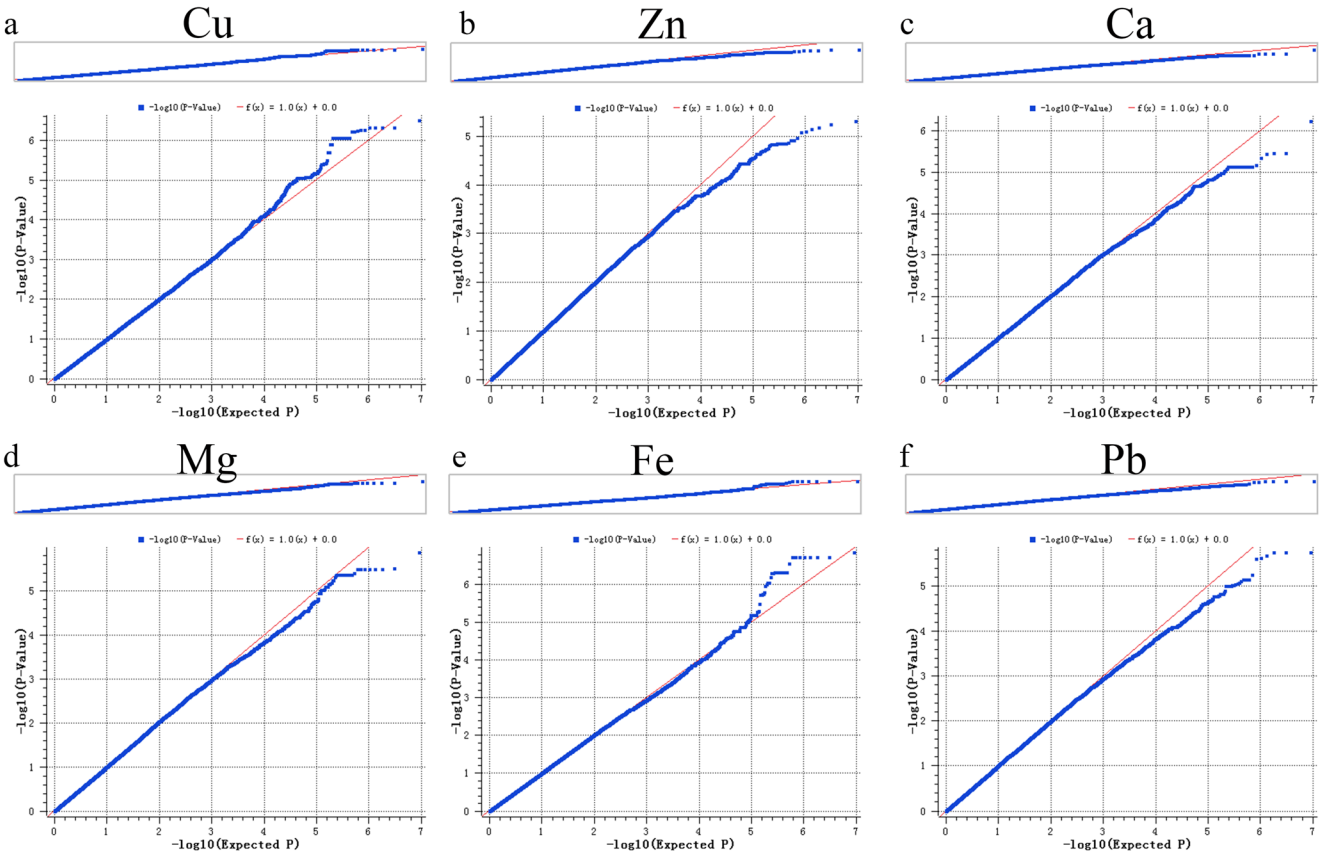

Fig. 2 Quantile-quantile (QQ) plot for serum levels of Cu (**a**), Zn (**b**), Ca (**c**), Mg (**d**), Fe (**e**), and Pb (**f**)

Table 2 Significant loci associated with mineral element from the GWAS cohorts (Top 19)

Characteristics	SNP ID	Chr	Position	REF/ ALT	SNP function	RefGene	MAF	β	SE	P
Cu	rs68128869	3	166096924	C/G	Intergenic	*BCHE;LOC105374194*	0.218	0.220	1.498	4.47E-06
	rs12673824	7	76919705	T/C	Intergenic	*DTX2P1-UPK3BP1-PMS2P11*	0.184	0.227	1.498	3.23E-06
	rs116919355	16	77860019	G/C	Intronic	*VAT1L*	0.170	0.428	1.497	2.02E-06
	rs186084489	18	76604657	T/C	Intergenic	*LINC00908;LINC00683*	0.028	0.315	1.496	3.18E-07
	rs17000827	22	49354482	C/T	Intergenic	*LINC01310;NONE*	0.047	0.322	1.491	3.75E-06
	rs6747410	2	98250312	A/G	Intronic	*VWA3B*	0.084	0.432	1.498	4.06E-06
Zn	rs17229526	9	18619468	C/G	Intronic	*ADAMTSL1*	0.049	0.047	1.946	4.96E-06
Ca	rs76917806	2	140911148	A/T	Intronic	*LRP1B*	0.018	− 0.031	0.434	5.9E-07
	rs111232694	3	196992573	T/C	Intergenic	*PIGZ;MELTF*	0.084	− 0.073	0.436	3.5E-06
	rs72684540	4	119895428	A/G	Intergenic	*LINC01365;LINC02502*	0.036	0.058	0.435	3.4E-06
	rs8039131	15	88893064	G/A	Exonic	*HAPLN3*	0.451	− 0.218	0.438	4.4E-06
Mg	rs2074379	4	112431743	A/G	Exonic	*ALPK1*	0.337	− 0.090	1.947	4.2E-06
	rs72728275	8	130680639	A/C	Intergenic	*ASAP1;ADCY8*	0.172	0.199	1.944	1.3E-06
	rs117060920	18	47182664	G/A	Intergenic	*IER3IP1;SKOR2*	0.082	− 0.006	1.946	3E-06
Fe	rs232870	1	58653448	G/A	Intergenic	*TACSTD2;MYSM1*	0.184	0.128	0.052	1.9E-06
	rs76917806	2	140911148	A/T	Intronic	*LRP1B*	0.016	0.032	0.045	5E-06
	rs28428945	8	130679278	A/C	Intergenic	*ASAP1;ADCY8*	0.168	0.135	0.051	1.4E-07
Pb	rs304234	3	62877794	G/A	Intergenic	*CADPS;LINC00698*	0.172	0.120	0.471	2.47E-06
	rs12666460	7	124480877	C/T	Intergenic	*LOC101928211;GPR37*	0.134	− 0.103	0.471	1.81E-06

GWAS, genome-wide association study; *SNP*, single-nucleotide polymorphism; *REF/ALT*, reference/alternates; *MAF*, minor allele frequency

cellular functions, including key metabolic pathways and life/death decisions [21]. Our study displayed that rs76917806 in *LRP1B*, rs111232694 in *PIGZ-MELTF*, rs72684540 in *LINC01365-LINC02502*, and rs8039131 in *HAPLN3* were related to serum Ca element levels. *LRP1B*, located on chromosome 2q22.1-q22.2, may participate in extracellular signal transduction via the different phosphorylation status [22]. *PIGZ* and *MELTF* genes are located on chromosome 3q29, and the association of *PIGZ* and *MELTF* genes with serum Zn element levels is still unknown. *HAPLN3* gene has been reported to be associated with calcitic biomineralization [23]. rs8039131is located on the exonic region of *HAPLN3* gene. The contribution of rs8039131 to circulating Ca concentration might be related to the expression or function of *HAPLN3*.

Mg is the second most abundant intracellular cation and is a cofactor in nucleic acid synthesis and many enzymatic reactions [24]. It is reported that serum Mg levels are associated with several common and chronic diseases, including cardiovascular disease, neurological disorders, and hypertension [25, 26]. Here, three SNPs also achieved the significant association with Mg element levels for rs2074379 in *ALPK1*, rs72728275 in *ASAP1-ADCY8*, and rs117060920 in *IER3IP1-SKOR2*, respectively. The possible association of *ASAP1* (chromosome 8q24.21-q24.22), *ADCY8* (chromosome 8q24.22), *IER3IP1* (chromosome 18q21.1), and *SKOR2* (chromosome 18q21.1) genes on circulating Cu concentration are unknown. Alpha-kinase 1 (*ALPK1*) on chromosome 4q25, a member of the alpha-kinase family, is related to cancer and chronic diseases such as chronic kidney disease and diabetes [27, 28]. rs2074379 (Ile732Met), located on the exonic region of *ALPK1* gene, has been reported to be associated with diabetes [27]. However, the functional relevance of rs2074379 variants of *ALPK1* to the contribution of circulating Mg concentration has not been determined.

Fe is an essential element for numerous fundamental biologic processes, such as oxygen transport, mitochondrial respiration, and cell signaling, but the imbalances in iron homeostasis contribute to disease [29]. In the study, rs232870 in the intergenic region of *TACSTD2-MYSM1*, rs76917806 in the intronic region of *LRP1B*, and rs28428945 in the intergenic region of *ASAP1-ADCY8* showed suggestive associations with serum Fe element levels. *MYSM1* (chromosome 1p32.1) has emerged as an important regulator of hematopoietic stem cell function, hematogenesis, immune response, and other mammalian physiology [30]. *LRP1B* (chromosome 2q22.1-q22.2) mutations existed twice in patients with pure red cell aplasia [31]. The role of *TACSTD2* (chromosome 1p32.1), *ASAP1* (chromosome 8q24.21-q24.22) and *ADCY8* (chromosome 8q24.22) on the Fe element levels need further research.

Lead chloride has a significant toxic effect on the membrane of platelets, which activates the release of platelet aggregation factors, thereby increasing its adhesion and aggregation properties [32]. Here, the two most significant SNPs associated with Pb were rs304234 in *CADPS-LINC00698* and rs12666460 in *LOC101928211-GPR37*. *LINC00698* and *LOC101928211*are long intergenic non-protein coding RNA whose function need further study. *CADPS* (chromosome 3p14.2) gene is mainly expressed in nerve and endocrine tissues and acts as a Ca sensor in regulated exocytosis [33]. *GPR37* (chromosome 7q31.33) is highly expressed in the brain and has been implicated in the neurological disorders [34]. However, the contribution of *CADPS* and *GPR37* genes to circulating Pb concentration has not been determined.

Several limitations should not be ignored. First, the major problem is that the sample size is relatively small and there are no replication study, and therefore, this study results need to be confirmed in a larger population. Second, the validity of the results was restricted to participants from Chinese Han populations, which means that our finding couldn't be generalized to other ethnic groups. Third, we have not performed functional studies on the identified variants, so further research is required to reveal the biological mechanism behind the observed associations.

Conclusion

In summary, we reported 19 suggestive loci associated with serum mineral elements in the Chinese Han population. These findings provided new insights into the potential mechanisms regulating serum mineral element levels. Further replication studies are required to confirm these findings.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12011-021-02854-4.

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Availability of Data and Materials All the data regarding the findings are available within the manuscript. Anyone who is interested in the information should contact the corresponding author.

Author Contribution Duojian Guo and Yu zhou: writing; Xingwei Wei, Shanshan Zhang, Tianbo Jin: methodology; Yutian Zhang, Mei Lin, Xiaoli Zhou: data curation; Yufei Xie, Chanyi He, Qi Lin: Sample collection; Ping He and Yipeng Ding: conceptualization.

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Declarations

Ethics Approval and Consent to Participate All of the participating cohort provided written informed consents. The protocols were approved by the institutional review boards of Hainan Affiliated Hospital of Hainan Medical University, and were in the Declaration of Helsinki.

Conflict of Interest The authors declare no competing interests.

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