European Review for Medical and Pharmacological Sciences 2016; 20: 3661-3671

Genetic association study of *ABCB1* gene polymorphisms with hypertension in Han Chinese population

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Abstract. – OBJECTIVE: Hypertension is a common disorder related to cardiovascular diseases and stroke. Identification of genetic variations related to hypertension may advance our knowledge of the molecular mechanism underlying blood pressure regulation. Here, we aimed to investigate the associations between ABCB1 gene polymorphisms and hypertension-related traits in 1154 Han Chinese subjects.

PATIENTS AND METHODS: A total of 13 SNPs in ABCB1 were genotyped.

RESULTS: Three SNPs were significantly associated with systolic blood pressure (SBP), including rs17327624 ($p = 6.167 \times 10^{-4}$, beta = 5.650), rs3789243 ($p = 4.331 \times 10^{-3}$, beta = 2.800), and rs4148734 ($p = 3.514 \times 10^{-3}$, beta = 3.692). Rs17327624 ($p = 2.818 \times 10^{-4}$, beta = 2.753) and rs3789243 ($p = 6.345 \times 10^{-3}$, beta = 1.497) were significantly associated with diastolic blood pressure (DBP) and rs17327624 was significantly associated with hypertension ($p = 1.746 \times 10^{-4}$, OR = 1.605). These three SNPs (rs17327624, rs3789243 and rs4148734) were also associated with hypertension in female subjects but no significant signal was detected in males.

CONCLUSIONS: Our results suggest that *ABCB1* polymorphisms may contribute to the blood pressure variation in Han Chinese population and the effect may be specific in females. Further studies performed in other populations are needed to confirm our findings and elucidate the underlying molecular mechanism.

Key Words:
Hypertension, *ABCB1*, SNP, Association, Han Chinese population.

Introduction

Hypertension is a common disorder and modifiable risk factor for cardiovascular disease and stroke[1,2]. High blood pressure affects almost one-third of adults and contributes to 13.5 million deaths worldwide each year[1,2]. Lifestyle factors, such as dietary sodium intake, alcohol excess, elevated body mass index and lack of exercise, are known to increase blood pressure[3]. Besides these factors, genetic factors have been reported to responsible for around 40-60% of the genetic variation in hypertension[4]. Several genome-wide association studies (GWAS) have been performed to identify common variants affecting blood pressure[5-12]. And dozens of loci have been reported to be associated with hypertension-related phenotypes. However, all these genes only account for a small part of genetic variance, leaving much more associated genes to be discovered[5-12].

ATP-binding cassette subfamily B member 1 gene (ABCB1), also known as multidrug resistance 1 gene (MDR1), encodes Permeability glycoprotein (P-gp) that abundantly expressed in excretory organs, such as the kidney and the liver. ABCB1 gene has been identified to be associated with blood pressure by two studies[13,14]. However, they only focused on one common synonymous polymorphism (C3435T, rs1045642). The vast majority of disease associated SNPs, however, are in non-transcribed regions[15]. Moreover, and the effect direction of T allele reported by these two studies was opposite. Therefore, the purpose of this study was to investigate the effect of genetic variations spanned the whole ABCB1 gene on hypertension in Han Chinese subjects.

Patients and Methods

Patients

This study was approved by the Institutional Review Boards of Second Hospital of Lanzhou University. Signed informed consent was ob-

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tained from all subjects before they entered the study. A total of 1154 unrelated Han Chinese patients were recruited, including 568 men and 586 women. For each subject, three consecutive measurements were measured by using electronic blood pressure monitor. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were defined as the mean of the three measurements. For subjects taking antihypertensive medication, the SBP and DBP values were added by 10 and 5 mmHg, respectively. Hypertension was defined as SBP ≥140 mmHg or DBP ≥ 90 mmHg, or self-reported of taking antihypertensive medication. For all participants, peripheral blood samples were collected for DNA extraction and their weight (kg) and height (cm) were also measured. Subjects with chronic disorders/conditions (such as renal failure) that might potentially affect blood pressure were excluded.

SNP Selection and Genotyping

DNA extraction was carried out by using the DNA isolation kit (Gentra Systems, Minneapolis, MN, USA). SNPs were selected based on public SNP databases including dbSNP (http://www.ncbi.nlm.nih.gov/SNP) and HapMap (http://www.hapmap.org). Thirteen SNPs were selected according to the following criteria: (1) validation status in Han Chinese population; (2) minor allele frequencies (MAF) > 0.05; and (3) reported to public SNP databases by various sources. SNP genotyping was performed by using the MALDI-TOF mass spectrometry. SNP calling was performed by using MassARRAY RT (version 3.0.0.4) and MassARRAY Typer (version 3.4, Sequenom). SNPs with MAF less than 0.05 and deviated from Hardy-Weinberg Equilibrium were excluded.

Statistical Analysis

For all patients, significant variables ($p < 0.05$) including age, sex, BMI were used as covariates. The distribution of the residuals of SPB and DBP values were tested for normality by Kolmogorov-Smirnov test in the software MINITAB (Minitab Inc., State College, PA, USA). Association analyses were carried out by using PLINK[16]. Haplotypes were inferred with the Haploview software[17]. Sex-stratified association analyses were also performed to detect sex-specific effects. A p-value < 0.05 was set as the nominally significant threshold and multiple testing corrections were performed using the Benjamini and Hochberg's method[18].

Results

The basic characteristics, including systolic blood pressure (SBP), diastolic blood pressure (DBP), hypertension and body mass index (BMI) are presented in Table I. As shown in Table II, 13 SNPs were successfully genotyped, spanning about 132 kb of *ABCB1*. Haplotype analysis identified two linkage disequilibrium (LD) blocks, including one block of 671 bp and another block of 15.53 kb (Figure 1).

Association analyses results in all patients are listed in Table III. Four SNPs were nominally associated with SBP. After multiple testing corrections, three SNPs remained significantly associated with SBP, including rs17327624 ($p = 6.167 \times 10^{-4}$, beta = 5.650), rs3789243 ($p = 4.331 \times 10^{-3}$, beta = 2.800), and rs4148734 ($p = 3.514 \times 10^{-3}$, beta = 3.692). Nominally significant associations were detected between three SNPs and DBP. After multiple testing corrections, rs17327624 ($p = 2.818 \times 10^{-4}$, beta = 2.753) and rs3789243 ($p = 6.345 \times 10^{-3}$, beta = 1.497) remained significantly associated with DBP. Rs17327624 was the only SNP significantly associated with hypertension after multiple testing corrections ($p = 1.746 \times 10^{-4}$, OR = 1.605). As shown in Table IV, for rs17327624, the mean raw SBP value in patients with the genotype of "TT" (145.4 mmHg) was higher than that in the subjects with the genotypes of "TG" (140.8 mmHg) and "GG" (135.7 mmHg). Similarly, the mean raw DBP value in subjects with the genotype of "TT" was higher than that in other subjects with the genotype of "TG" or "GG". For rs3789243, the mean raw SBP value and DBP value were higher in subjects with the genotype of "AA" than those in

Table I. Basic characteristics of the study subjects.

Trait	Chinese sample
Number	1154
Female/Male	586/568
Age (years)	56.44 (12.26)
SBP (mmHg)	136.42 (19.98)
DBP (mmHg)	78.84 (9.68)
HTN (%)	50.09%
BMI	23.66 (2.73)

Note: Data are shown as mean (standard deviation, SD). SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; BMI, body mass index. Hypertension is defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or taking antihypertensive medication.

Table II. Basic characteristics of SNPs in ABCB1 gene.

No.	SNP	CHR	Position	A1	A2	MAF
1	rs1045642	7	87138645	A	G	0.395
2	rs4437575	7	87139316	G	A	0.188
3	rs10808071	7	87140808	G	A	0.056
4	rs12673269	7	87155359	A	T	0.054
5	rs10244266	7	87188467	G	T	0.035
6	rs4148734	7	87193597	A	G	0.156
7	rs1024409	7	87198367	A	G	0.103
8	rs1202184	7	87213901	C	T	0.258
9	rs17327624	7	87216817	T	G	0.087
10	rs3789243	7	87220886	A	G	0.327
11	rs2188524	7	87230435	C	T	0.103
12	rs17149810	7	87233989	T	C	0.139
13	rs6465118	7	87330423	A	G	0.115

Note: A1 is minor allele. MAF: Minor allele frequency.

other patients with the genotype of "AG" or "GG". For rs4148734, the mean raw SBP value in subjects with the genotype of "AA" was higher than that in the patients with the genotypes of "AG" and "GG".

Sex-stratified analyses were also performed. In female subjects, as shown in Table V, three SNPs were nominally associated with SBP. Only rs17327624 remained significantly associated with SBP after multiple testing corrections (p = 5.540 × 10^{-3}, beta = 6.360). The mean raw SBP value of female subjects with the genotype of "TT" was 150.8 mmHg, while the raw values in subjects with the genotype of "TG" and "GG" were 141.6 mmHg and 136.3 mmHg, respectively. Similar to SBP, the SNP rs17327624 was the

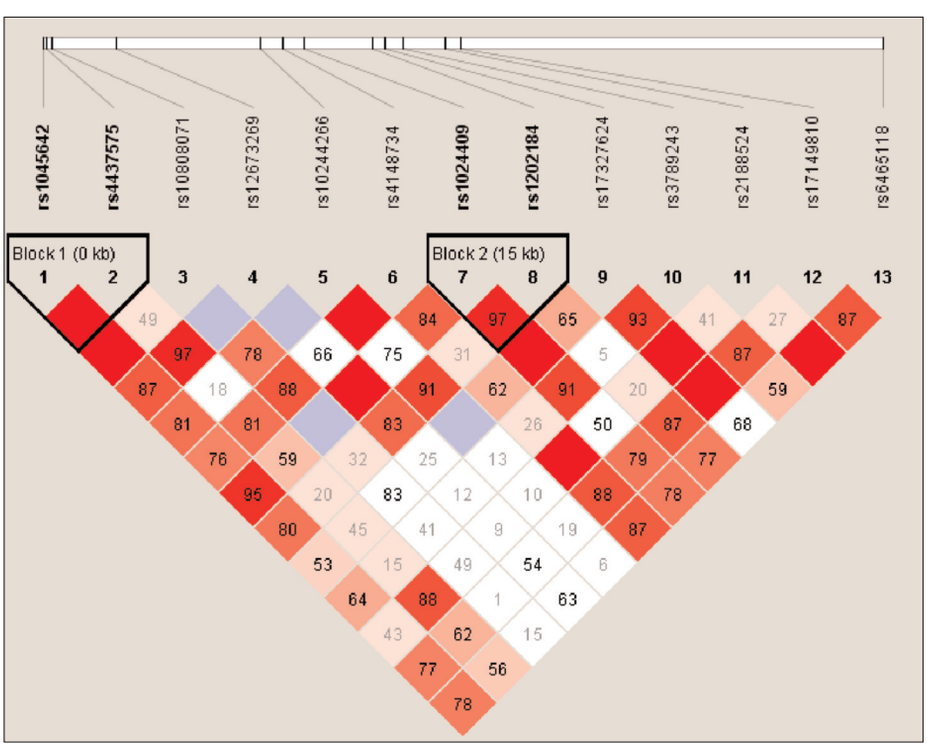

Figure 1. Linkage disequilibrium (LD) blocks for ABCB1 gene. a LD blocks are marked with triangles. The boxes are shown according to the standard Haploview color scheme: LOD > 2 and D′ = 1, red; LOD > 2 and D′ < 1, shades of pink/red; LOD < 2 and D′ = 1, blue; LOD < 2 and D′ < 1, white. LOD is the log of the likelihood odds ratio, a measure of confidence in the value of D′.

Table III. Association results between SNPs and hypertension related phenotypes.

SNP	SBP			DBP			Hypertension	
	Beta	SE	*p*	Beta	SE	*p*	*p*	OR (95% CI)
rs1024409	-0.194	1.506	0.897	0.487	0.838	0.561	0.487	0.909 (0.6939-1.191)
rs10244266	0.429	2.568	0.867	-1.803	1.432	0.208	0.918	0.977 (0.622-1.534)
rs1045642	-1.341	0.937	0.153	-0.702	0.523	0.180	0.807	0.979 (0.828-1.159)
rs10808071	0.305	1.957	0.876	-1.010	1.092	0.356	0.733	0.939 (0.652-1.350)
rs1202184	2.222	1.040	**0.033**	1.452	0.580	**0.012**	**0.042**	1.216 (1.007-1.468)
rs12673269	-0.081	2.020	0.968	-1.428	1.128	0.206	0.716	1.070 (0.744-1.539)
rs17149810	-0.252	1.340	0.851	0.283	0.749	0.706	0.888	0.983 (0.775-1.247)
rs17327624	5.650	1.645	**6.167×10^{-4}***	2.753	0.920	**2.818×10^{-4}***	**1.746×10^{-4}***	1.605 (1.191-2.163)
rs2188524	2.109	1.548	0.173	0.758	0.868	0.382	0.157	1.216 (0.927-1.595)
rs3789243	2.800	0.980	**4.331×10^{-3}***	1.497	0.547	**6.345×10^{-3}***	**0.017**	1.238 (1.039-1.475)
rs4148734	3.692	1.262	**3.514×10^{-3}***	0.841	0.708	0.235	0.062	1.242 (0.989-1.559)
rs4437575	2.270	1.203	0.059	-0.008	0.673	0.991	0.574	1.062 (0.861-1.310)
rs6465118	-0.586	1.453	0.687	-0.059	0.812	0.942	0.828	0.972 (0.751-1.258)

Note: Data are shown as mean (standard deviation, SD). SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; BMI, body mass index. a Hypertension is defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or taking anti-hypertensive medication. Significant *p*-values after multiple testing correction using the Benjamini & Hochberg method.

only significant SNP associated with DBP after multiple testing corrections ($p = 2.881 \times 10^{-3}$, beta = 3.703). The mean raw DBP value of female subjects with the genotype of "TT" was 86.80 mmHg, while the raw values in subjects with the genotype of "TG" and "GG" were 80.28 mmHg and 77.42 mmHg, respectively. Three SNPs were significantly associated with hypertension after

Table IV. Genotype means for DBP and SBP in three SNPs.

SNP		Genotype means for DBP and SBP		
rs17327624		T/T	T/G	G/G
	DBP			
	Total	87.12 (12.56)	80.33 (13.19)	78.60 (12.15)
	Female	86.80 (6.686)	80.28 (12.27)	77.42 (11.85)
	Male	87.67 (21.50)	80.38 (14.19)	79.80 (12.35)
	SBP			
	Total	145.4 (21.45)	140.8 (25.74)	135.7 (23.79)
	Female	150.8 (21.50)	141.6 (14.19)	136.3 (12.35)
	Male	136.3 (35.10)	139.9 (25.14)	135.0 (22.41)
rs3789243		A/A	A/G	G/G
	DBP			
	Total	80.75 (13.14)	79.6 (12.41)	77.86 (12.02)
	Female	79.63 (12.15)	79.11 (12.01)	76.35 (11.67)
	Male	82.35 (14.41)	80.10 (12.81)	79.34 (12.21)
	SBP			
	Total	140.7 (21.49)	137.4 (24.65)	134.8 (24.15)
	Female	140.4 (21.67)	139.0 (25.98)	134.6 (25.37)
	Male	141.0 (21.46)	135.8 (23.17)	134.9 (22.95)
rs4148734		A/A	A/G	G/G
	DBP			
	Total	80.21 (14.06)	79.18 (12.05)	78.81 (12.41)
	Female	79.32 (15.27)	78.76 (12.06)	77.58 (11.74)
	Male	82.11 (11.68)	79.60 (12.07)	80.06 (12.97)
	SBP			
	Total	144.9 (26.02)	138.4 (24.96)	135.6 (23.72)
	Female	149.4 (24.91)	139.6 (25.90)	135.9 (24.92)
	Male	135.6 (27.25)	137.1 (24.02)	135.3 (22.45)

Note: Data are shown as mean (standard deviation, SD). SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table V. Association results between SNPs and hypertension related phenotypes in female sample.

SNP	SBP			DBP			Hypertension	
	Beta	SE	*p*	Beta	SE	*p*	*p*	OR (95% CI)
rs1024409	-3.114	2.209	0.159	-0.827	1.192	0.488	0.175	0.762 (0.515-1.129)
rs10244266	4.180	4.056	0.303	-1.299	2.205	0.556	0.514	1.262 (0.626-2.541)
rs1045642	-0.810	1.351	0.549	-0.418	0.732	0.569	0.297	0.882 (0.696-1.117)
rs10808071	4.361	2.923	0.136	-1.322	1.585	0.405	0.535	1.184 (0.694-2.018)
rs1202184	1.500	1.504	0.319	1.295	0.813	0.112	0.316	1.147 (0.877-1.500)
rs12673269	5.815	2.978	0.051	-0.424	1.623	0.794	0.258	1.351 (0.800-2.281)
rs17149810	-1.100	1.933	0.570	0.468	1.048	0.656	0.578	0.909 (0.648-1.273)
rs17327624	6.360	2.283	**5.540×10^{-3}***	3.703	1.237	**2.881×10^{-3}***	**1.581×10^{-3}***	1.959 (1.284-2.991)
rs2188524	1.507	2.297	0.512	0.682	1.249	0.586	0.409	1.178 (0.798-1.741)
rs3789243	2.935	1.368	**0.032**	1.803	0.741	**0.015**	**7.534×10^{-3}***	1.394 (1.092-1.778)
rs4148734	3.979	1.745	**0.023**	1.221	0.950	0.199	**7.529×10^{-3}***	1.539 (1.118-2.119)
rs4437575	3.217	1.718	0.062	-0.164	0.935	0.861	0.062	1.326 (0.986-1.783)
rs6465118	-1.812	2.027	0.372	-0.987	1.101	0.370	0.950	0.989 (0.691-1.414)

Note: Data are shown as mean (standard deviation, SD). SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; BMI, body mass index. Hypertension is defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or taking antihypertensive medication. *Significant p-values after multiple testing correction using the Benjamini & Hochberg method.

multiple testing corrections, including rs17327624 ($p = 1.581 \times 10^{-3}$, OR = 1.959), rs3789243 ($p = 7.534 \times 10^{-3}$, OR = 1.394) and rs4148734 ($p = 7.529 \times 10^{-3}$, OR = 1.539).

In male patients, nominally significant associations between three SNPs and SBP were detected. As shown in Table VI, after multiple testing corrections, no significant association was detected in males.

The three SNPs (rs17327624, rs3789243 and rs4148734) significantly associated with hypertension-related phenotypes were subjected to functional annotation using the ENCODE data in the UCSC database. Information in cell lines that might be correlated with hypertension was included, such as GM12878 (B-lymphocyte, lymphoblastoid), CD20+ and human umbilical vein endothelial cells (HUVEC). As shown in Figure 2-4, the positions of the three SNPs overlap the CTCF binding region in all three cell lines. They also locate in the region of histone marks of H3K4me1 in GM12878 and H3K27ac in HUVEC. Their positions also overlap with the chromatin state segmentation of "repressed" in

Table VI. Association results between SNPs and hypertension related phenotypes in male sample.

SNP	SBP			DBP			Hypertension	
	Beta	SE	*p*	Beta	SE	*p*	*p*	OR (95% CI)
rs1024409	2.519	2.052	0.220	1.691	1.180	0.153	0.695	1.078 (0.741-1.568)
rs10244266	-2.296	3.313	0.489	-2.216	1.898	0.244	0.524	0.823 (0.452-1.500)
rs1045642	-1.873	1.302	0.151	-0.993	0.749	0.186	0.450	1.097 (0.863-1.393)
rs10808071	-3.289	2.623	0.210	-0.755	1.513	0.618	0.311	0.770 (0.464-1.278)
rs1202184	2.935	1.439	0.042	1.603	0.829	0.054	0.055	1.298 (0.995-1.693)
rs12673269	-5.405	2.729	0.048	-2.341	1.572	0.137	0.552	0.855 (0.511-1.431)
rs17149810	0.612	1.859	0.742	0.096	1.072	0.929	0.704	1.067 (0.763-1.493)
rs17327624	4.814	2.379	0.044	1.663	1.372	0.226	0.233	1.295 (0.846-1.984)
rs2188524	2.662	2.094	0.204	0.817	1.210	0.500	0.226	1.262 (0.866-1.840)
rs3789243	2.713	1.409	0.055	1.168	0.813	0.152	0.556	1.079 (0.837-1.391)
rs4148734	3.327	1.834	0.070	0.405	1.061	0.703	0.907	0.981 (0.706-1.363)
rs4437575	1.282	1.684	0.447	0.152	0.970	0.875	0.266	0.843 (0.623-1.139)
rs6465118	0.845	2.088	0.686	0.999	1.200	0.405	0.794	0.952 (0.656-1.381)

Note: Data are shown as mean (standard deviation, SD). SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; BMI, body mass index. Hypertension is defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or taking antihypertensive medication. *Significant p-values after multiple testing correction using the Benjamini & Hochberg method.

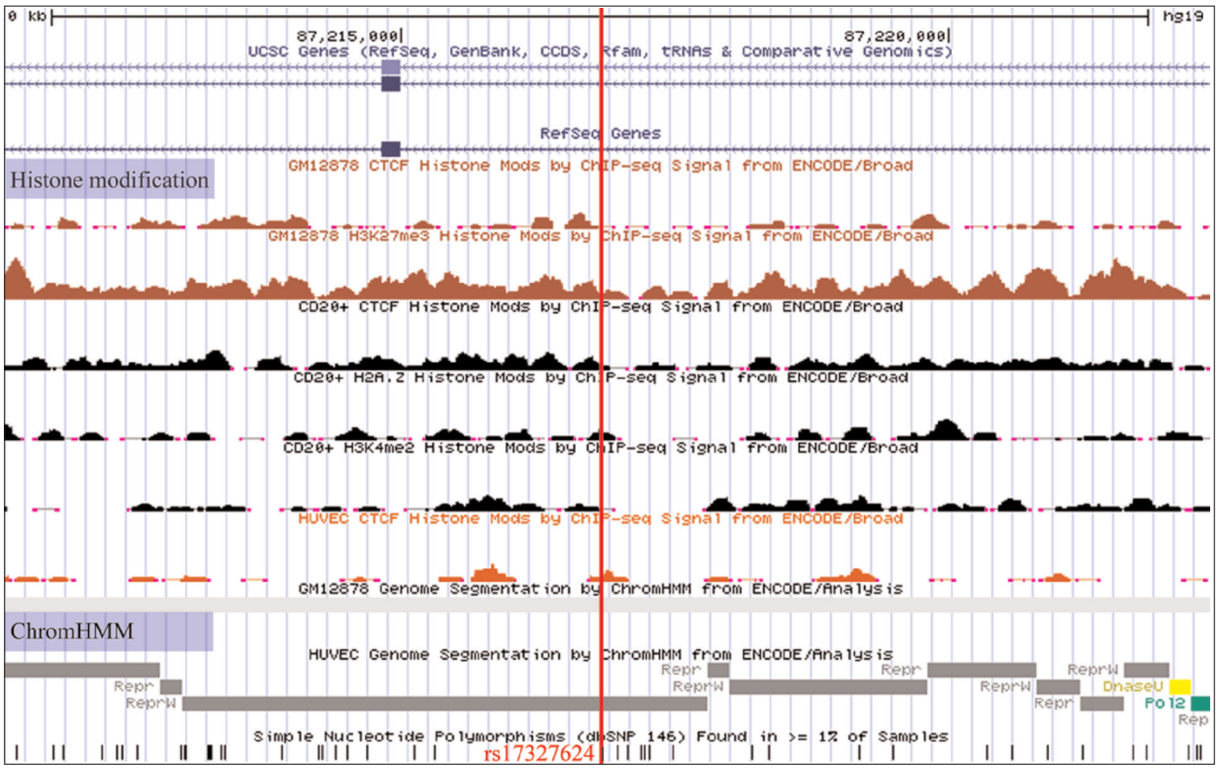

Figure 2. Functional annotation of rs17327624 in the cell lines of GM12878, human umbilical vein endothelial cells (HUVEC) and CD20+.

GM12878 and HUVEC. In addition, rs17327624 and rs4148734 also locate in the region of histone marks of H3K4me3 in GM12878. The position of rs4148734 also overlaps with H3K4me3 and H3K4me1 in HUVEC.

Discussion

In this study, we analyzed the associations between *ABCB1* polymorphisms and hypertension-related traits. Three SNPs, rs17327624, rs3789243 and rs4148734 were associated with hypertension-related traits even after multiple testing corrections. Sex- stratified analyses suggested that the association may be female-specific.

The associations between the three identified SNPs and hypertension have not been reported before. However, rs17327624 was strongly associated with renal function in Caucasians[19]. Ma et al[20] also detected the nominal association signal between rs17327624 and allograft survival in kidney transplantation. A recent review[21] has summarized that increased oxidative stress in kidney plays important roles in the development of essential hypertension. Therefore, it is possible that rs17327624 could affect hypertension through its effects on renal function. The SNP rs3789243 was associated with colorectal cancer risk[22] and it was also associated with low *ABCB1* expression level in morphologically normal sigmoid tissue in adenoma patients[23]. Further studies are needed to investigate whether it could affect blood pressure through influencing the expression of *ABCB1*.

The three SNPs we identified locate in the intron region of *ABCB1*. Although introns are not coding sequences, they may be involved in the mRNA expression regulation[24]. Functional annotation of these SNPs by ENCODE data from UCSC revealed that their positions overlap with CTCF binding region. CTCF is a multifunctional transcription factor in regulating gene expression[25]. They also locate in the chromatin state segmentation region of "repressed" and the region of histone marks of H3K4me1 and H3K27ac. Rs17327624 and rs4148734 also locate in the region of histone marks of H3K4me3. Active enhancers can be identified according to the enrichment of H3K4 H3K4me1 and H3K27ac[26,27] and H3K4me3 contains information of cell identity and transcriptional consisten-

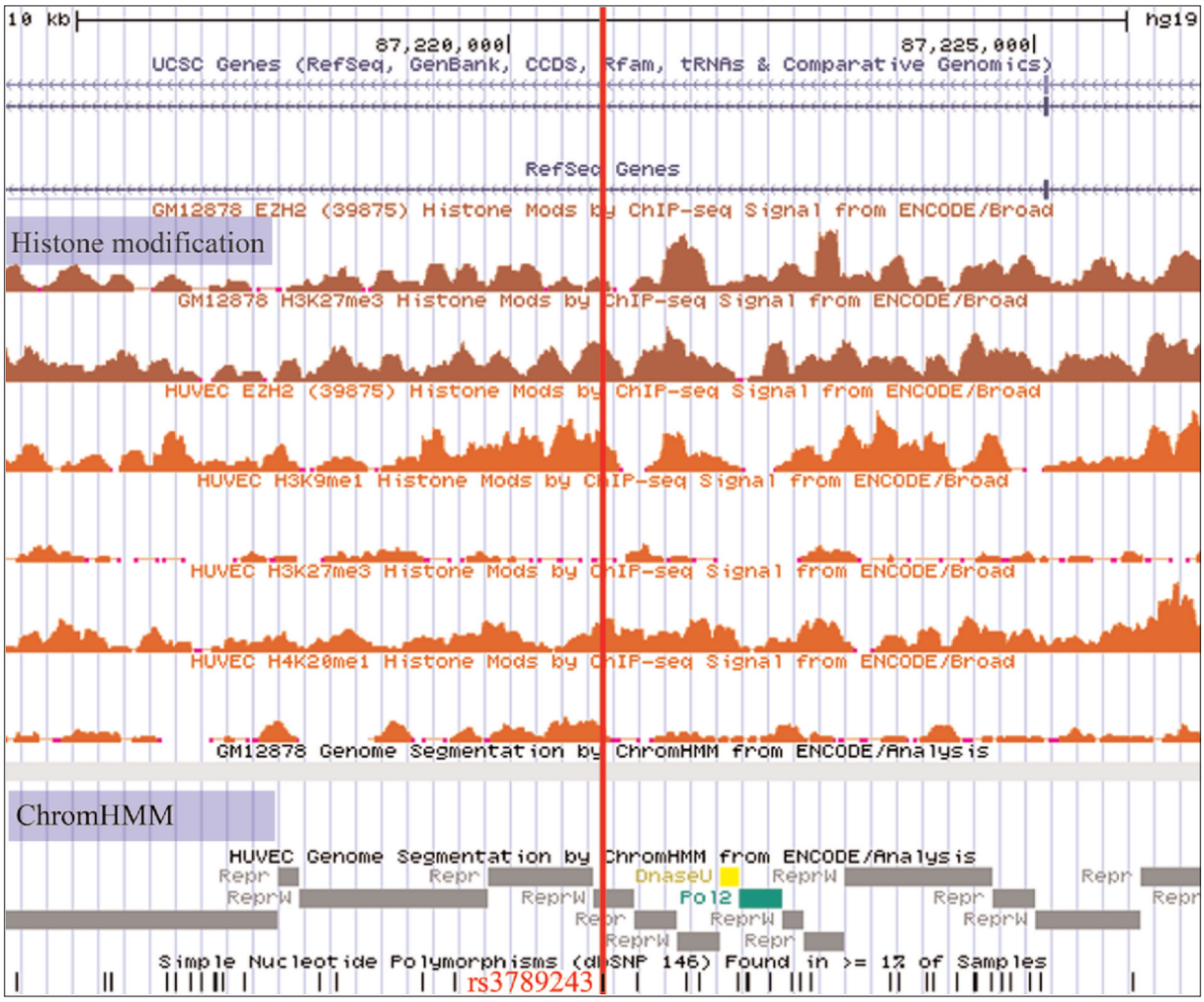

Figure 3. Functional annotation of rs3789243 in the cell lines of GM12878, human umbilical vein endothelial cells (HUVEC) and CD20+.

cy[28]. Further studies needed to investigate whether the base change of these SNPs could affect the function of these epigenomic elements.

The associations between rs1045642 in *ABCB1* and hypertension-related traits were not significant in this study. However, Lacchini et al[13] have found an association between this SNP and hypertension. The inconsistence may be caused by the following differences: first, Lacchini et al[29] carried out their study in white and black populations, the different results may be caused by ethnic differences; second, the sample size of their study was limited (105 controls, 137 patients responsive to treatment, and 83 resistant patients), which may overestimate the magnitude of the effect of rs1045642. Liu et al[14] also reported that rs1045642 was associated with SPB and pulse pressure in CKD patients. The inconsistence may be due to the difference between CKD patients and subjects without kidney disorders.

Some limitations of this study should be addressed. We only focused on the association analyses of *ABCB1* polymorphisms and hypertension-related traits in Han Chinese subjects. Our results may be not applicable to other populations. Further association studies in other populations are encouraged to validate our results.

Conclusions

In this study, we provided the association evidence between *ABCB1* polymorphisms and hypertension-related traits in Han Chinese subjects. Our findings further advance our understanding of the genetic architecture of hypertension.

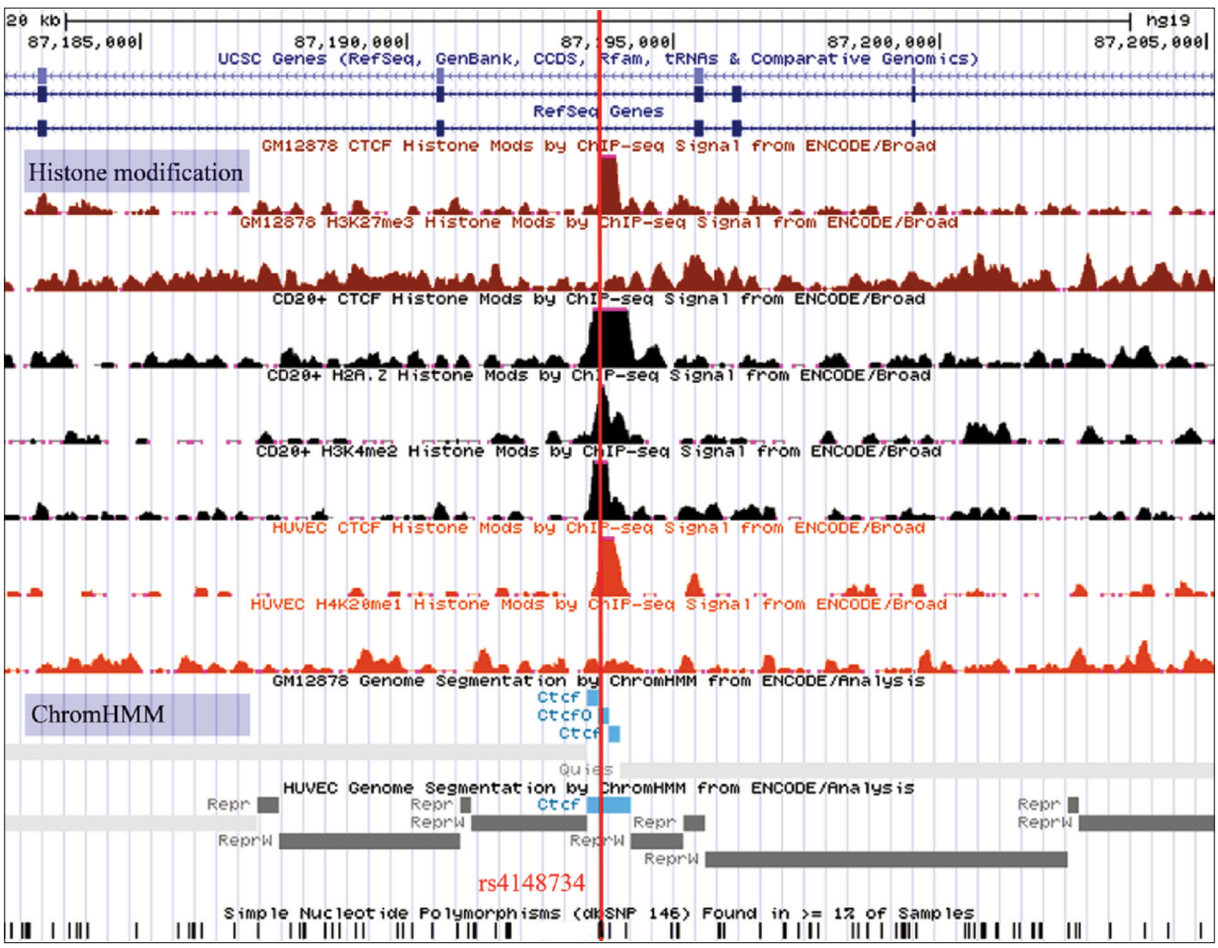

Figure 4. Functional annotation of rs4148734 in the cell lines of GM12878, human umbilical vein endothelial cells (HUVEC) and CD20+.

Acknowledgements

This work was supported by west light foundation of the Chinese academy of sciences, the natural science foundation of Gansu province (1501RJZA003), and the science projects of Lanzhou city (2015-2-51).

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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