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Comparison of Erythrocyte Traits Among European, Japanese and Korean

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Abstract

Erythrocyte traits are heritable and indirect indicators of blood diseases caused by erythrocyte, but their genetic factors are largely unknown. So we performed genome-wide association study in 8,842 Korean individuals to identify genetic factors influencing erythrocyte traits. We identified 40 associations for three erythrocyte traits at genome-wide significance levels ($p < 1 \times 10^{-6}$). We compared these associated loci with those reported in genome-wide association studies of European and Japanese. Our findings include previously identified loci (HBS1L-MYB, TMPRSS6, USP49 and CCND3) in other studies and novel associations (MRDS1/OFCC1, CSDE1, NRAS and 8 other loci). For example, SNP rs4895440 of HBS1L-MYB intergenic region on chromosome 6q23.3 is one of the most associations influencing erythrocyte traits ($p = 8.33 \times 10^{-27}$).

Keywords: erythrocyte, GWAS, hematocrit, hemoglobin, red blood cell

Introduction

Erythrocytes (Red blood cells) such important cells as a function of delivering Oxygen (O_2) to the body tissues are the most common type of blood cell. The count and volume of the erythrocytes in blood are high heritable and it is different between individuals. Erythrocyte traits include the hemoglobin (Hb), hematocrit (Hct), red blood cell (RBC) which are commonly used indicators in the clinic. Blood diseases caused by erythrocyte are anemias, hemolysis, polycythemias. These are widely associated with other diseases such as cardiovascular diseases, hypertension, but genetic factors of erythrocyte traits are poorly proved.

Genome-wide association studies (GWAS) identify a number of loci associated with common diseases with quantitative traits. We analyzed GWA scanning data of erythrocyte traits for 8,842 Korean individuals (Fig. 1). To date, samples of several studies associated with erythrocyte traits are European origin, Japanese, and Chinese, and it remains unclear whether the same loci affect erythrocyte traits in Korean. Hence we compared genetic variations that affected erythrocyte traits among European, Japanese and Korean (Fig. 2).

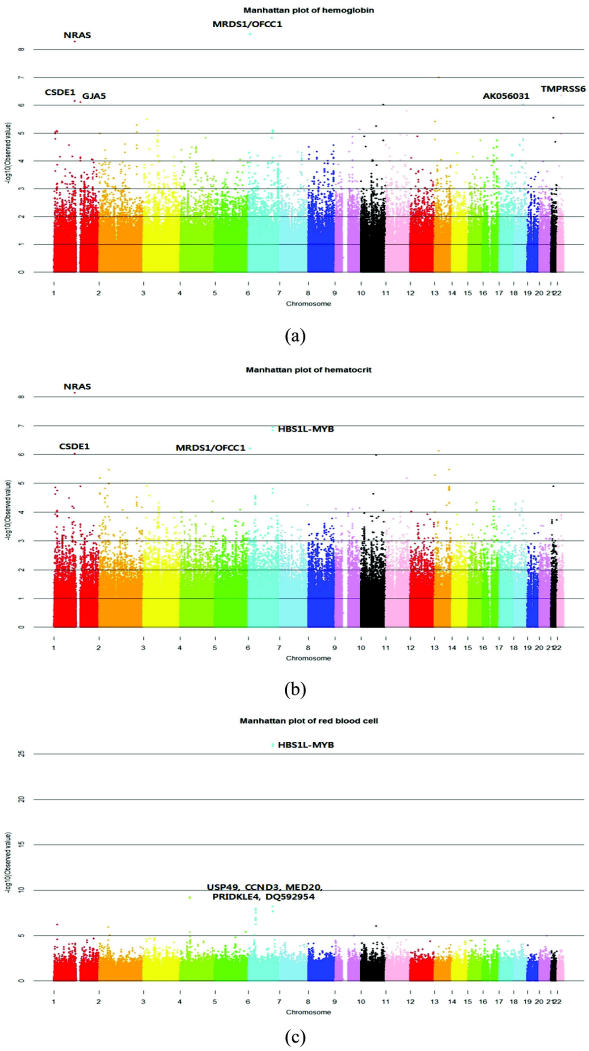

Fig. 1. Genome-wide association study of 8,842 Korean individuals for erythrocyte traits: (a) Hb, (b) Hct, and (c) RBC. Manhattan plots of log-transformed p-values with chromosome location.

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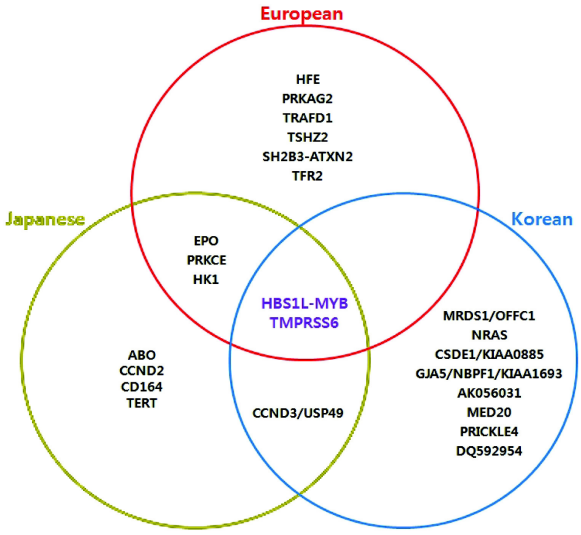

Fig. 2. Comparison of genes influencing erythrocyte traits among European, Japanese, and Korean. Two loci, HBS1L-MYB and TMPRSS6, were common among the three populations.

Methods

Study samples and genotype data

The samples and genotype data used in this study have been described by Cho *et al.* (2009). Briefly, through the Korea Association Resource (KARE) project that was initiated in 2007 10,038 participants were recruited from Ansan (n=5,020) and Ansung (n=5,018) population-based cohorts aged 40 to 69. Among them 10,004 were genotyped using the Affymetrix Genome-Wide Human SNP array 5.0. After removing samples and markers that failed quality control test, a total of 352,228 markers in 8,842 individuals were used (Cho *et al.*, 2009).

SNP imputation

SNP imputation has been described by Lee and Kim (2009). Briefly, using PLINK (Purcell *et al.*, 2007) the KARE genotypes were supplemented by imputing SNP genotypes based on those of the unrelated Chinese in Beijing (CHB) and Japanese in Tokyo (JPT) panel of HapMap Phase II.

Association analyses

Erythrocyte traits were tested for association by linear regression analysis with an additive model after adjustment for age, sex and bmi as covariates using PLINK. The genome-wide level of significance threshold was set at $p < 1 \times 10^{-6}$.

Results

In the current study, we performed GWAS for the three erythrocyte traits of 8,842 samples that are divided as 4,183 men and 4,659 women. Hb, Hct and RBC of erythrocyte traits are commonly used in the diagnosis of anemia. Single marker association p-values were estimated from linear regression after adjusting age, sex and bmi, and then 40 loci were identified as strongly associated with erythrocyte traits having p values lower than 1.00×10^{-6} (Table 1, Fig. 1). These loci were mapped to 6 Hb, 4 Hct and 6 RBC genes. We confirmed the previously reported associations of erythrocyte traits with the following four loci-: HBS1L-MYB, TMPRSS6, USP49 and CCND3 (Table 2, Fig. 3).

In the HBS1L-MYB intergenic region on chromosome 6q23, several SNPs showed genome-wide significant associations with Hct and RBC. While the role of HBS1L is unknown, MYB has been associated with proliferation, survival, and differentiation of hematopoietic progenitor cells. In addition the intergenic region of the HBS1L gene and the MYB gene has been identified to be a quantitative trait locus controlling fetal hemoglobin level, and this region influences erythrocyte, platelet, and monocyte counts as well as erythrocyte volume and hemoglobin content. Like our findings, SNP rs4895441 is strongly associated with Hct and RBC ($p=9.7 \times 10^{-10}$, $p=2.2 \times 10^{-15}$) in GWAS of European population. Other SNPs of HBS1L-MYB intergenic region were located in complete LD block with rs4895441 ($D'=1.000$, $R^2=0.999$). In the RBC, six SNPs of HBS1L-MYB intergenic region are as follows:rs11759553 ($p=8.33 \times 10^{-27}$), rs4895440 ($p=8.33 \times 10^{-27}$), rs9389269 ($p=8.44 \times 10^{-27}$), rs9402686 ($p=8.44 \times 10^{-27}$), rs4895441 ($p=1.44 \times 10^{-26}$) and rs9376092 ($p=1.46 \times 10^{-26}$). Rs9402686, rs4895441 and rs9376092 were identified to associate with erythrocytes in previous studies of Europe, Japan and China.

TMPRSS6 encodes a type II transmembrane serine protease produced by the liver that regulates the expression of hepcidin (Finberg *et al.*, 2008), which blocks iron absorption. And it is known that mutation in TMPRSS6 gene causes iron-refractory iron deficiency anemia (IRIDA) from other study. SNP rs5756505 in TMPRSS6 gene was associated with Hb ($p=4.57 \times 10^{-7}$) and in complete LD with rs5756504 that was associated with Hb in GWAS of Japanese population ($R^2=0.988$) (Table 1).

CCND3 gene has roles in hematopoiesis. For example, $Ccdn3^{-/-}$ mice showed lethality due to heart abnormalities combined with severe anemia in other study (Katarzyna *et al.*, 2004). Two SNPs in CCND3

Table 1. Genome-wide association studies for erythrocyte traits in 8,842 Korean individuals

Trait	Chr	Gene	SNP	bp	Minor allele	MAF	Beta	p-value
New associations								
Hb	1	NRAS	Rs14804	115051366	A	0.01644	−2.316	5.27×10^{-9}
Hb	1	CSDE1/KIAA0885	Rs7555948	115089224	T	0.01942	−1.607	7.10×10^{-7}
Hb	1	GJA5/NBPF1	Rs10793705	145706931	T	0.4204	−0.08616	7.72×10^{-7}
Hb	6	MRDS1/OFCC1	Rs3765276	10090486	G	0.006144	−3.332	2.73×10^{-9}
Hb	6	MRDS1/OFCC1	Rs3765277	10090422	G	0.006146	−3.332	2.74×10^{-9}
Hb	6	MRDS1/OFCC1	Rs17621965	10105418	A	0.01103	−3.332	2.84×10^{-9}
Hb	6	MRDS1/OFCC1	Rs17543708	10069924	T	0.01136	−3.332	2.86×10^{-9}
Hb	6	MRDS1/OFCC1	Rs10484262	10089479	A	0.01142	−3.332	2.86×10^{-9}
Hb	6	MRDS1/OFCC1	Rs17544450	10097751	A	0.01142	−3.332	2.86×10^{-9}
Hb	6	MRDS1/OFCC1	Rs10484261	10091850	T	0.01148	−3.332	2.86×10^{-9}
Hb	18	AK056031	Rs9676158	53555113	T	0.09701	−0.287	9.50×10^{-7}
Hct	1	NRAS	Rs14804	115051366	A	0.01644	−6.696	7.33×10^{-9}
Hct	1	CSDE1/KIAA0885	Rs7555948	115089224	T	0.01942	−4.638	9.54×10^{-7}
Hct	6	MRDS1/OFCC1	Rs3765277	10090422	G	0.006146	−8.157	6.16×10^{-7}
Hct	6	MRDS1/OFCC1	Rs3765276	10090486	G	0.006144	−8.158	6.16×10^{-7}
Hct	6	MRDS1/OFCC1	Rs17621965	10105418	A	0.01103	−8.157	6.36×10^{-7}
Hct	6	MRDS1/OFCC1	Rs17543708	10069924	T	0.01136	−8.156	6.38×10^{-7}
Hct	6	MRDS1/OFCC1	Rs10484262	10089479	A	0.01142	−8.155	6.38×10^{-7}
Hct	6	MRDS1/OFCC1	Rs10484261	10091850	T	0.01148	−8.155	6.38×10^{-7}
Hct	6	MRDS1/OFCC1	Rs17544450	10097751	A	0.01142	−8.155	6.38×10^{-7}
RBC	6	USP49	Rs33954419	41894114	G	0.4314	0.03213	9.91×10^{-9}
RBC	6	USP49	Rs2488338	41916329	G	0.4309	0.03193	1.55×10^{-8}
RBC	6	USP49	Rs2249703	41922738	G	0.4308	0.03193	1.55×10^{-8}
RBC	6	USP49	Rs2253961	41934989	G	0.4309	0.03193	1.55×10^{-8}
RBC	6	USP49	Rs2251084	41946097	C	0.4309	0.03193	1.55×10^{-8}
RBC	6	USP49	Rs10498752	41876488	T	0.4309	0.03193	1.55×10^{-8}
RBC	6	USP49	Rs2185798	41881554	G	0.4309	0.03193	1.55×10^{-8}
RBC	6	USP49	Rs7753507	41892072	C	0.4309	0.03193	1.55×10^{-8}
RBC	6	USP49	Rs2025951	41935171	G	0.4313	0.03216	9.87×10^{-9}
RBC	6	USP49	Rs2254474	41951022	G	0.4309	0.03193	1.55×10^{-8}
RBC	6	USP49	Rs2254805	41954088	G	0.4309	0.03193	1.55×10^{-8}
RBC	6	USP49	Rs9381096	41929115	A	0.2128	0.05017	2.02×10^{-7}
RBC	6	USP49	Rs1887718	41965669	T	0.4309	0.03193	1.55×10^{-8}
RBC	6	CCND3	Rs4623235	42032831	A	0.4409	0.0324	1.70×10^{-8}
RBC	6	CCND3	Rs11970772	42033268	A	0.4894	−0.03015	3.47×10^{-8}
RBC	6	MED20	Rs2274578	41996805	G	0.4309	0.03193	1.55×10^{-8}
RBC	6	PRICKLE4	Rs6905726	41858790	T	0.4309	0.03193	1.55×10^{-8}
RBC	6	PRICKLE4	Rs6925777	41858800	C	0.4309	0.03193	1.55×10^{-8}
RBC	6	DQ592954	Rs8393	41865814	C	0.4309	0.03193	1.55×10^{-8}
Replication of previous reports								
Hb	22	TMPRSS6	Rs5756505 (Kamatani *et al.*)	35797300	C	0.4987	0.08523	4.57×10^{-7}
Hct	6	HBS1L-MYB	Rs9389269 (Ganesh *et al.*)	135468852	C	0.3541	−0.2985	1.12×10^{-7}
Hct	6	HBS1L-MYB	Rs9402686 (Ganesh *et al.*)	135469510	A	0.3542	−0.2985	1.12×10^{-7}
Hct	6	HBS1L-MYB	Rs11759553 (Ganesh *et al.*)	135463989	T	0.354	−0.2985	1.12×10^{-7}
Hct	6	HBS1L-MYB	Rs4895440 (Ganesh *et al.*)	135468251	T	0.3541	−0.2985	1.12×10^{-7}
Hct	6	HBS1L-MYB	Rs9376092 (Ganesh *et al.*)	135468837	A	0.3538	−0.2958	1.45×10^{-7}
Hct	6	HBS1L-MYB	Rs4895441 (Ganesh *et al.*)	135468266	G	0.3538	−0.2957	1.46×10^{-7}
RBC	6	USP49	Rs6899876 (Kamatani *et al.*)	41904948	C	0.2329	0.04638	1.40×10^{-7}
RBC	6	USP49	Rs9381097 (Kamatani *et al.*)	41955778	A	0.2327	0.04683	1.09×10^{-7}
RBC	6	MED20	Rs3806113 (Kamatani *et al.*)	41984313	T	0.2357	0.04418	5.81×10^{-7}
RBC	6	HBS1L-MYB	Rs11759553 (Ganesh *et al.*)	135463989	T	0.354	−0.06687	8.33×10^{-27}
RBC	6	HBS1L-MYB	Rs4895440 (Ganesh *et al.*)	135468251	T	0.3541	−0.06687	8.33×10^{-27}
RBC	6	HBS1L-MYB	Rs9389269 (Ganesh *et al.*)	135468852	C	0.3541	−0.06686	8.44×10^{-27}
RBC	6	HBS1L-MYB	Rs9402686 (Ganesh *et al.*)	135469510	A	0.3542	−0.06686	8.44×10^{-27}
RBC	6	HBS1L-MYB	Rs4895441 (Ganesh *et al.*)	135468266	G	0.3538	−0.06653	1.44×10^{-26}
RBC	6	HBS1L-MYB	Rs9376092 (Ganesh *et al.*)	135468837	A	0.3538	−0.06652	1.46×10^{-26}

Table 2. Comparison of the results of the current study for erythrocyte traits with previous studies in European and Japanese

Ref	Trait	Chr	Gene	SNP	Effect allele	Freq% (CEU)	Effect size	SNP	Freq% (JPT)	Effect size	p-value	Current study				
												SNP	Effect allele	Freq% (KOR)	Effect size	p-value
Ganesh *et al.*	Hb	2	PRKCE	Rs10495928	A	66	0.063		83	0.032	4.61×10^{-6}					
Ganesh *et al.*	Hb	6	HFE	Rs1800562	A	4	0.162									
Ganesh *et al.*	Hb	7	PRKAG2	Rs10224002	A	74	0.071									
Ganesh *et al.*	Hb	10	HK1	Rs16926246	T	11	0.110									
Ganesh *et al.*	Hb	12	TRAFD1	Rs11065987	G	34	0.059									
Ganesh *et al.*	Hb	20	TSHZ2	Rs6013509	A	18	−0.065									
Ganesh *et al.*	Hb	22	TMPRSS6	Rs855791	A	39	−0.092		60	−0.100	4.82×10^{-10}	Rs5756505	C	50	0.08523	4.57×10^{-7}
Ganesh *et al.*	Hct	2	PRKCE	Rs10168349	G	66	0.188		83	0.317	5.07×10^{-7}					
Ganesh *et al.*	Hct	6	HFE	Rs1800562	A	4	0.307									
Ganesh *et al.*	Hct	6	HBS1L-MYB	Rs9483788	T	82	0.217		65	0.202	1.59×10^{-5}	Rs4895441	G	35	−0.2957	1.46×10^{-7}
Ganesh *et al.*	Hct	7	TFR2	Rs7385804	A	62	−0.151									
Ganesh *et al.*	Hct	7	PRKAG2	Rs10224002	A	74	0.196									
Ganesh *et al.*	Hct	10	HK1	Rs16926246	T	11	0.332									
Ganesh *et al.*	Hct	12	SH2B3/ATXN2	Rs11065987	A	66	−0.171									
Ganesh *et al.*	Hct	22	TMPRSS6	Rs2413450	T	38	−0.174		59	−0.204	5.33×10^{-6}					
Ganesh *et al.*	RBC	6	HBS1L-MYB	Rs9483788	T	82	0.014		65	0.051	6.19×10^{-21}	Rs4895441	G	35	−0.06653	1.44×10^{-26}
Kamatani *et al.*	RBC	6	USP49/CCND3					Rs3218097	19	0.097	1.09×10^{-10}	Rs9381097	A	43	0.04683	1.09×10^{-7}
Soranzo *et al.*	RBC	7	TFR2	Rs7385804	C	38	0.006									
Ganesh *et al.*	RBC	7	EPO	Rs2075671	A	23	0.007		14	0.031	1.08×10^{-4}					

Fig. 3. Significant associations on chromosome 6 in RBC. HBS1L-MYB, CCND3 and USP49 loci were also previously reported in other studies.

gene on chromosome 6p21.1 were associated with RBC (rs4623235, $p=1.70\times10^{-8}$ and rs11970772, $p=3.47\times10^{-8}$); rs11970772 was significantly associated with mean corpuscular volume (MCV) of erythrocyte traits in previous study.

USP49 gene is located so close to the CCND3 gene. Two SNPs of USP49 found associated with RBC in our study were in high LD with SNP rs3218097 of CCND3 reported in Japanese GWAS (rs9381097 D'=0.952 R^2=0.893, rs6899876 D'=0.952 R^2=0.893). SNP rs3806113 of MED20 gene was also in high LD with SNP 3218097 (D'=0.972, R^2=0.851) (Table 1, 2).

We found several loci associated with erythrocyte traits that have not been reported previously as follows: MRDS1/OFCC1, NRAS, CSDE1, GJA5/NBPF1, MED20, PRICKLE4, DQ592954, and AK056031 (Table 1). Most of these loci were located on chromosome 6. For example, newly found genes such as MED 20, PRICKLE4 and DQ592954 as well as previously reported USP49 and CCND3 are located on chromosome 6p21.1. While their roles in erythrocyte traits are largely unknown, we presume that these loci affect RBC.

Discussion

In the current study, we identified 40 associations for three erythrocyte traits at genome-wide significance levels ($p<1\times10^{-6}$) in 8,842 Korean. Of these loci, ten SNPs were previously reported, while 30 were novel, and their neighboring genes were known to be involved with iron homeostasis, erythropoiesis, and globin synthesis. Measurement of RBC, Hb and Hct, which are mainly quantitative measures of hemoglobin per erythrocytes, are parameters for the detection of blood disease associated erythrocyte in clinic. Across the three erythrocyte traits studied, the strongest signal was

found in the HBS1L-MYB locus on chromosome 6q23 (Table 1). Although its association with Hct and RBC only is listed in Table 1, its SNPs also have associations with Hb (rs11759553 $p=8.07\times10^{-6}$, rs4895440 $p=8.07\times10^{-6}$, rs9402686 $p=8.41\times10^{-6}$, rs9389269 $p=8.41\times10^{-6}$, rs4895441 $p=9.82\times10^{-6}$, rs9376092 $p=1.02\times10^{-5}$). CCND3 encodes cyclin D3, which has been known to be critical for the expansion of hematopoietic stem cells, as mice lacking D-cyclins develop severe anemia in experiment[7]. Hence it is likely that genetic factors in cyclin-related genes influence erythrocyte traits. Comparisons of erythrocyte traits among European, Japanese and Korean, confirm that HBS1L-MYB and TMPRSS6 loci are strongly associated with erythrocyte traits both in European and Asian. On the other hand, CCND3 and USP49 genes influencing RBC are identified in only Asian. Besides, many other genes belonged exclusively to each population (Fig. 2).

The novel loci reported in the current study need further study to confirm whether they have roles in biological processes associated erythrocytes.

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