# Genome-Wide Association Study Reveals Constant and Specific Loci for Hematological Traits at Three Time Stages in a White Duroc × Erhualian F₂ Resource Population

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## Abstract

Hematological traits are important indicators of immune function and have been commonly examined as biomarkers of disease and disease severity in humans. Pig is an ideal biomedical model for human diseases due to its high degree of similarity with human physiological characteristics. Here, we conducted genome-wide association studies (GWAS) for 18 hematological traits at three growth stages (days 18, 46 and 240) in a White Duroc × Erhualian F₂ intercross. In total, we identified 38 genome-wide significant regions containing 185 genome-wide significant SNPs by single-marker GWAS or LONG-GWAS. The significant regions are distributed on pig chromosomes (SSC) 1, 4, 5, 7, 8, 10, 11, 12, 13, 17 and 18, and most of significant SNPs reside on SSC7 and SSC8. Of the 38 significant regions, 7 show constant effects on hematological traits across the whole life stages, and 6 regions have time-specific effects on the measured traits at early or late stages. The most prominent locus is the genomic region between 32.36 and 84.49 Mb on SSC8 that is associated with multiple erythroid traits. The KIT gene in this region appears to be a promising candidate gene. The findings improve our understanding of the genetic architecture of hematological traits in pigs. Further investigations are warranted to characterize the responsible gene(s) and causal variant(s) especially for the major loci on SSC7 and SSC8.

## Citation

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## Competing Interests

The authors have declared that no competing interests exist.

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significant loci for hematological traits. However, only one locus for RDW on pig chromosome (SSC) 12 was consistently detected in the two studies, implying the complexity and heterogeneity of hematological traits.

In our previous studies, we conducted a whole genome linkage mapping in a White Duroc × Erhualian F2 resource population using 183 microsatellite markers, and identified a number of QTL affecting hematological traits measured at 3 growth stages [17,18]. To fine map the identified QTL and uncover new genetic variants associated with hematological traits, we herein performed GWAS on the F2 resource population using the PorcineSNP60 Genotyping BeadChip technology (Illumina, USA). The experimental data are available upon the readers’ request.

Materials and Methods

Ethics Statement

All the procedures involving animals are in compliance with the care and use guidelines of experimental animals established by the Ministry of Agriculture of China. The ethics committee of Jiangxi Agricultural University specifically approved this study.

Animals and Phenotypic Measurements

A detail description of the White Duroc × Erhualian F2 resource population and phenotype recording have been presented in our previous publications [17–19]. Briefly, the three-generation resource population comprising 1912 F2 individuals was developed by crossing 2 White Duroc boars and 17 Erhualian sows. All animals were reared under a consistent standard pigpen and were fed with same diet at the experimental farm of Jiangxi Agricultural University. Eighteen hematological parameters were measured for 1449 individuals at three age stages: days 18, 46 and 240. Blood samples of 5 ml were collected from each animal and were directly injected into Eppendorf tubes containing 30 ul of 20% EDTA in polybutadiene-styrene. A standard set of hematological data were recorded using a CD1700 whole blood analyzer (Abbott, USA) at the First Affiliated Hospital of NanChang University, China. The 18 hematological parameters include 7 baseline erythroid traits (hematocrit (HCT), hemoglobin (HGB), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), red blood cell count (RBC), and red blood cell volume distribution width (RDW) ), 7 leukocyte traits (granulocyte count (GRAN), granulocyte count percentage (GRAR), monocyte count (MON), monocyte count percentage (MONR), lymphocyte count (LYM), lymphocyte count percentage (LYMA), and white blood cell count (WBC ) ), and 4 platelet traits (plateletcrit (PCT), platelet distribution width (PDW), platelet count (PLT), and mean platelet volume (MPV) ).

Genotyping and Quality Control

Genomic DNA was extracted from ear tissues using a standard phenol/chloroform method. All DNA samples were qualified and standardized into a final concentration of 20 ng/ul. A total of 1020 individuals in the F2 pedigree were genotyped for the Porcine SNP60 BeadChips on an iScan System (Illumina, USA) following the manufacturer’s protocol. Quality control was executed to exclude SNPs with call rate <95%, minor allele frequency (MAF) <5%, severely Hardy Weinberg disequilibrium (P<10E-5) and Mendelian inconsistency rate >10%. Moreover, individuals with missing genotypes >10% or Mendelian errors >5% were discarded from the data set.

Statistical Analyses

Single-marker GWAS. The allelic difference of each SNP in phenotypic traits was tested using a general linear mixed model [20–22]. The model included a random polygenic effect, and the variance-covariance matrix was proportionate to genome-wide identity-by-state [23]. The formula of the model in mathematic is: $T = Xb + Zz + e$ where Y is the vector of phenotypes, b is the estimator of fixed effects including sex and batch, z is the SNP substitution effect and u is the random additive genetic effect following multinomial distribution $u \sim N(0, \sigma_e^2)$. In here G is the genomic relationship matrix that was constructed based on SNP markers as described in Eding et al [24], and $\sigma_e^2$ is the polygenetic additive variance. X, Z are the incidence matrices for b and u, S is incidence vector for z, e is a vector of residual errors with a distribution of N (0, $\sigma_e$2). All single-marker GWAS were conducted by GenABEL packages [25,26]. The genome-wide significant threshold was determined by Bonferroni correction. It was defined as 0.05/N, where N is number of tested SNPs. In this study, the number of qualified SNPs is 39622 and the corresponding genome-wide threshold is 1.26e-6.

GWAS of time serials data. As all experimental individuals were recorded for hematological traits at three time stages (days 18, 46 and 240). We assumed that measurements at different stages in the same individual would be more correlated than those obtained from different individuals. To conceptualize this assumption, phenotypic records on the three age stages were analyzed together using a mixed-effect approach to distinguish the correlations within and/or among individuals [27,28]. The model was similar to the above-mentioned single-marker GWAS model except that the phenotypic variance was partitioned to five parts rather than four parts: variance explained by SNPs, by fixed factors such as sex and batch, by polygenic effects, and by the time stage and by residual errors. The longitudinal GWAS were performed by LONG-GWAS [29] to adjust the variance and covariance structure among the three age stages. The genome-wide significant threshold was determined by Bonferroni correction as mentioned above.

Haplotype-based association studies and linkage disequilibrium (LD) analysis. A haplotype-based association study [30] was also performed to identify genomic regions associated with the tested hematological traits. Haplotypes corresponding to a predetermined number (K = 20) of hidden haplotype states [31] was conducted with a hidden Markov model via PHASEBOOK [32]. Association between phenotypes and the hidden haplotypes was detected under a generalized linear mixed framework that corrected population stratification by fitting a random polygenic effect. The mathematic formula of the mixed model was the same as the single-marker analysis, except that S was incidence matrices of hidden haplotype states rather than SNP genotypes and that the estimated haplotype effects were set as random effects. LD extents were estimated for significant SNPs using HAPLOVIEW [33].

Results

Phenotype Statistics and SNP Characteristics

Descriptive statistics of the measured traits in the current experimental population are presented in Table 1. Of the 7 baseline erythroid traits, 4 parameters including HCT, HGB, MCHC and RBC increased with age and one measurement (RDW) declined with age, while MCV and MCH first decreased and subsequently increased. Of the 7 leukocyte traits, GRAN and GRAR increased while LYMA decreased with age. The tendency
of the other leukocyte traits varied irregularly. No consistent variation pattern was observed for platelet traits.

After quality control, 3077 SNPs with call rate <90%, 15711 SNPs with MAF <0.05, 6502 SNPs showing Hardy Weinberg disequilibrium (P<10E-5) and 208 markers exhibiting Mendelian inconsistency were excluded for further analyses. All individuals are qualified samples. A final set of 39622 SNPs on 1020 individuals were explored for the subsequent GWAS.

**Summary of Significant Loci Identified by GWAS**

For GWAS on F2 populations, a cluster of significant SNPs would typically be detected at a significant locus due to large LD extent in such populations. If the distance between two genome-wide significant SNPs was smaller than 10 Mb, the two SNPs were treated as the same locus otherwise they were considered two independent loci in this study. According to this criterion, 13 genomic regions on 11 autosomes were strongly associated with blood cell parameters by single-marker GWAS or LONG-GWAS (Table 2 & Table S1). The 13 regions harbor 185 significant SNPs and 91 annotated genes (data not shown). Of the 185 SNPs, 119 SNPs corresponding to 63 genes were evidenced by both association strategies. In the single-marker GWAS, 147 significant SNPs representing 78 genes were identified in comparison with 158 associated SNPs from 76 genes revealed by LONG-GWAS.

**Loci for Erythrocyte Traits**

In total, we found 140 and 118 SNPs significantly associated with 7 erythrocyte traits by single-marker GWAS and LONG-GWAS, respectively. The corresponding Manhattan plots are shown in Figure 1 and Figure S1.

**Single-marker GWAS for erythrocyte traits.** For HCT and HGB, we identified 3 genome-wide significant loci on SSC7. The loci cover the region from 33 to 56 Mb and had the effect exclusively on the measurements at day 240. The lead SNPs within the regions are identical for the two traits. No genome-wide significant SNP was found for these traits at days 18 and 46. For MCH, MCV and RBC, all significant SNPs were detected on SSC8 which appeared to harbor two independent associated regions (32.36–50.1 Mb and 66.03–84.49 Mb). The regions consistently regulate red blood cells at different stages. Moreover, we uncovered two novel loci for HGB on SSC1 and for MCV, MCH and RBC on SSC8, all significant SNPs were detected within the regions are identical for the two traits. No genome-wide significant level for the trait measured at day 46.

**LONG-GWAS for erythrocyte traits.** A total of 118 SNPs within 10 genomic regions showed strong association with erythrocyte-related traits by LONG-GWAS. The results confirmed the findings of single-marker GWAS for HCT on SSC7, and for MCV, MCH and RBC on SSC8. It indicates that these loci consistently regulate red blood cells at different stages. Moreover, we uncovered two novel loci for HGB on SSC1 and SSC12 with the lead SNPs at 65994430 (ss131260759 at 4248936 bp on SSC4) and 29107229 (ss131459230) bp on the two chromosomes, respectively.

**Loci for White Blood Cell Counts**

Only 6 genome-wide significant SNPs on 4 autosomes were identified for leukocyte traits by single-marker GWAS (Figure 2).
Two SNPs within the *RAB44* gene on SSC7 were associated with WBC at day 240. Two significant SNPs (ss131349087 and ss131349087) for GRAR at days 18 and 46 were found at different positions (40.78 Mb and 26.31 Mb) on SSC8. Moreover, one SNP (ss131544979) at 2971217 bp on SSC17 was associated with LYM at the age of 18 days. A single SNP (ss478935524) at the position of 5860648 bp on SSC18 was associated with LYMA by LONG-GWAS.

### Loci for Platelet Traits

Analysis of platelet traits revealed two significant loci on SSC13 and SSC5 by single-marker GWAS and 39 associated loci by LONG-GWAS (Figure 2). In simple GWAS results, ss131296370 at 95971272 bp on SSC5 and ss107854351 at 14841832 bp on SSC13 were associated with PLT and PDW at day 46 with *P*-values of 1.14 E-8 and 3.94 E-7 respectively. For LONG-GWAS, two significant loci for PDW were detected on SSC8. The lead SNPs at the two loci were SS131365505 at 40852645 bp and ss131371056 at 75662581 bp with a distance of 34.81 Mb, implying at least 2 loci controlling PDW on chromosome 8.

### Discussion

**GWAS versus QTL Mapping**

We have previously performed genome scans on the F2 population using 183 microsatellites. We detected 46 genome-wide significant QTL for baseline erythroid traits, 8 for leucocyte-related traits and 6 for platelet-related traits. These QTL are distributed on SSC1, 2, 7, 8, 10, 12, 13, 15 and X [17,18]. In the present study, we did not test the association of SNPs on chromosome X as the currently available GWAS statistical models are hard to handle the random inactivation situation on the sexual chromosome. By using single-marker GWAS or LONG-GWAS on the 60K SNP data, we confirmed the previously identified QTL on SSC7 and SSC8 accounting for 46% of the total detected QTLs, and uncovered two additional genome-wide loci for HCT and HGB on SSC11 and SSC12, respectively. QTL mapping studies in F2 populations were generally conducted by comparing the phenotypic difference between F2 individuals inheriting different alleles from the founder breeds under the assumption that QTL alleles were alternatively fixed in each founder breed of the F2 intercross. The advantage of this mapping strategy is that we can anchor genomic regions affecting phenotypic traits using...
Figure 1. Manhattan plots for the single-marker analysis of erythrocyte traits. Log10(1/p) values are shown for all SNPs that passed quality control. The dotted line denotes the Bonferroni-corrected genome-wide significant threshold. SNPs surpassing the genome-wide threshold are highlighted in pink and SNPs reaching the suggestive threshold in green. HCT240: hematocrit at 240 days; HGB240: hemoglobin at 240 days; MCH240: mean corpuscular hemoglobin at 240 days; MCHC46: mean corpuscular hemoglobin content at 46 days; MCV18, MCV46, MCV240: mean corpuscular volume at 18, 46 and 240 days; RBC18 and RBC240: red blood cell count and at 240 days.

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Figure 2. Manhattan plots for the single-marker analysis of white blood cell and platelet traits. Log10(1/p) values are shown for all SNPs that passed quality control. The dotted line denotes the Bonferroni-corrected genome-wide significant threshold. SNPs surpassing the genome-wide threshold are highlighted in pink and SNPs reaching the suggestive threshold in green. GRAR18 and GRAR46: granulocyte count percentage at 18 and 46 days; LYM18: lymphocyte count at 18 days; WBC240: white blood cell count at 240 days; PDW46: platelet distribution width at 46 days; PLT46: plateletcrit at 46 days.

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sparse markers. However, it could result in false negative signals if QTL alleles are segregating within founder lines. Moreover, the confidence intervals of most QTL were larger than 20 cM. In our QTL mapping study, the smallest intervals were 3 and 4 cM for MCV and MCH at day 10 on SSC8, respectively [17]. In comparison, GWAS test the average phenotypic difference grouped by alternative alleles of high density markers and without any assumption; thereby it could identify significant signals even if QTL is not fixed in founder breeds. Moreover, GWAS could narrow down the confidence interval of QTL to small genomic regions. In the current study, the confidence interval for MCV at day 18 on SSC8 were 0.80 Mb based on the 1.5 Lods drop rule [34]. Only a handful of genes exist in such small regions.

QTL Replication with Other Studies

Until now, there were only two very recent GWAS papers describing significant genomic loci for hematological parameters in pigs [15,16]. Luo et al. [15] detected 62 genome-wide significant and 3 chromosome-wide significant SNPs associated with erythrocyte traits by performing GWAS on a Large White × Chinese Min F₂ intercross. All significant SNPs were found on SSC7 and SSC8 except one SNP associated with RBC on SSC1 and two SNPs for RDW on SSC12. Our results confirmed all of these findings. Wang et al. [16] identified 111 SNPs including 10 genome-wide significant SNPs and 101 chromosome-wide significant SNPs for 15 hematological traits in 2 Western breeds and one Chinese synthetic breed. The 111 SNPs are distributed on all autosomes except for SSC7, SSC8 and SSC18. However, none of these SNPs were replicated in our study. The reasons for the inconsistence could be different genetic background of experimental populations in the two studies, the complex genetic basis of hematological related cells, and different trait recording methods. Wang et al. [16] measured hematological traits on pigs at day 35 after immunized with classical swine fever vaccine at day 21.

Time Constant and Specific QTL

The single-marker GWAS revealed that the significant locus on SSC8 was consistently associated with MCV measured at days 18, 46, and 240, suggesting that a common variant regulates MCV at the whole life stage. The constant effect of this locus on MCV was further confirmed by LONG-GWAS that treated MCV data at the three ages together and obtained the same finding as the single-marker GWAS. In contrast, ss131544979 at 2971217 bp on SSC17 showed time specific effect on LYM at day 18. SNPs within two different regions on SSC8 were associated with GRAR at days 18 and 46, respectively, indicating that distinct genes are involved in development stages of granulocyte cells. Time specific loci were also evidenced for PLT and PDW on SSC5 and SSC13 as the association signals were observed only from the data at day 46. A high proportion of SNPs on SSC7 and SSC8 were identified for erythroid traits and leukocytes traits at day 240. Notably, the SNPs on SSC7 for HCT, HGB and WBC had a significant effect only at day 240 (Table 2) and therefore can be viewed as a late-acting QTL. It should be noted that all significant SNPs on SSC7 were not located in the SLA region (24.7 Mb - 29.8 Mb), which is response for immune system and is related to a range of diseases.

LONG-GWAS Analysis

Currently, standard GWAS (e.g. GenABEL) only utilized one time point for each individual. If QTL constantly control the traits during the whole life process, it is reasonable to assume that jointly analysis of data at all-time points may be more powerful than the single-time-point approach. We thus used LONG-GWAS that utilized multiple phenotype measurements for each individual as proposed by Furlotte et al. [29]. We not only replicated the linkage mapping results for hematological trait, but also identified five new QTL affecting HGB, MCHC, HCT and LYMA on chromosomes 1, 12, 10, 11 and 18, respectively. One disadvantage of LONG-GWAS is that the significant signal may be overwhelmed by putting all time point’s data together if QTL effects vary during time stage. In this study, 5 time-specific expressed QTL for MCH, MCHC, PLT, PWD and LYM at early stage from 18 to 46 days were identified by the singer-marker GWAS, whereas these loci were not detected by LONG-GWAS.

Haplotype Analysis for Single SNP Associated with Measured Phenotypes

In the standard GWAS, a prominent locus is usually featured by a lead SNP and a cluster of surrounding significant SNPs within a genomic region especially in the F₂ pedigrees, in which high LD extents are expected. However, only one genome-wide significant SNP was associated with GRAR at days 18 and 46 (Table S2). None of suggestive SNP was detected in the neighboring region of the top SNP. To test if the signal was false positive result or real association, we conducted a haplotype based GWAS for this trait (Figure S2). We showed that dozens of genome-wide SNPs in a large interval were uncovered for GRAR at day 46, and the position of the top SNP was exactly the same to the lead SNP in the single-marker GWAS. For GRAR at day 18, the most significant SNPs were moved to another position (86.8 Mb), but the second top marker was identical to the top SNP identified in the single-marker GWAS. The findings support the reliability of the single significant marker for GRAR.

Plausible Candidate Genes at the Significant Locus on SSC8

In the present study, the most interesting finding is the major locus for multiple hematological traits on SSC8. More than half of the detected regions (14 regions) were located on SSC8 that were associated with 9 hematological traits. Hundreds of significant SNPs in a large single region of more than 45 Mb on SSC8 were identified for MCH and MCV at day 240. In contrast, two segments in the ~45 Mb region appeared to be independently associated with the two measurements at day 18 as no significant SNP was found in the inter-segment region (Table 2). To investigate whether one or two loci affect MCV and MCH on this chromosome, we re-analyzed MCH and MCV data conditional on the allelic effect of the lead SNPs (Figure S3). For MCH at day 18, after controlling for the effect of ss131369293, the second significant region disappeared. Also, no SNP showed association with MCH and MCV at day 240 after correcting for the effect of the lead SNP (ss131369293). Moreover, the complete LD (D' = 1) was observed for the two top SNPs (ss131369009 at 44.93 Mb and ss107827400 at 66.03 Mb) for MCV at day 240 in the two intervals within the ~45 Mb region on SSC8. These observations support one major locus for the tested hematological traits on this chromosome. However, we can not rule out the possibility that two neighboring genes contribute to the phenotypic traits as the conditional analysis can not distinguish the effects of two adjacent loci due to LD.

We noticed that SNPs associated with MCH, MCV, RBC and GRAR at the early stage mainly reside in the region of 36.31 to 50.10 Mb. The stem cell growth factor receptor (KIT) gene around 43.55 Mb on this chromosome stands out as a compelling candidate gene as it is essential for the development of hematopoietic stem cells and has been highly expressed in hematopoietic cells [35,36]. Several mutations in KIT have
significant influence in RBC in the mouse [37]. Johansson et al. [30] showed strong association of KIT variants with erythroid traits in pigs. Moreover, Fésus et al. [39] reported the mild effect of KIT on hematological parameters in adult pigs. Our observation of the KIT region associated with hematological traits reinforces the assumption [40] that the KIT gene has a significant effect on peripheral blood cell measures in pigs.

**Conclusion**

In conclusion, a total of 185 genome-wide significant SNPs corresponding to 91 genes were identified for 18 hematological traits at the three growth ages in the White Duroc × Erhualian F2 intercross. These loci confirmed the previously identified QTL and showed both time constant and specific effects on the measured traits. Of these findings, the most prominent one was the genomic region between 32.36 and 84.49 Mb on SSC8 that is associated with multiple erythroid traits. The KIT gene on this chromosome appears to be a promising candidate gene. The findings improve our understanding of the genetic architecture of hematological traits in pigs. Further investigations are warranted to characterize the responsible gene(s) and causal variant(s) especially for the major loci on SSC7 and SSC8.

**Supporting Information**

Figure S1  Manhattan plots for the LONG-GWAS analysis of hematological traits. log10(p-value) values are shown for all SNPs that passed quality control. The dotted line denotes the Bonferroni-corrected genome-wide significant threshold. SNPs surpassing the genome-wide threshold are highlighted in pink and SNPs reaching the suggestive threshold in green. HCT: hematocrit; HGB: hemoglobin; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin content; MCV: mean corpuscular volume; RBC: red blood cell; LYMA: lymphocyte count percentage; PDW: platelet distribution width.

**Figure S2**  Manhattan plots for the hidden haplotypes analysis of GRAR at 18 and 46 days on SSC8 where only one SNP was associated with each trait in the single-marker analysis. SNPs surpassing the genome-wide threshold are highlighted in pink and SNPs reaching the suggestive threshold in green.

**Figure S3**  Manhattans plots for conditional GWAS of MCV. (A–C) Results are shown for MCV at 18 (A), 46 (B) and 240 (C) days. Grey and blue dots denote the results for SNPs before and after controlling for the top SNP (rs13136293) at 50.10 Mb on SSC8, respectively. Grey lines represent the genome-wide significant threshold.

**Table S1**  Genome-wide significant SNPs associated with hematological traits by LONG-GWAS.

**Table S2**  Simple statistic results for GRAR at 18 and 46 days classified by the genotypes of the top SNPs.

**Author Contributions**

Conceived and designed the experiments: LH JR. Performed the experiments: YH JG WZ. Analyzed the data: ZZ. Contributed reagents/materials/analysis tools: SX JM. Wrote the paper: ZZ JR LH.
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