Admixture Mapping of White Cell Count: Genetic Locus Responsible for Lower White Blood Cell Count in the Health ABC and Jackson Heart Studies

Michael A. Nalls,[1] James G. Wilson,[2] Nick J. Patterson,[3] Arti Tandon,[3] Joseph M. Zmuda,[4] Scott Huntsman,[5] Melissa Garcia,[1] Donglei Hu,[5] Rongling Li,[6] Brock A. Beamer,[7] Kushang V. Patel,[1] Ermeg L. Akylbekova,[8] Joe C. Files,[9] Cheryl L. Hardy,[9] Sarah G. Buxbaum,[8] Herman A. Taylor,[10] David Reich,[3,11] Tamara B. Harris,[1,*] and Elad Ziv[5]

White blood cell count (WBC) is an important clinical marker that varies among different ethnic groups. African Americans are known to have a lower WBC than European Americans. We surveyed the entire genome for loci underlying this difference in WBC by using admixture mapping. We analyzed data from African American participants in the Health, Aging, and Body Composition Study and the Jackson Heart Study. Participants of both studies were genotyped across $\geq$ 1322 single nucleotide polymorphisms that were preselected to be informative for African versus European ancestry and span the entire genome. We used these markers to estimate genetic ancestry in each chromosomal region and then tested the association between WBC and genetic ancestry at each locus. We found a locus on chromosome 1q strongly associated with WBC ($p < 10^{-12}$). The strongest association was with a marker known to affect the expression of the Duffy blood group antigen. Participants who had both copies of the common West African allele had a mean WBC of 4.9 (SD 1.3); participants who had both common European alleles had a mean WBC of 7.1 (SD 1.3). This variant explained ~20% of population variation in WBC. We used admixture mapping, a novel method for conducting genetic-association studies, to find a region that was significantly associated with WBC on chromosome 1q. Additional studies are needed to determine the biological mechanism for this effect and its clinical implications.

Introduction

Peripheral white blood cell count (WBC) is a common clinical measurement, used to determine evidence of acute inflammation or infection. Peripheral WBC is the sum of several cell types including neutrophils and lymphocytes, which are the most common types of WBC, as well as less common cell types such as eosinophils, basophils, and monocytes. Elevated WBC has been associated with risk of coronary heart disease,[1] cancer,[2] and all-cause mortality.[3] White blood cell levels have widespread clinical applications including assessment of patients undergoing chemotherapy[4] and evaluation of infection.[5]

Peripheral WBC is known to vary among different racial and ethnic groups. WBC is lower among African Americans when compared to European Americans[6,7] (NEUTROPENIA, CHRONIC FAMILIAL [MIM %162700]). Nongenetic factors that influence WBC include smoking, socioeconomic status, systemic inflammatory diseases, and acute infection.[8,9] However, the difference in WBC between racial and ethnic groups has not been explained by any of these factors. In addition, some studies have demonstrated a familial component to variation in WBC.[10]

Admixture mapping is a technique for localizing genetic variants in recently mixed populations[11] in which linkage disequilibrium (LD) extends tens of megabases because the chromosomes have not had much time to break up by recombination.[12,13] The extended LD implies that in populations like those of African Americans, whole genome association studies are possible with 1,000–2,000 markers.[14,15] Admixture mapping in African Americans has already identified putative loci affecting hypertension, prostate cancer, multiple sclerosis, and serum inflammatory markers.[16–21]

We studied variation in WBC among participants in the Health, Aging, and Body Composition study (Health ABC). We first compared WBC among African Americans and European Americans in the study and thus confirmed a significant difference. We then used ancestry informative markers to estimate the individual ancestry of the African Americans in the study and demonstrated that there was a significant association of low WBC with a higher proportion of African ancestry. Finally, we utilized an admixture mapping approach to identify a novel locus that influences WBC levels, which we also independently identified in a separate admixture scan in the Jackson Heart Study (JHS). The peaks of association in both studies localize to

[1]Laboratory of Epidemiology, Demography and Biometry, Intramural Research Program, National Institute on Aging, Bethesda, MD 20892, USA; [2]V.A. Medical Center and the University of Mississippi Medical Center, Jackson, MS 39216, USA; [3]Broad Institute of Harvard and MIT, Cambridge, MA 02142, USA; [4]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15261, USA; [5]Institute for Human Genetics, Division of General Internal Medicine, Department of Medicine, University of California, San Francisco, San Francisco, CA 94143, USA; [6]Department of Preventive Medicine, Division of Biostatistics and Epidemiology, University of Tennessee, Memphis, Memphis, TN 38163, USA; [7]Division of Geriatric Medicine and Gerontology, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA; [8]Jackson Heart Study Coordinating Center, Jackson State University, Jackson, MS 39213, USA; [9]Department of Medicine, Division of Hematology, University of Mississippi Medical Center, Jackson, MS 39216, USA; [10]Jackson State University, Tougaloo College, and the University of Mississippi Medical Center, Jackson, MS 39216, USA; [11]Department of Genetics, Harvard Medical School, Boston, MA 02115, USA

*Correspondence: harris99@nia.nih.gov

DOI 10.1016/j.ajhg.2007.09.003.

a region ~0.9 Mb centered on the Duffy Antigen Receptor for Chemokines gene (*DARC* [MIM 110700]).

Subjects and Methods

Description of the Health, Aging, and Body Composition Cohort

Health ABC is a cohort of 3075 community-dwelling men and women between the ages of 70–79. The participants in the Health ABC study were recruited from among Medicare beneficiaries residing in the metropolitan areas of Pittsburgh, PA, and Memphis, TN, and were selected to have high functional status at baseline. This study focuses on the African American subset of Health ABC. The clinical collection and genetic analysis for the Health ABC study has been approved by the institutional review boards of the University of Pittsburgh, the University of Tennessee, Memphis, and the University of California, San Francisco.

Genotyping

Within the Health ABC population, 1281 participants identified themselves as African American. From this subsample, 1184 participants were genotyped at the Broad Institute at 1536 single nucleotide polymorphisms (SNPs) with whole-genome amplified DNA and an Illumina BeadLab platform.[22] Details of the genotyping for this experiment are described by Reich et al.[19] After quality checks, including the requirement that at least 85% of SNPs were successfully genotyped for each sample and that none of the SNPs were in linkage disequilibrium in the ancestral populations, 201 SNPs were excluded. The physical genome positions used in this study are based on build 35 of the public genome reference, and the genetic positions are based on the Oxford high-resolution map.[23,24]

Health ABC Samples Used in Admixture Scanning

A total of 863 African Americans and 1339 European Americans from Health ABC were used in the analysis. Included in the analysis were participants with WBC who were within two standard deviations of the population mean and who also had information on all relevant covariates. For ANCESTRYMAP analyses, we identified 216 cases in the highest quartile of WBC levels and 216 controls in the lowest quartile of WBC levels. Related participants were not included in the admixture scan.

Phenotypes Used in the Analysis

The phenotype we studied is total white blood cell count (WBC) measured on a Coulter counter and expressed in terms of thousands of white blood cells per microliter. This measurement was taken at the third year of the Health ABC clinic visit. No differential counts were available for Health ABC.

Covariates included gender, age at enrollment in Health ABC, smoking status (from the year 3 exam), Health ABC study site (Memphis or Pittsburgh), and percentage of European ancestry. Gender, age, and smoking status (current or nonsmoker) were all self-reported. The percentage of European ancestry was estimated for each individual on the basis of the STRUCTURE software.[25] A larger set of covariates initially examined in analyses also included body-mass index, socioeconomic status, self-reported comorbidity, medications (for cancer, hypertension, hypercholesterolemia, and diabetes), recent hospital stay, alcohol consumption, and physical-activity levels; these factors were not significant in models that included an association to our genomic region of interest, and so in what follows, we do not report analyses including any of these factors.

Admixture Scan

We used STRUCTURE, ADMIXMAP, and ANCESTRYMAP to perform admixture mapping analyses. We used STRUCTURE 2.1[25] to obtain locus-specific ancestry estimates, by using the "linkage" model within STRUCTURE to obtain multilocus estimates of genetic ancestry in each region. This program utilizes an expectation maximization algorithm within a Bayesian Markov Chain Monte Carlo (MCMC) to calculate probabilities that a particular genotype or group of genotypes derive from a particular ancestral population.[26] Ancestry is output as a probability per locus as well as an overall estimate for each individual. We calculated the percent ancestry at each locus for each individual based on the probability of 0, 1, or 2 European chromosomes across 2500 iterations of the MCMC, with a burn-in period of 500 iterations. We used linear regression models to test for the association of the locus specific ancestry from STRUCTURE and the WBC outcome, adjusting the models on the basis of the covariates of genome-wide ancestry estimate, study site, smoking status, gender, and age. This analysis provided us with an output of T statistics and p values.

We also used the program ADMIXMAP v.3.5.3.[27] ADMIXMAP uses a similar MCMC algorithm as STRUCTURE to model probability distributions conditional on genotype, phenotypic values, and a priori ancestral genotype frequencies.[28] In our ADMIXMAP runs, we adjusted for study site, individual ancestry, locus-specific ancestry, smoking status, gender, and age over 2500 MCMC iterations, with 500 burn-in iterations. The models from ADMIXMAP calculate results in terms of standard normal Z statistics and p values.

We finally used the ANCESTRYMAP software, which also uses a MCMC-based methodology.[12] ANCESTRYMAP is optimized for dichotomous phenotypes, and so we did not perform a quantitative trait analysis on all samples with this software. After removing individuals with WBC greater than two standard deviations from the mean, we designated all individuals with WBC values in the highest quartile to be cases, and all individuals with WBC in the lowest quartile were assigned to be controls; this totaled 437 participants for analysis. We tested risk models of 1.1, 1.3, 1.5, 1.7, 1.8, 2.1, 2.4, 2.7, and 3.0 for cases, and 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, and 0.4 for controls. To accumulate evidence of association in these models, we averaged the Bayes factors emerging from each model at each point in the genome, taking the log-base-10 of this number to produce a LOD score. As reported in Reich and Patterson (2005), a LOD score for association at a particular locus of >5 is approximately genome-wide significant.[29] To obtain a formal assessment of statistical significance on a genome-wide level, we calculated an additional statistic that averaged the risks specified in the models as genome-wide Bayes factors and took the log-base-10; a value >2 indicates statistically significant association to the phenotype (we report a genome-wide Bayes factor of a LOD score of ~6.2).[12,29] We ran ANCESTRYMAP for a burn-in period of 100 iterations with 200 follow-on iterations, which yielded almost identical results to runs with 200 iteration burn-in and 500 follow-on iterations. To calculate the 99% confidence interval for the position of the disease locus once we found an association, we first summarized the evidence for association by taking the sum of the likelihood ratios across the entire locus. Then, starting at the peak of the

Table 1. Descriptive Statistics of Analysis Populations

	African American Population Used in Genome-Wide Scans						
	Male		Female		Total		European Americans
Study	Health ABC	JHS	Health ABC	JHS	Health ABC	JHS	Health ABC
n Individuals	350	1107	513	1739	863	2846	1339
Age—Mean (SD)	73.6 (2.7)	55.6 (11.5)	73.3 (2.9)	57.2 (11.4)	73.4 (2.8)	56.6 (11.5)	73.8 (2.9)
Percentage of Memphis Site	50.8	N/A	54	N/A	52.7	N/A	48.9
Percentage of Current Smoker	14.1	17.8	11	9.8	7.5	12.9	4.6
White blood Cell —Mean (SD)	5.36 (1.49)	5.16 (1.41)	5.57 (1.49)	5.55 (1.39)	5.48 (1.50)	5.40 (1.41)	6.35 (1.65)
Percentage of European Ancestry—Mean (SD)	21.8 (14.3)	15.5 (3.9)	22.8 (15.5)	15.6 (4.0)	22.4 (15.0)	15.6 (4.0)	N/A

White blood cell measurements in thousands/μl are shown. White blood cell count differences between genders are not significant, although differences between African American and European American Health ABC participants were significant as evaluated by t tests ($p \leq 10^{-12}$). All extreme statistical outliers were removed.

locus, we moved in both directions until the region included 99% of the value of the sum. This corresponds to a LOD score decrease of 2.2.

Independent Detection of Admixture Association in the Jackson Heart Study

We independently carried out an admixture scan for variants affecting WBC in African Americans from the Jackson Heart Study (JHS),[30] a community-based cohort of men and women ages 21–84 from three counties surrounding Jackson, Mississippi. To carry out a whole genome admixture scan on these samples, we used the Illumina BeadLab technology[22] and an updated version of the panel of 1536 markers that had been studied in Health ABC. The SNPs used in our final analyses included those that were typed in both the Health ABC and JHS panels. These two SNP panels are highly comparable because the updated JHS panel includes all of the SNPs from the Health ABC panel that had passed necessary quality-control measures in both studies. A complete list of SNPs used is included in Table S1 available online. A total of 4581 individuals were successfully genotyped. We restricted the present analysis to one randomly chosen individual from each family in JHS to remove related individuals who could confound analyses. We also excluded individuals with WBC greater than two standard deviations from the mean (the same procedure that was used to prepare the Health ABC data set). These exclusions resulted in a final analysis population of 2846 participants from the JHS cohort. For ANCESTRYMAP runs, we identified 775 cases in the top quartile of WBC levels and 775 controls in the bottom quartile of WBC levels. Replication of the STRUCTURE and ADMIXMAP analyses from Health ABC were also later carried out in the JHS cohort with the same covariates (see Table 2 for a comparison of results).

Results

High WBC Levels Are Associated with European Ancestry

There is a significant difference ($p < 10^{-12}$) in mean WBC between African Americans and European Americans in the Health ABC study (Table 1). Within African Americans, European ancestry estimates obtained by STRUCTURE analysis vary from 0.1% to 71.1%. WBC increases significantly with percent European ancestry (Figure 1) ($p = 3.3 \times 10^{-9}$ from regression of residual), consistent with the difference across ethnic groups shown in Table 1.

Admixture Mapping to Search for Loci Affecting WBC Levels

We used three methods to screen for loci affecting WBC levels. By using the locus-specific ancestry estimates from STRUCTURE, we found a strong association between a locus on chromosome 1 and WBC (Table 2). The strongest associations were between 152.72 Mb and 158.68 Mb with the strongest single association at rs2817784 at 155.99 Mb ($p < 10^{-12}$). We found very similar results by using the program ADMIXMAP (Table 2). These results from STRUCTURE and ADMIXMAP were similarly replicated within the JHS cohort using identical analytic methods (Table 2).

We also used the program ANCESTRYMAP to search for associated loci. Significant scores for the genotype-phenotype association with ANCESTRYMAP were found on chromosome 1 in the same region (Figure 2) (LOD score of 13.4). No score of greater than LOD 2.2 was observed elsewhere in the genome. The 99% confidence interval of 153.98–158.39 Mb includes rs2814778 and none of the other SNPs in our scan (Figure 3).

Independent Admixture Association in the Jackson Heart Study

We next carried out a screen for loci affecting WBC levels in the Jackson Heart Study. With this larger sample size, we obtain a score for association of LOD = 96.8, centered at rs2814778. This result far exceeds the threshold of LOD ~5 for statistical significance. The 99% confidence interval for the position of the disease causing variant is ~900,000 bp in this study, spanning 155.46–156.36 Mb. In both data sets, a single SNP, rs2814778, is at the center of the peak, and the posterior probability distribution excludes the neighboring SNPs as consistent with explaining the peak (rs11264422 at 152.72 Mb and rs1962508 at 158.68 Mb; see Figure 3).

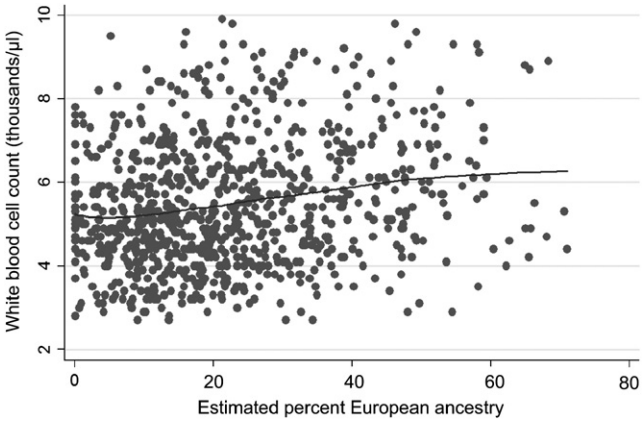

Figure 1. Association of White Blood Cell Count with Increasing Percent European Ancestry from STRUCTURE Estimates in the Health ABC Population

Results from nonparametric lowess smoothing analysis, trend significance $p = 3.3 \times 10^{-9}$.

Effect at rs2814778, the *DARC* Gene

The SNP in our scan that gives the strongest association is rs2814778 at 155.99 Mb on chromosome 1. This is a SNP in the *DARC* gene that is known to eliminate expression of the Duffy blood group antigen (FY+ or FY−).[31] This is one of the SNPs in the genome with the largest allele frequency difference between West Africans and European Americans. It has been hypothesized that this is due to the null allele conferring protection to malaria in West Africans.[32] However, there has never been any suggestion that it affects WBC levels as well.

We next tested whether African Americans who are homozygous for the functional allele at this SNP (the one more common in Europeans) have a WBC level comparable to that in Europeans (see Table 3). African Americans who are homozygous for the functional allele have mean WBC of 7.1 k/µl, significantly higher than in European Americans (t test, $p = 0.009$). Thus, this SNP is, by itself, sufficient to account for the difference in WBC levels across populations and explained 20.4% of the variance in WBC among African Americans.

We finally sought to determine whether there is evidence of residual association with any other SNPs in the region after adjustment for the rs2814778 genotype. Regression models adjusted for SNP rs2814778 indicate that the flanking SNPs show marginal association with WBC at best ($p = 0.07$). Further mapping is necessary to test whether the FY- variant itself is causative or whether other variants in the ~0.9 Mb confidence interval might be responsible for some or all of the effect.

Discussion

We utilized a genome-wide admixture scan to localize on chromosome 1 a region that affects baseline WBC among African Americans. We found a remarkably strong association between African ancestry at this region and lower WBC. At least one genotype at this locus explains ~20% of the variance in baseline WBC among African Americans, indicating the presence of a genetic variant with a profound influence on WBC. After adjustment for ancestry at this locus, there is no association between overall

Table 2. Genome-Wide Admixture Scan Results

	Location on Chromosome 1 (Physical Position in Mb)	Locus-Specific Ancestry Association Z Statistic from ADMIXMAP		Locus-Specific Ancestry Association T Statistic from STRUCTURE		Locus-Specific Ancestry LOD Scores from ANCESTRYMAP	
		Health ABC	JHS	Health ABC	JHS	Health ABC	JHS
SNP							
rs6702883	104.96	5.1*	6.4**	4.1*	4.8*	N.S	N.S
rs4311917	107.44	5.6*	6.5**	4.3*	4.5*	N.S	N.S
rs345275	108.21	6.0*	7.1***	4.3*	4.4*	N.S	N.S
rs2365669	112.07	6.8**	9.1***	5.2**	2.6	5.9	7.9
rs7523839	115.89	6.7**	10.1***	5.5**	0.12	6.9	13
rs850610	116.66	6.7**	10.4***	5.7**	0.7	7.2	14.3
rs10923929	120.22	6.8**	12.3***	6.1**	2.77	7.7	18.5
rs11240089	144.29	7.7***	15.0***	6.3***	6.1**	8.8	29.9
rs12740969	151.3	12.8***	22.4***	10.3***	12.9***	20.6	61.7
rs11264422	152.72	13.7***	24.3***	11.1***	13.8***	22.4	69.1
rs2814778	155.99	17.3***	31.7***	13.9***	16.0***	30.1	96.8
rs1962508	158.68	13.9***	25.1***	11.8***	11.9***	25.8	71.7
rs2806424	159.42	13.2***	23.5***	11.4***	11.0***	24.5	65.5
rs6426893	161.76	10.5***	17.3***	9.6***	8.4***	19.3	44.6
rs919679	162.99	9.7***	15.5***	8.9***	7.8***	17.6	37.3

SNPs were tested so that association of loci with WBC in both studies could be evaluated. SNPs less significant than $p < 1 \times 10^{-5}$ or LOD < 5 have been omitted; 95% CI for associations with WBC are in the shaded area. Significance levels indicated by *$p < 10^{-5}$; **$p < 10^{-9}$; and ***$p < 10^{-12}$. Only SNPs used in both Health ABC and JHS were reported in the table; 95% CI for associations between SNPs and WBC is denoted by shaded area.

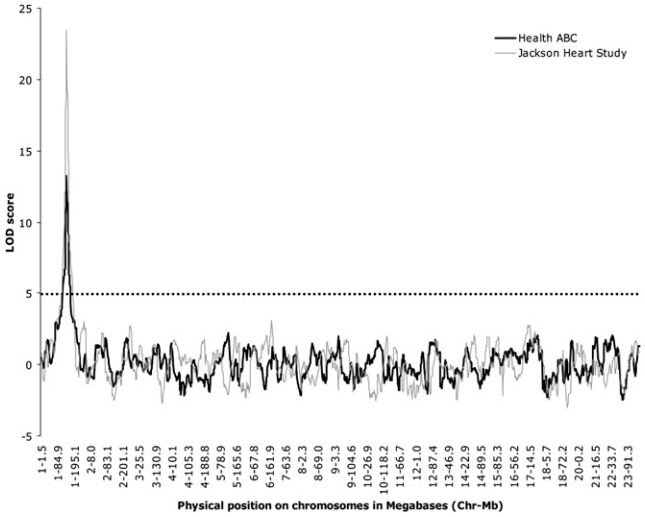

Figure 2. LOD Scores of Case-Control Analysis
Results from ANCESTRYMAP for initial genome-wide scan in Health ABC, as well as replication in the Jackson Heart Study cohort. Broken line signifies significance threshold.

European ancestry and higher WBC among African Americans; this locus appears to explain most (possibly all) of the difference in mean WBC between individuals of African and European ancestry.

All 3 statistical programs used (ADMIXMAP, STRUCTURE, and ANCESTRYMAP) demonstrate a very strong association at rs2814778. It is difficult to directly compare the significance values from the three programs because each program calculates a different statistic for association. In addition, our analysis with ANCESTRYMAP is not directly comparable to the others because it was restricted to individuals with the most extreme phenotypes. To compare the significance levels from the different methods by using p values, we need to rely on the assumptions used to derive p values from the statistics for each distribution. However, for each analysis, the peak represents such an extreme outlier in the distribution that it is unclear whether

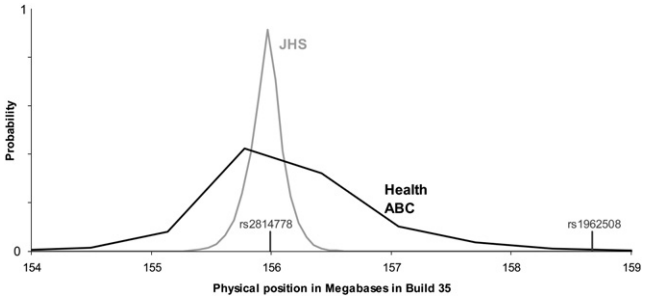

Figure 3. Posterior Probability Distribution for the Position of the Disease Locus, Based on ANCESTRYMAP Scans in the Health ABC Study, Represented by the Black Line, and Jackson Heart Study, Represented by the Gray Line
The 99% confidence interval for the position of the disease locus in the Jackson Heart Study is 155.46-156.36 Mb and is centered on rs2814778.

Table 3. Summary of WBC Mean Values in Health ABC, Comparing African American Genotypic Variation in WBC

	Mean (SD)	Frequency of Genotype in Analysis Population
DARC homozygote (FY−/−)	4.9 (1.3)	62.60%
DARC heterozygote (FY+/−)	6.3 (1.4)	32.00%
DARC homozygote (FY+/+)	7.1 (1.3)	5.30%
European American	6.3 (1.6)	—

Mean WBC measured in 10^{-9} cells per liter. The third column shows the percentage of participants possessing the related genotype. European Americans are included as a reference group for comparison.

the assumptions used to approximate p values are appropriate for comparison across the unique distributions used in the calculations carried out by the different analysis packages. Thus, throughout the paper, we report $p << 10^{-12}$ for extremely significant results, rather than trying to provide a precise p value.

The signal for association with WBC is very strong. In the JHS study, we are able to narrow the 99% confidence interval to a ~0.9 Mb region in the q terminal arm of chromosome 1 from 155.46–156.36 Mb in Build 35 of the reference sequence. The region is centered on SNP rs2814778, known to be within the *DARC* gene.[31] Additional studies with more markers should be able to determine whether this SNP is actually causal.

Although an effect of the FY variation on WBC has never previously been suggested, the known biology at the *DARC* locus is consistent with it affecting levels of WBC. Other studies have suggested that production of arginine 91 at this locus might influence leukocyte activity in nitric oxide metabolism in the lungs.[33] Duffy antigen null (FY−) mice have been shown to have attenuated recruitment of neutrophils into the lungs.[34] It is biologically plausible that the *DARC* gene is involved in leukocyte recruitment, most probably related to its function of chemokine-receptor binding and leukocyte trafficking. The presence of the FY− allele of this SNP has been shown to alter the expression of Duffy antigen on red blood cells and thus render individuals homozygous for this allele resistant to infection from *Plasmodium vivax* malaria (malaria, susceptibility to [MIM #611162]), which uses the Duffy antigen as a receptor.[32,35] Haplotype diversity studies suggest a history of natural selection at this locus, consistent with its protective effect from malaria infection.[36] There is no statistical association between rs2814778 and red blood cell count, therefore allowing us to conclude that this association is not directly a result of generalized bone-marrow function but is specific to WBC.

Variation in baseline WBC is perhaps most clinically relevant as a factor in clinical decision making. Clinical studies would be needed to determine whether knowledge of genotype leads to any more useful clinical assessments or outcomes. Variation in WBC is often a determinant of dosing of cytotoxic therapies such as chemotherapy or therapy for autoimmune diseases.[37] Ranges of the expected

baseline WBC in individual patients could be inferred genetically in African Americans by genotyping rs2814778 and might help clinicians titrate the dose of these drugs in a more individualized way. Further work on this locus should allow for the identification of the causative variant(s) underlying the phenotype and shed light on their biological and clinical implications.

Supplemental Data

One table is available at http://www.ajhg.org/cgi/content/full/82/1/81/DC1/.

Acknowledgments

Research support for this study was provided by the Intramural Research Program of the National Institute on Aging, contracts N01-AG-6-2101, N01-AG-6-2103, and N01-AG-6-2106. Additional support was provided by the National Heart, Lung, and Blood Institute and the National Center on Minority Health and Health Disparities through National Institutes of Health (NIH) contracts N01-HC-95170, N01-HC-95171, and N01-HC-95172. Participation of J.W., N.P., H.T., and D.R. was supported NIH R01: HL084107-02, and D.R. was supported by a Burroughs Wellcome Career Development Award in the Biomedical Sciences.

Received: August 1, 2007
Revised: August 31, 2007
Accepted: September 11, 2007
Published online: January 10, 2007

Web Resources

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim

References

1. Madjid, M., Awan, I., Willerson, J.T., and Casscells, S.W. (2004). Leukocyte count and coronary heart disease: Implications for risk assessment. J. Am. Coll. Cardiol. *44*, 1945–1956.
2. Shankar, A., Wang, J.J., Rochtchina, E., Yu, M.C., Kefford, R., and Mitchell, P. (2006). Association between circulating white blood cell count and cancer mortality: A population-based cohort study. Arch. Intern. Med. *166*, 188–194.
3. Weijenberg, M.P., Feskens, E.J., and Kromhout, D. (1996). White blood cell count and the risk of coronary heart disease and all-cause mortality in elderly men. Arterioscler. Thromb. Vasc. Biol. *16*, 499–503.
4. Oncology Nursing Society (2005). Chemotherapy and biotherapy guidelines and recommendations for practice. Oncology Nursing Society (Pittsburgh, PA: ONS), p. p246.
5. Panel on Antiretroviral Guidelines for Adults and Adolescents (2006). Guidelines for use of antiretroviral agents in HIV-1-infected adults and adolescents (Bethesda, MD: Department of Health and Human Services), p. p116.
6. Reed, W.W., and Diehl, L.F. (1991). Leukopenia, neutropenia, and reduced hemoglobin levels in healthy American blacks. Arch. Intern. Med. *151*, 501–505.
7. Bain, B., Seed, M., and Godsland, I. (1984). Normal values for peripheral blood white cell counts in women of four different ethnic origins. J. Clin. Pathol. *37*, 188–193.
8. Ramsay, S., Lowe, G.D., Whincup, P.H., Rumley, A., Morris, R.W., and Wannamethee, G. (2007). Relationships of inflammatory and haemostatic markers with social class: Results from a population-based study of older men. Atherosclerosis, in press.
9. Pollitt, R.A., Kaufman, J.S., Rose, K.M., Diez-Roux, A.V., Zeng, D., and Heiss, G. (2007). Early-life and adult socioeconomic status and inflammatory risk markers in adulthood. Eur. J. Epidemiol. *22*, 55–66.
10. Garner, C., Tatu, T., Reittie, J.E., Littlewood, T., Darley, J., Cervino, S., Farrall, M., Kelly, P., Spector, T.D., and Thein, S.L. (2000). Genetic influences on F cells and other hematologic variables: A twin heritability study. Blood *95*, 342–346.
11. McKeigue, P.M. (1997). Mapping genes underlying ethnic differences in disease risk by linkage disequilibrium in recently admixed populations. Am. J. Hum. Genet. *60*, 188–196.
12. Patterson, N., Hattangadi, N., Lane, B., Lohmueller, K.E., Hafler, D.A., Oksenberg, J.R., Hauser, S.L., Smith, M.W., O'Brien, S.J., Altshuler, D., et al. (2004). Methods for high-density admixture mapping of disease genes. Am. J. Hum. Genet. *74*, 979–1000.
13. Chakraborty, R., and Weiss, K.M. (1988). Admixture as a tool for finding linked genes and detecting that difference from allelic association between loci. Proc. Natl. Acad. Sci. USA *85*, 9119–9123.
14. Stephens, J.C., Briscoe, D., and O'Brien, S.J. (1994). Mapping by admixture linkage disequilibrium in human populations: limits and guidelines. Am. J. Hum. Genet. *55*, 809–824.
15. McKeigue, P.M. (1998). Mapping genes that underlie ethnic differences in disease risk: Methods for detecting linkage in admixed populations, by conditioning on parental admixture. Am. J. Hum. Genet. *63*, 241–251.
16. Reiner, A.P., Carlson, C.S., Ziv, E., Iribarren, C., Jaquish, C.E., and Nickerson, D.A. (2007). Genetic ancestry, population sub-structure, and cardiovascular disease-related traits among African-American participants in the CARDIA Study. Hum. Genet. *121*, 565–575.
17. Tang, H., Jorgenson, E., Gadde, M., Kardia, S.L., Rao, D.C., Zhu, X., Schork, N.J., Hanis, C.L., and Risch, N. (2006). Racial admixture and its impact on BMI and blood pressure in African and Mexican Americans. Hum. Genet. *119*, 624–633.
18. Freedman, M.L., Haiman, C.A., Patterson, N., McDonald, G.J., Tandon, A., Waliszewska, A., Penney, K., Steen, R.G., Ardlie, K., John, E.M., et al. (2006). Admixture mapping identifies 8q24 as a prostate cancer risk locus in African-American men. Proc. Natl. Acad. Sci. USA *103*, 14068–14073.
19. Reich, D., Patterson, N., Ramesh, V., De Jager, P.L., McDonald, G.J., Tandon, A., Choy, E., Hu, D., Tamraz, B., Pawlikowska, L., et al. (2007). Admixture mapping of an allele affecting interleukin 6 soluble receptor and interleukin 6 levels. Am. J. Hum. Genet. *80*, 716–726.
20. Oksenberg, J.R., Barcellos, L.F., Cree, B.A., Baranzini, S.E., Bugawan, T.L., Khan, O., Lincoln, R.R., Swerdlin, A., Mignot, E., Lin, L., et al. (2004). Mapping multiple sclerosis susceptibility to the HLA-DR locus in African Americans. Am. J. Hum. Genet. *74*, 160–167.
21. Reich, D., Patterson, N., De Jager, P.L., McDonald, G.J., Waliszewska, A., Tandon, A., Lincoln, R.R., DeLoa, C., Fruhan, S.A.,

Cabre, P., et al. (2005). A whole-genome admixture scan finds a candidate locus for multiple sclerosis susceptibility. Nat. Genet. *37*, 1113–1118.
22. Fan, J.B., Oliphant, A., Shen, R., Kermani, B.G., Garcia, F., Gunderson, K.L., Hansen, M., Steemers, F., Butler, S.L., Deloukas, P., et al. (2003). Highly parallel SNP genotyping. Cold Spring Harb. Symp. Quant. Biol. *68*, 69–78.
23. Myers, S., Bottolo, L., Freeman, C., McVean, G., and Donnelly, P. (2005). A fine-scale map of recombination rates and hotspots across the human genome. Science *310*, 321–324.
24. Thorisson, G.A., Smith, A.V., Krishnan, L., and Stein, L.D. (2005). The International HapMap Project Web site. Genome Res. *15*, 1592–1593.
25. Falush, D., Stephens, M., and Pritchard, J.K. (2003). Inference of population structure using multilocus genotype data: linked loci and correlated allele frequencies. Genetics *164*, 1567–1587.
26. Pritchard, J.K., Stephens, M., and Donnelly, P. (2000). Inference of population structure using multilocus genotype data. Genetics *155*, 945–959.
27. McKeigue, P.M., Carpenter, J.R., Parra, E.J., and Shriver, M.D. (2000). Estimation of admixture and detection of linkage in admixed populations by a Bayesian approach: application to African-American populations. Ann. Hum. Genet. *64*, 171–186.
28. Tsai, H.J., Choudhry, S., Naqvi, M., Rodriguez-Cintron, W., Burchard, E.G., and Ziv, E. (2005). Comparison of three methods to estimate genetic ancestry and control for stratification in genetic association studies among admixed populations. Hum. Genet. *118*, 424–433.
29. Reich, D., and Patterson, N. (2005). Will admixture mapping work to find disease genes? Philos. Trans. R. Soc. Lond. B Biol. Sci. *360*, 1605–1607.
30. Taylor, H.A. Jr., Wilson, J.G., Jones, D.W., Sarpong, D.F., Srinivasan, A., Garrison, R.J., Nelson, C., and Wyatt, S.B. (2005). Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. Ethn. Dis. *15*, S6–4–17.
31. Maglott, D., Ostell, J., Pruitt, K.D., and Tatusova, T. (2007). Entrez gene: Gene-centered information at NCBI. Nucleic Acids Res. *35*, D26–D31.
32. Miller, L.H., Mason, S.J., Dvorak, J.A., McGinniss, M.H., and Rothman, I.K. (1975). Erythrocyte receptors for (Plasmodium knowlesi) malaria: Duffy blood group determinants. Science *189*, 561–563.
33. Parasol, N., Reid, M., Rios, M., Castilho, L., Harari, I., and Kosower, N.S. (1998). A novel mutation in the coding sequence of the FY*B allele of the Duffy chemokine receptor gene is associated with an altered erythrocyte phenotype. Blood *92*, 2237–2243.
34. Lee, J.S., Frevert, C.W., Wurfel, M.M., Peiper, S.C., Wong, V.A., Ballman, K.K., Ruzinski, J.T., Rhim, J.S., Martin, T.R., and Goodman, R.B. (2003). Duffy antigen facilitates movement of chemokine across the endothelium in vitro and promotes neutrophil transmigration in vitro and in vivo. J. Immunol. *170*, 5244–5251.
35. Hadley, T.J., and Peiper, S.C. (1997). From malaria to chemokine receptor: The emerging physiologic role of the Duffy blood group antigen. Blood *89*, 3077–3091.
36. Hamblin, M.T., Thompson, E.E., and Di Rienzo, A. (2002). Complex signatures of natural selection at the Duffy blood group locus. Am. J. Hum. Genet. *70*, 369–383.
37. Drobyski, W.R., Keever, C.A., Roth, M.S., Koethe, S., Hanson, G., McFadden, P., Gottschall, J.L., Ash, R.C., van Tuinen, P., Horowitz, M.M., et al. (1993). Salvage immunotherapy using donor leukocyte infusions as treatment for relapsed chronic myelogenous leukemia after allogeneic bone marrow transplantation: efficacy and toxicity of a defined T-cell dose. Blood *82*, 2310–2318.