Supplemental Data

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Sequence Variants in Three Loci Influence Monocyte Counts and Erythrocyte Volume

Manuel A. R. Ferreira, Jouke-Jan Hottenga, Nicole M. Warrington, Sarah E. Medland, Gonneke Willemsen, Robert W. Lawrence, Scott Gordon, Eco J. C. de Geus, Anjali K. Henders, Johannes H. Smit, Megan J. Campbell, Leanne Wallace, David M. Evans, Margaret J. Wright, Dale R. Nyholt, Alan L. James, John P. Beilby, Brenda W. Penninx, Lyle J. Palmer, Ian H. Frazer, Grant W. Montgomery, Nicholas G. Martin, and Dorret I. Boomsma

Figure S1. Power ($\alpha = 3.5\text{x}10^{-9}$) provided by the combined Australian and Dutch analysis to detect a quantitative trait locus (QTL) explaining 0.1% to 1.5% of the total phenotypic variance (h^2). Power was estimated as the proportion of 1,000 datasets simulated with Merlin [1] under the null hypothesis of no association with a $P < 3.5\text{x}10^{-9}$. Datasets were simulated while preserving the original missingness patterns and assuming a trait with a total heritability of 75% and a sibling correlation of 0.4. Eighty percent power (horizontal line) was achieved for a QTL heritability of 0.82% (vertical line).

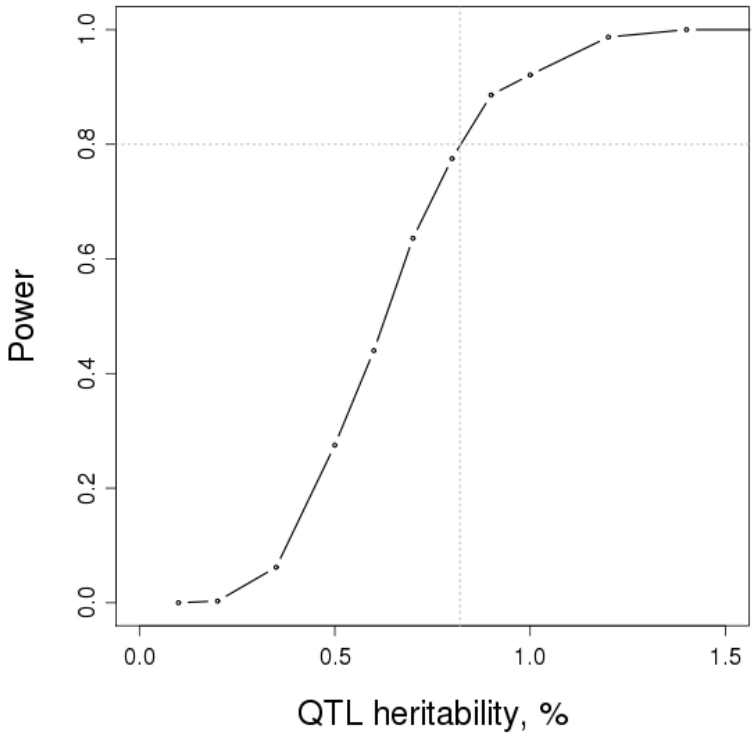

Figure S2. Quantile-quantile plots for the thirteen traits tested. The upper and lower boundaries of the 95% confidence bands are represented by the red lines. The corresponding genomic inflation factor (λ) is also shown for each trait. Observed *P*-values were truncated at 10^{-10}. HB: hemoglobin; MCH: mean cell hemoglobin; MCHC: mean cell hemoglobin concentration; RBC: red blood cell count; HT: hematocrit; MCV: mean cell volume; PLT: platelet count; WBC: white blood cell count; NEUT: neutrophil count; LYMPH: lymphocyte count; MONO: monocyte count; EOS: eosinophil count; BASO: basophil count.

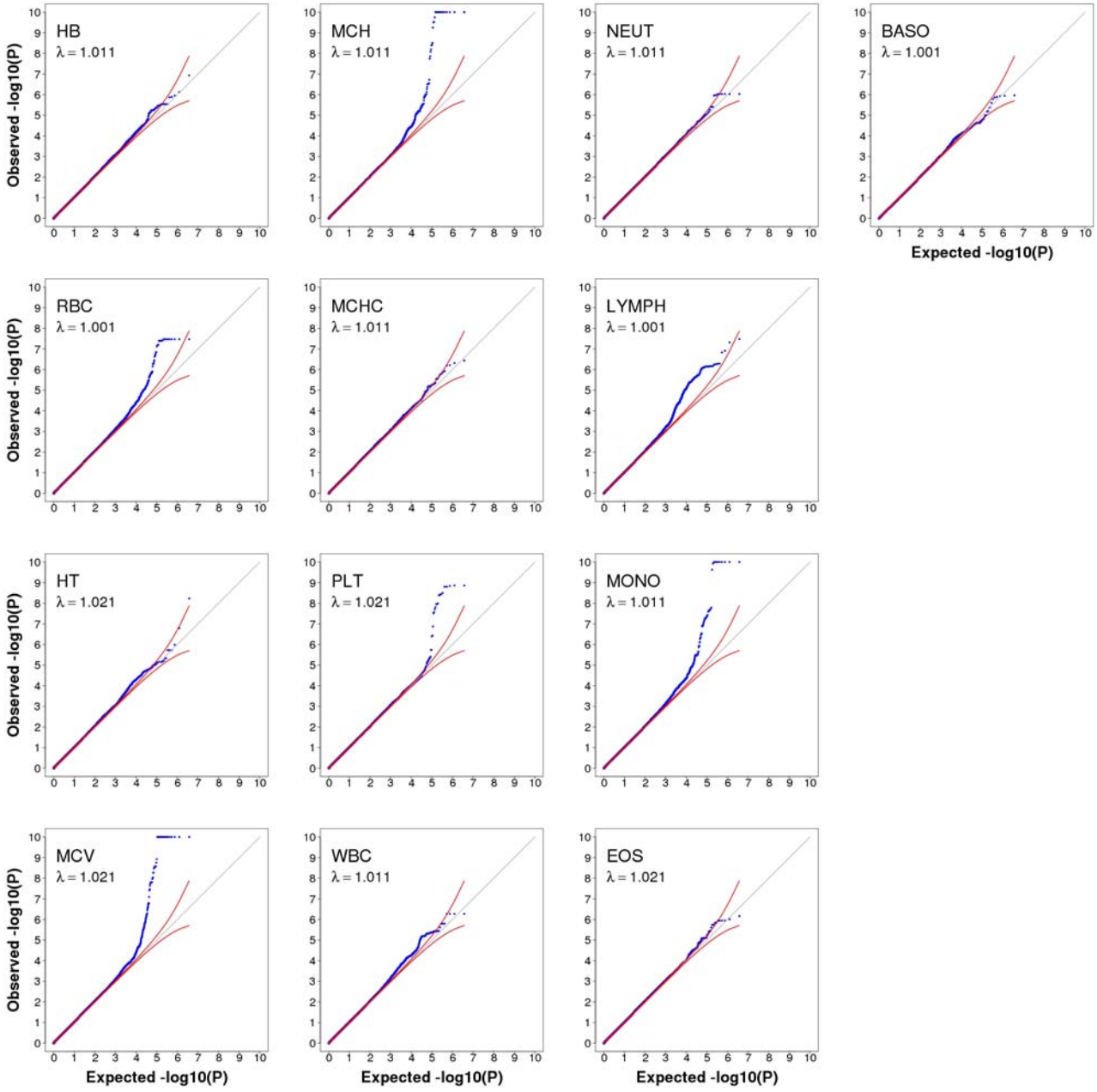

Figure S3. Genome-wide association results for hemoglobin composition, red blood cell indices and platelet count in the combined analysis of the Australian and Dutch GWAS datasets. Horizontal line indicates a *P*-value of 5.5×10^{-9}. SNPs with a *P*-value < 1×10^{-5} are highlighted in green.

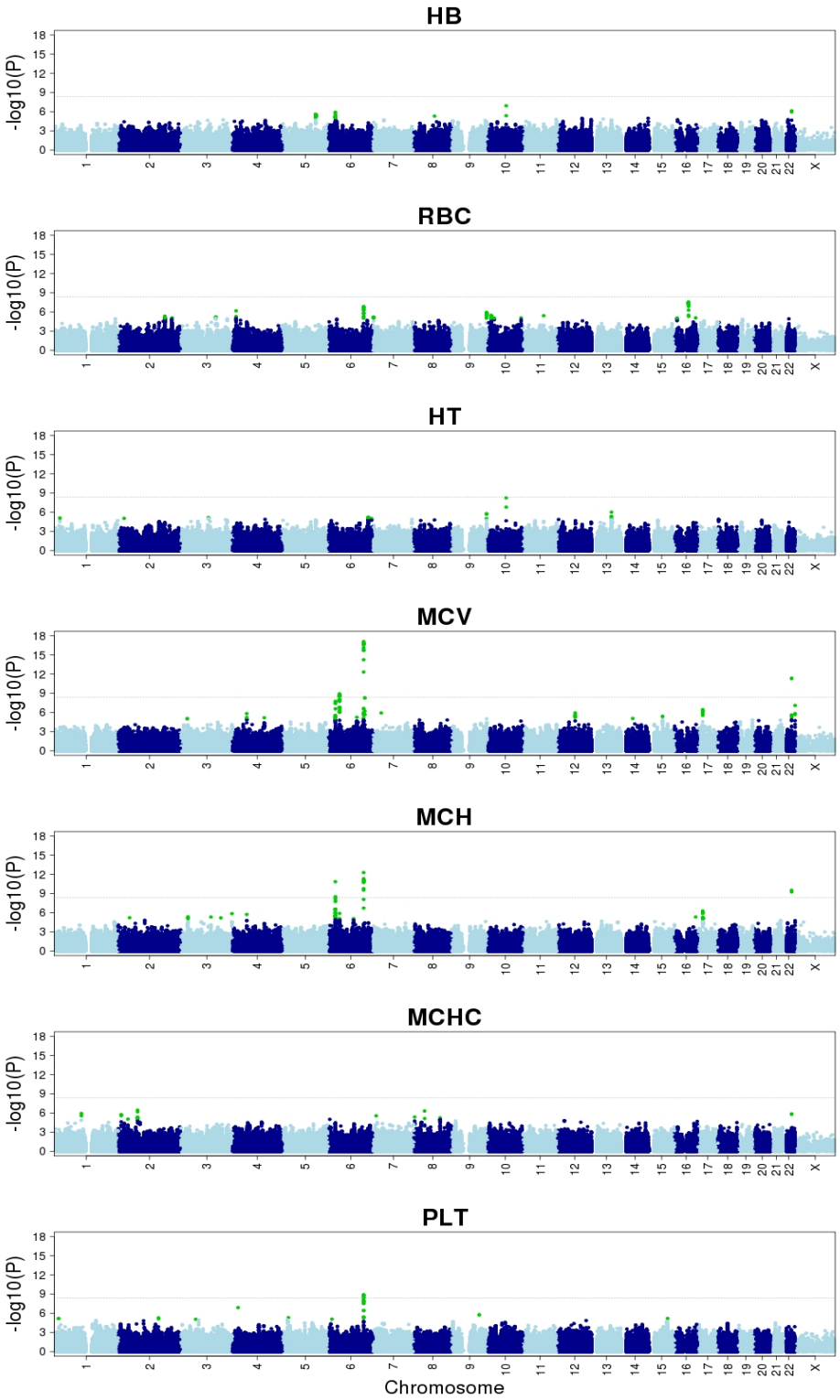

Figure S3 (continued). Genome-wide association results for white blood cell indices in the combined analysis of the Australian and Dutch datasets. Horizontal line indicates a *P*-value of 5.5×10^{-9}. SNPs with a *P*-value < 1×10^{-5} are highlighted in green.

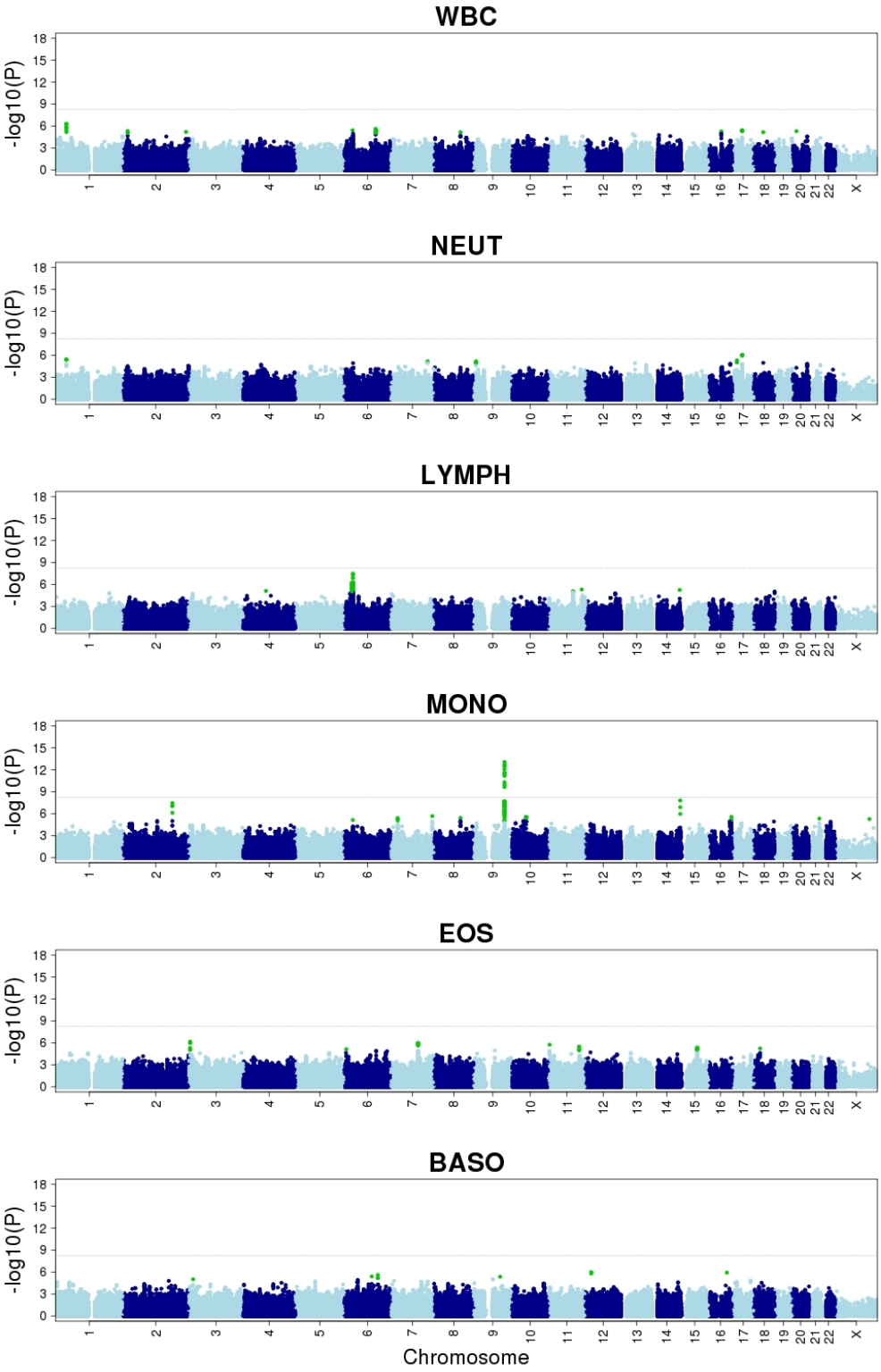

Figure S4. Summary of results from the genome-wide heterogeneity analysis between the Australian and Dutch datasets. For each trait, we tested whether the effect size (i.e. regression coefficient from linear regression) for individual SNPs across the genome differed between the Australian and Dutch cohorts. Each panel plots the observed *P*-value for the test of heterogeneity against the expected null distribution. There was no evidence for widespread heterogeneity of effects between the two cohorts, as evidenced by the close agreement between the distribution of observed P-values and that expected based on the null hypothesis of no heterogeneity.

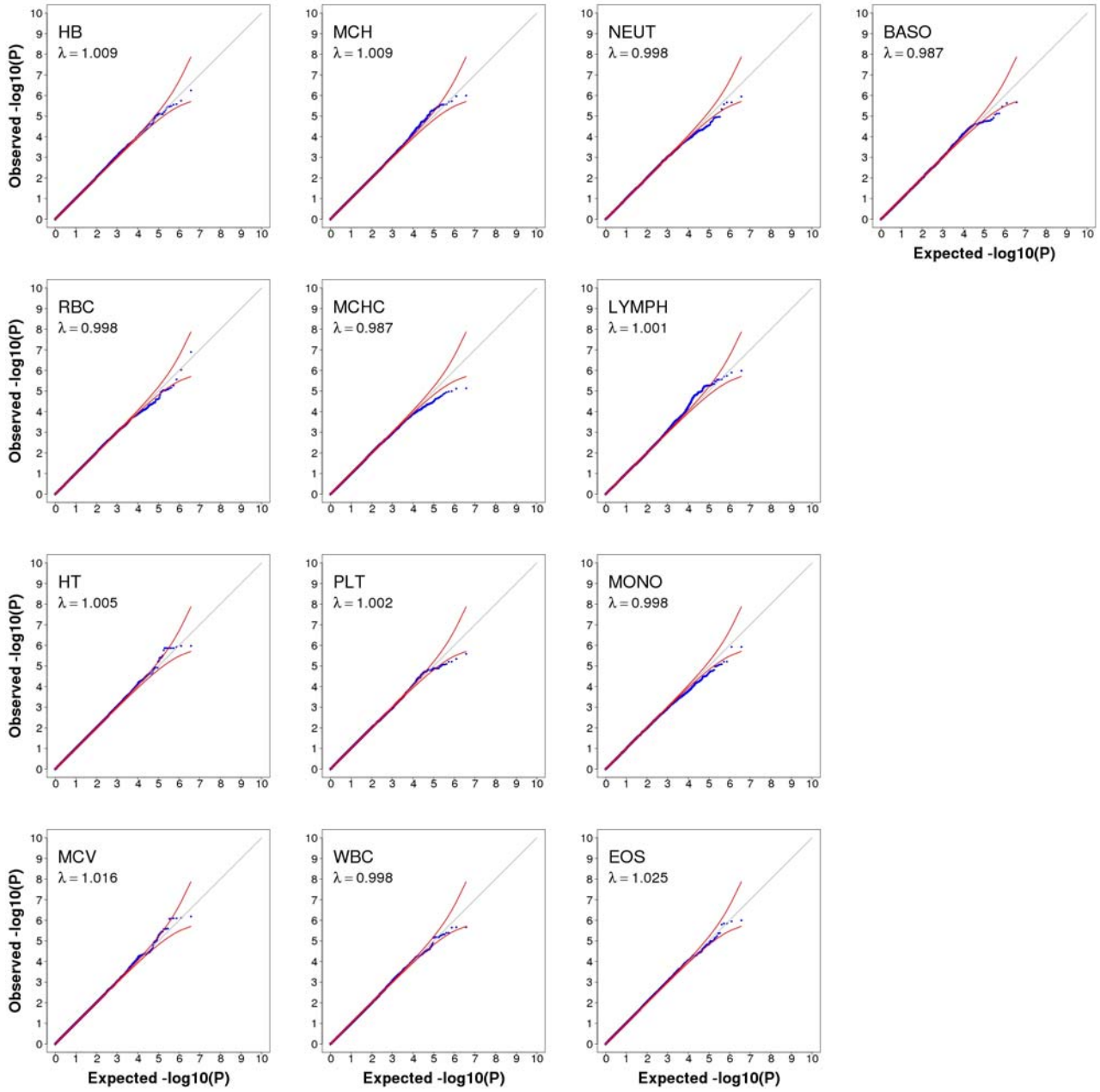

Figure S5. Genome-wide association results for hemoglobin composition, red blood cell indices and platelet count in the analysis of the Australian GWAS dataset. Horizontal line indicates a *P*-value of 5.5×10^{-9}. SNPs with a *P*-value < 1×10^{-5} are highlighted in green.

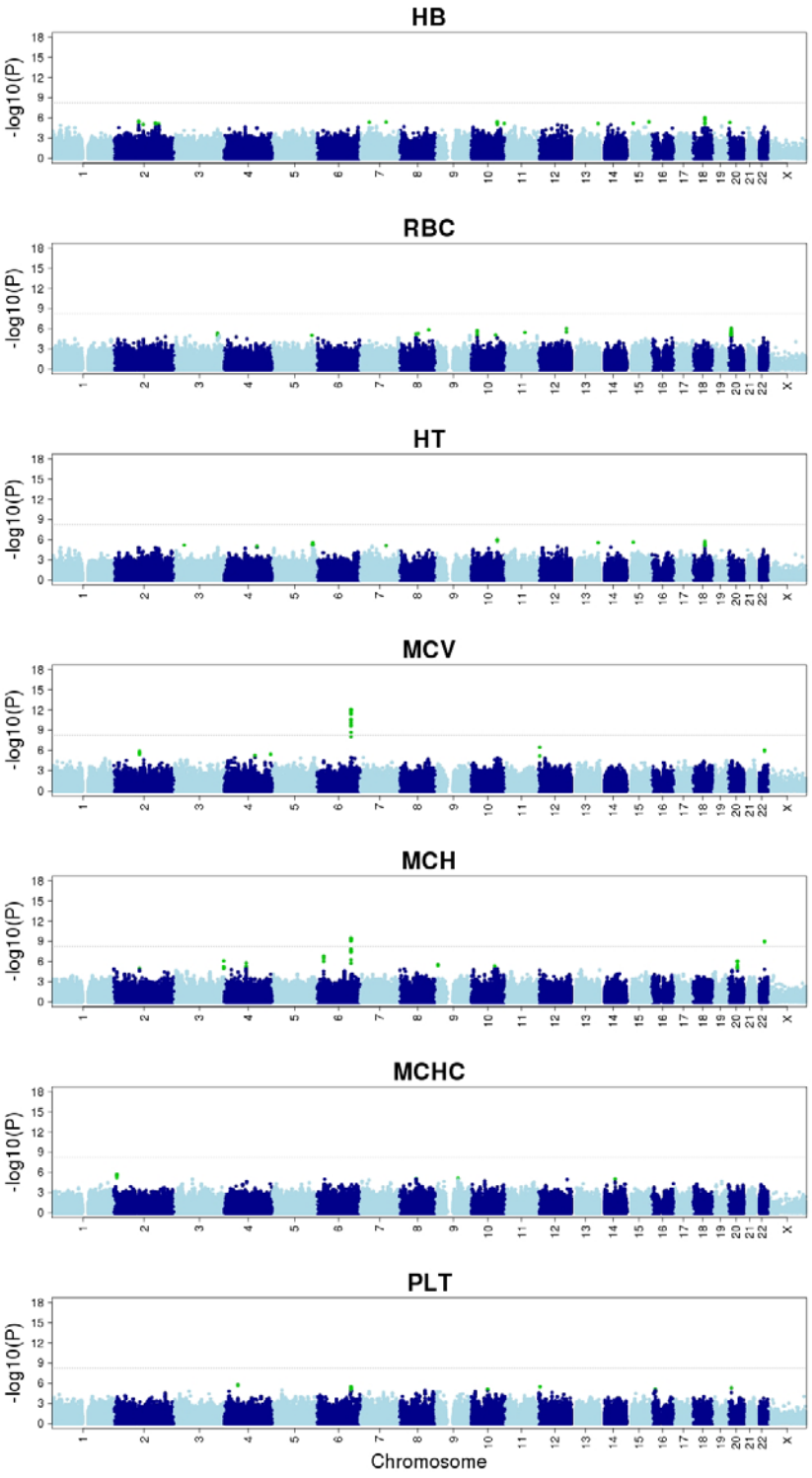

Figure S5 (continued). Genome-wide association results for white blood cell indices in the analysis of the Australian dataset. Horizontal line indicates a *P*-value of 5.5×10^{-9}. SNPs with a *P*-value < 1×10^{-5} are highlighted in green.

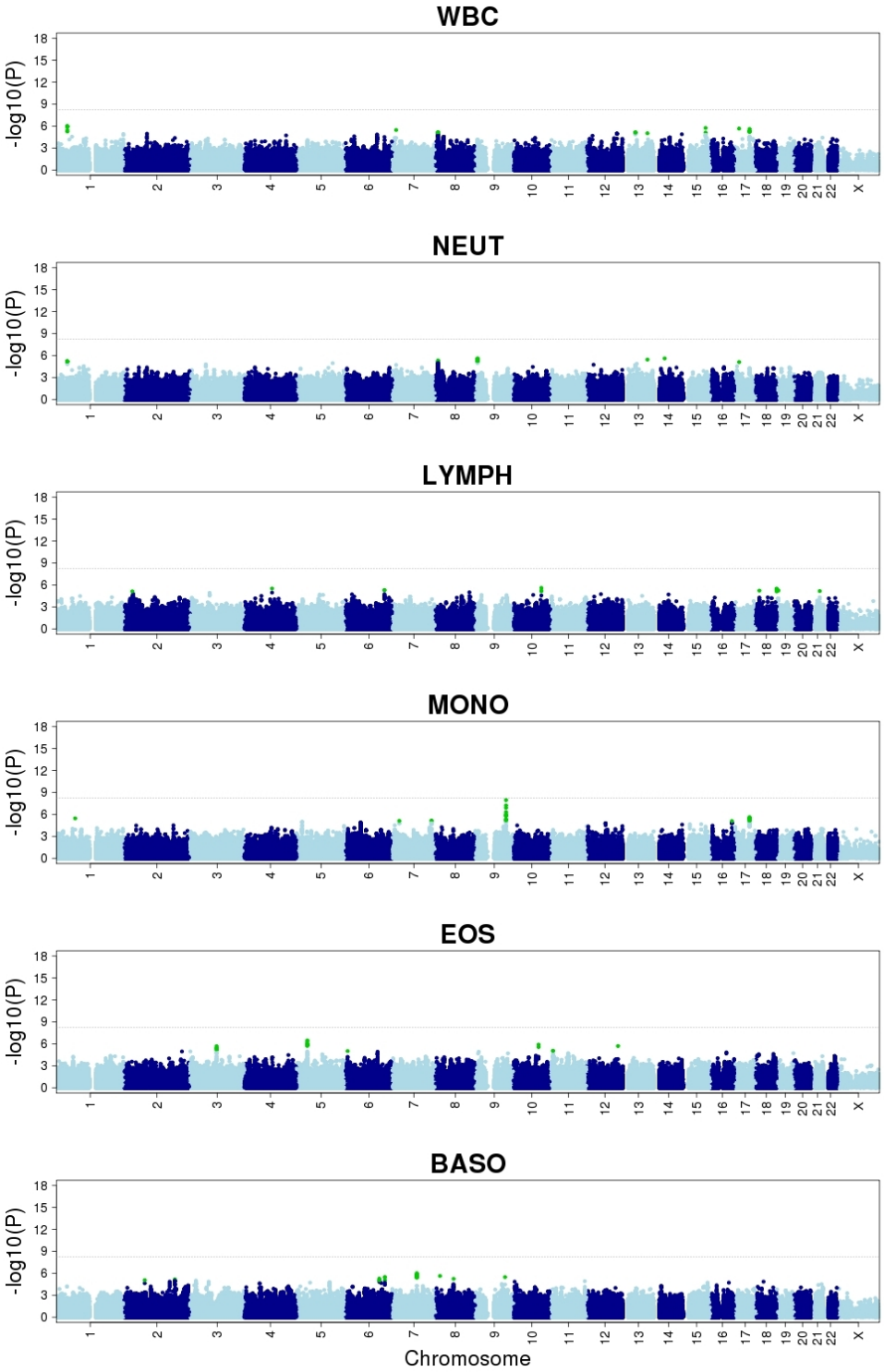

Figure S6. Genome-wide association results for hemoglobin composition, red blood cell indices and platelet count in the analysis of the Dutch GWAS dataset. Horizontal line indicates a *P*-value of 5.5×10^{-9}. SNPs with a *P*-value < 1×10^{-5} are highlighted in green.

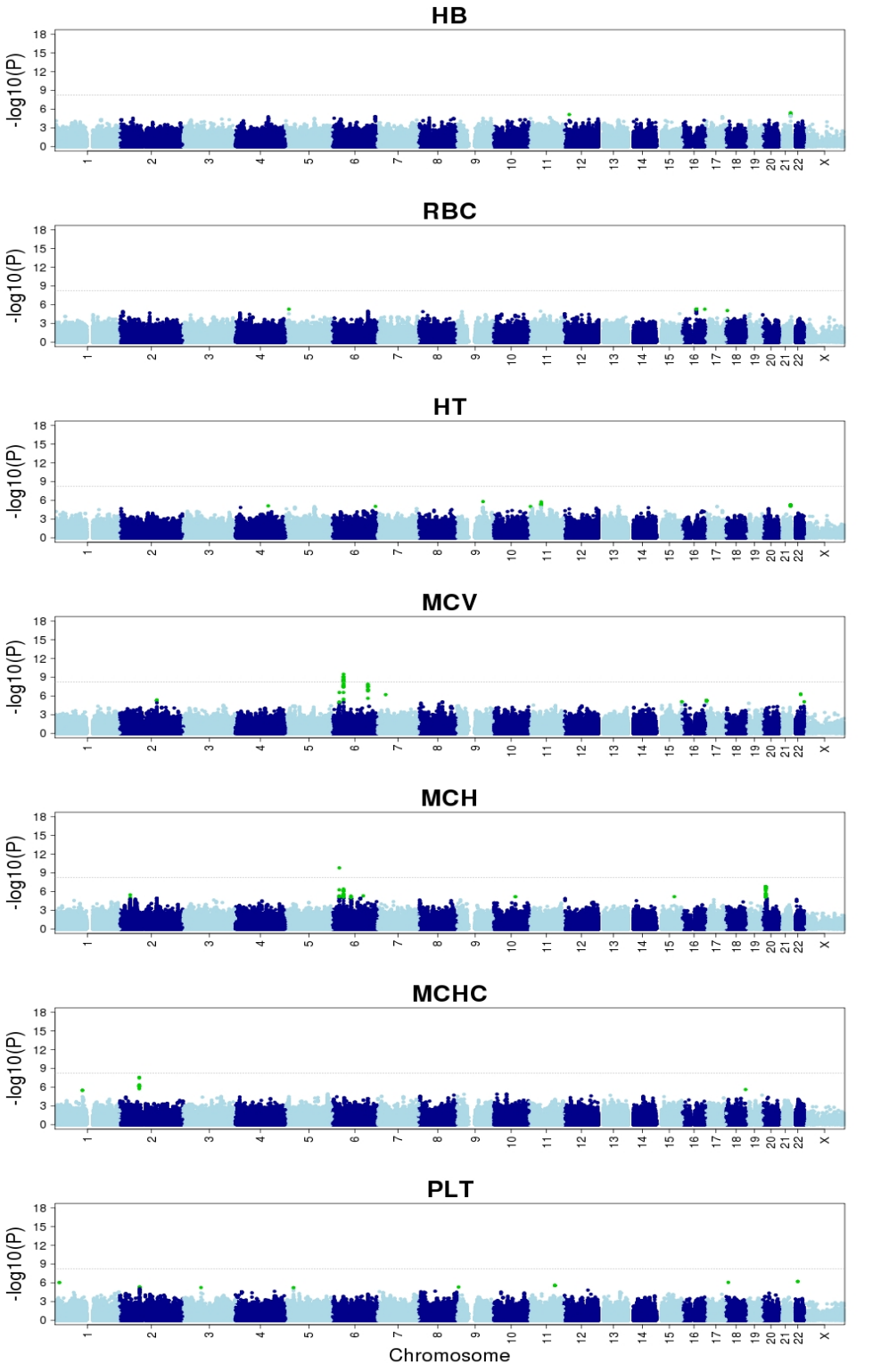

Figure S6 (continued). Genome-wide association results for white blood cell indices in the analysis of the Dutch dataset. Horizontal line indicates a *P*-value of 5.5×10^{-9}. SNPs with a *P*-value < 1×10^{-5} are highlighted in green.

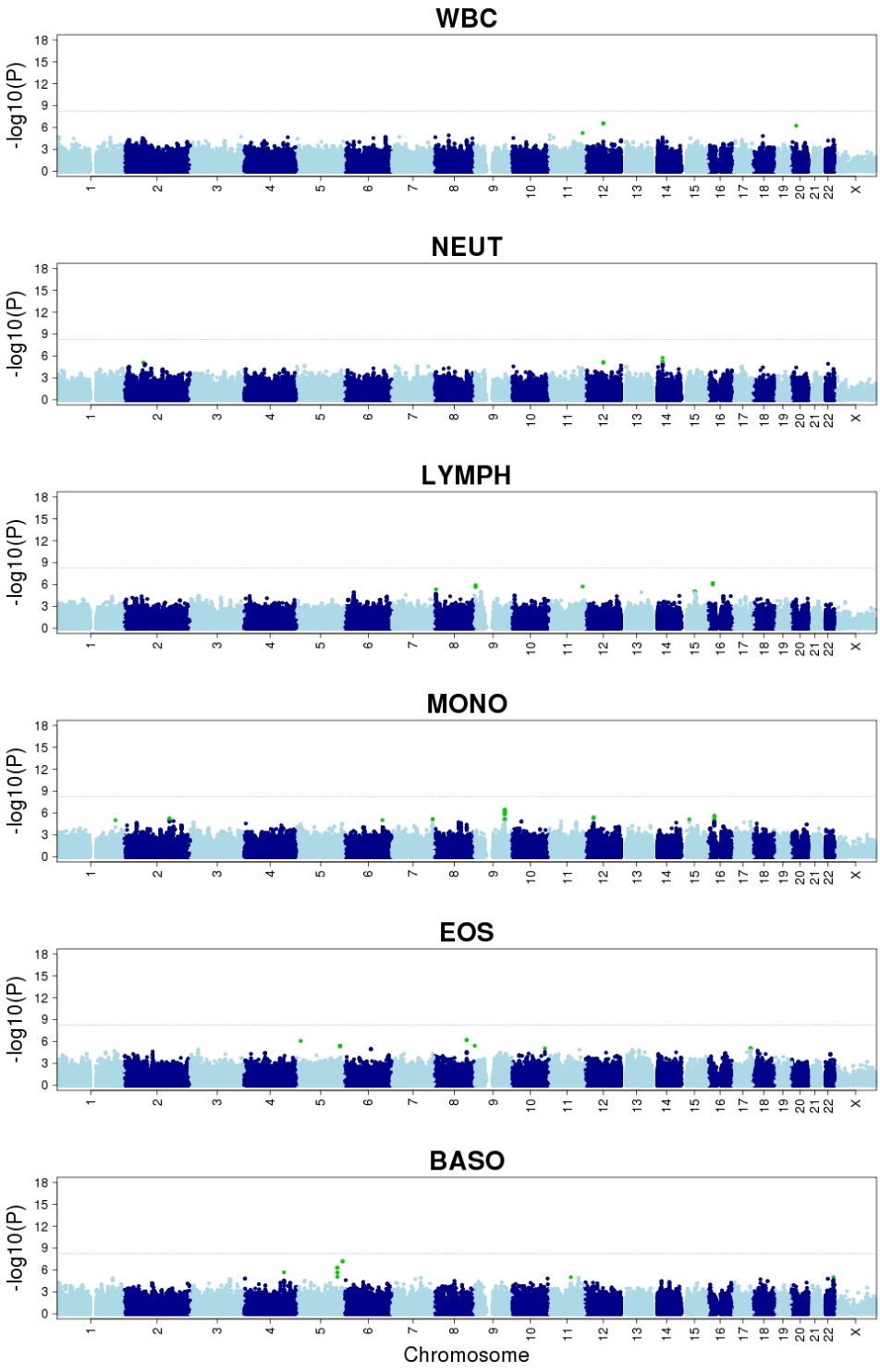

Table S1. Characteristics of the study participants for the two GWAS cohorts studied

	Australian cohort	**Dutch cohort[a]**	
		NTR subset	NESDA subset
	N individuals		
Genotyped (& clinical)[b]	3,995 (2,538)	1,740 (1,740)	1,737 (1,737)
	Demographics[c]		
Female sex, %	51	64	68
Mean age (range), years	15 (10-37)	45 (18-81)	42 (18-65)
	Mean trait levels (SD, range)[c]		
Hemoglobin composition:			
Hb, g/L	137.5 (9.6, 110-174)	140.9 (12.9, 77.3-185.3)	139.6 (12.4, 90.2-178.9)
MCH, picograms/cell	29.0 (1.3, 22.7-34.0)	30.6 (1.7, 22.4-38.0)	-
MCHC, g/L	331.2 (8.2, 293.5-356.1)	333.4 (7.5, 291.2-363.4)	338.7 (9.6, 291.1-374.9)
Red blood cell indices:			
RBC, 10^{12} cells/L	4.8 (0.34, 3.7-6.4)	4.6 (0.42, 3.1-6.3)	-
HT, %	0.42 (0.03, 0.34-0.51)	0.42 (0.04, 0.26-0.56)	0.41(0.03, 0.28-0.51)
MCV, fL/cell	87.4 (3.7, 73-103)	92.0 (4.3, 67.9-111.9)	89.4 (4.4, 68-112)
PLT, 10^9 cells/L	270.1 (52.1, 115-550)	252.1 (60.0, 30-497)	-
White blood cell indices:			
WBC, 10^9 cells/L	7.1 (1.5, 3.1-14.9)	6.5 (1.8, 2.3-15.4)	-
NEUT, 10^9 cells/L	3.7 (1.2, 1.0-10.4)	3.5 (1.3, 0.1-9.5)	-
LYMPH, 10^9 cells/L	2.5 (0.57, 0.52-4.9)	2.2 (0.68, 0.3-5.5)	-
MONO, 10^9 cells/L	0.54 (0.15, 0.03-1.2)	0.54 (0.17 ,0.1-1.3)	-
EOS, 10^9 cells/L	0.31 (0.22, 0-1.7)	0.20 (0.12 ,0-0.8)	-
BASO, 10^9 cells/L	0.03 (0.02, 0-0.17)	0.02 (0.05, 0-0.2)	-
	Core family configuration N families (N individuals) analysed[d]		
2 parents, 4+ offspring	42 (256)	0	0
2 parents, 3 offspring	154 (771)	0	0
2 parents, 2 offspring	519 (2,076)	0	0
2 parents, 1 offspring	14 (42)	0	0
1 parent, 4 offspring	1 (5)	0	0
1 parent, 3 offspring	2 (8)	0	0
1 parent, 2 offspring	14 (42)	0	0
1 parent, 1 offspring	1 (2)	0	0
0 parents, 4+ offspring	17 (71)	0	0
0 parents, 3 offspring	77(233)	0	0
0 parents, 2 offspring	229 (465)	0	0
0 parents, 1 offspring	19 (24)	1,740 (1,740)	1,737 (1,737)

Total	1,089 (3,995)	1,740 (1,740)	1,737 (1,737)

[a] The Dutch participants were drawn from the GAIN-MDD study, which is a case-control study of major depressive disorder in unrelated individuals aged 18-60 years[2]. Subjects eligible for inclusion in the GAIN-MDD study came from two Dutch longitudinal projects: the Netherlands Study of Depression and Anxiety (NESDA, www.nesda.nl), and from the Netherlands Twin Registry (NTR, www.tweelingenregister.org). Before the start of the NESDA and NTR biological sample collection, processing and storage protocols were harmonized.

[b] For the Australian cohort, parents were not phenotyped for hematology traits but 1,457 were genotyped to improve genotype error detection and the power of association analysis.

[c] Figures are based on individuals that were both genotyped and clinically tested.

[d] Counts consider founders in a family if genotyped and non-founders if both genotyped and clinically tested. For a small number of Australian families, data were included from relatives other than those part of the core family configuration (eg. spouses of twins). For this reason, the total number of individuals may differ from that expected from the main family configuration and number of families with data.

Hb: hemoglobin; MCH: mean cell hemoglobin; MCHC: mean cell hemoglobin concentration; RBC: red blood cell count; HT: hematocrit; MCV: mean cell volume; PLT: platelet count; WBC: white blood cell count; NEUT: neutrophil count; LYMPH: lymphocyte count; MONO: monocyte count; EOS: eosinophil count; BASO: basophil count.

Table S2. Heritabilities[a] (main diagonal) and cross-trait phenotypic correlations[b] (below main diagonal) for the thirteen phenotypes tested.

	Hb	**MCH**	**MCHC**	**RBC**	**HT**	**MCV**	**PLT**	**WBC**	**NEUT**	**LYMPH**	**MONO**	**EOS**	**BASO**
Hb	90												
MCH	0.20	86											
MCHC	0.21	0.47	79										
RBC	0.62	-0.30	-0.08	94									
HT	0.76	0.10	-0.12	0.62	78								
MCV	0.16	0.85	-0.02	-0.29	0.21	87							
PLT	-0.03	-0.08	-0.07	0.03	0.00	-0.06	79						
WBC	0.08	0.00	-0.02	0.05	0.08	-0.01	0.30	72					
NEUT	0.07	-0.01	-0.01	0.08	0.08	-0.01	0.24	0.87	63				
LYMPH	0.08	0.04	0.02	0.02	0.07	0.03	0.22	0.58	0.19	77			
MONO	0.06	0.03	-0.01	0.01	0.09	0.02	0.21	0.57	0.43	0.34	68		
EOS	0.06	-0.01	0.01	0.01	0.02	-0.02	0.14	0.35	0.17	0.24	0.25	69	
BASO	-0.01	-0.01	-0.06	-0.01	0.01	0.00	0.12	0.23	0.15	0.18	0.15	0.17	35

[a] Heritabilities were estimated in the Australian cohort with Merlin[3] after excluding phenotypic outliers, adjusting for age and sex, and normalising each trait. For more detailed heritability analyses, please see ref. 4.

[b] Cross-trait phenotypic correlations were estimated on a subset of up to 4,612 unrelated individuals from the combined Australian and Dutch cohorts.

Hb: hemoglobin; MCH: mean cell hemoglobin; MCHC: mean cell hemoglobin concentration; RBC: red blood cell count; HT: hematocrit; MCV: mean cell volume; PLT: platelet count; WBC: white blood cell count; NEUT: neutrophil count; LYMPH: lymphocyte count; MONO: monocyte count; EOS: eosinophil count; BASO: basophil count.

Table S3. Breakdown of SNP and sample filtering during QC of the Australian GWAS dataset. The QC process for the Dutch cohort is described in detail elsewhere[5].

		SNPs	Individuals
N at start of QC		599,011	4,406
N dropped at QC step:			
1	BeadStudio GenCall score < 0.7	47,418	-
2	Individuals with call rate < 0.95	-	1
3	SNPs with call rate < 0.95	539	-
4	SNPs with HWE failure $P < 10^{-6}$	813	-
5	SNPs with MAF < 0.01	20,520	-
6	Individuals from families with pedigree errors[a]	-	21
7	SNPs with Mendel failure rate in > 0.05 families	0	-
8	Individuals from families with Mendel failure rate in > 0.05 SNPs	-	0
9	Population stratification gross outliers[b]	-	88
10	Individuals from families with no available hematology data		301
N at end of QC		529,721	3,995

[a] We compared self-reported with genotype-inferred family relationships, the latter based on genome-wide IBS sharing. Forty-eight families with pedigree errors were identified; 21 samples from these families were excluded to correct errors which could not be resolved.

[b] We excluded 88 individuals identified as outliers from populations of European descent through the estimation of genetic ancestry using EIGENSTRAT[6] and data from eleven populations of the HapMap 3 and five Northern European populations genotyped by the GenomeEUtwin consortium.

Table S4. Three loci that showed strong evidence for association ($P < 5.5x10^{-9}$) in the combined genome-wide analysis of the Australian and Dutch cohorts and have previously been reported to associate with variation in hematology traits.

Locus	Trait	SNP, Allele	Sample size	Allele frequency	Effect[a]	SE	h^2, %	Association *P*-value	Heterogeneity *P*-value[b]
HBS1L/MYB	MCV	rs7775698, C	5945	0.74	-0.19	0.02	1.3	7.8E-18	0.056
	MCH	rs7775698, C	4241	0.74	-0.19	0.03	1.3	5.1E-13	0.101
	PLT	rs9399137, T	4247	0.74	-0.16	0.03	1.0	1.4E-09	0.637
TMPRSS6	MCV	rs4820268, A	5945	0.53	0.13	0.02	0.9	4.4E-12	0.400
	MCH	rs4820268, A	4241	0.53	0.15	0.02	1.0	3.1E-10	0.043
HFE	MCH	rs1408272, T	4235	0.94	-0.32	0.05	1.3	1.4E-11	0.009

[a] Effect corresponds to standard deviation units for the transformed phenotype, while h^2 represents the proportion of phenotypic variance explained by the SNP.

[b] Results for the test of heterogeneity of effect size between the two samples that form the GWAS panel (Australian and Dutch cohorts). A significant *P*-value indicates significant evidence for heterogeneity.

MCH: mean cell hemoglobin; MCV: mean cell volume; PLT: platelet count. SE: standard error.

Table S5. Loci with less stringent evidence for association ($5.5x10^{-9} < P < 10^{-5}$) with variation in hemoglobin composition and red blood cell indices in the combined analysis of the Australian and Dutch GWAS datasets.

Trait	Chromosome, bp position	SNP, allele	Nearest gene, bp distance[a]	Sample size	Allele frequency	Effect[b]	SE	h^2, %	*P*-value
HB	10,70769894	rs10159477,G	HK1,61749,*	5949	0.86	-0.15	0.03	0.5	1.2E-07
HB	22,35799537	rs4820268,A	TMPRSS6,8113,*	5950	0.53	0.09	0.02	0.4	7.4E-07
HB	6,25749179	rs932316,T	SCGN,11228,	5944	0.81	-0.12	0.03	0.4	1.3E-06
HB	5,130441588	rs1422660,C	HINT1,81187,	5950	0.75	-0.10	0.02	0.4	2.8E-06
HB	6,26233321	rs129128,T	HIST1H2AC,912,*	5950	0.86	-0.13	0.03	0.4	3.1E-06
HB	8,79879091	rs3888020,C	IL7,1222,*	5941	0.65	-0.09	0.02	0.4	5.0E-06
MCH	6,25562994	rs10498725,C	LRRC16A,165743,*	4240	0.81	-0.17	0.03	0.9	6.4E-09
MCH	17,19933199	rs11867585,G	CYTSB,2273,*	4239	0.57	0.12	0.02	0.7	5.3E-07
MCH	6,42033268	rs11970772,T	CCND3,16146,	4241	0.81	-0.14	0.03	0.6	1.3E-06
MCH	3,197338676	rs7625441,C	TFRC,45318,	4240	0.73	-0.12	0.03	0.6	1.4E-06
MCH	4,55102662	rs218262,C	KIT,116189,	4237	0.89	-0.17	0.04	0.6	1.9E-06
MCH	3,26858666	rs10865809,T	LRRC3B,131397,	4224	0.68	0.11	0.03	0.6	4.4E-06
MCH	16,81386902	rs4783277,G	CDH13,168824,*	4238	0.66	0.11	0.03	0.6	4.7E-06
MCH	3,116047902	rs1543247,C	ZBTB20,225010,*	4236	0.94	-0.22	0.05	0.6	4.7E-06
MCH	2,43961246	rs2954804,G	ABCG8,2137,	4241	0.72	-0.12	0.03	0.5	6.1E-06
MCH	3,154195486	rs9822081,A	P2RY1,156953,	4239	0.84	0.15	0.03	0.6	6.5E-06
MCH	6,28893064	rs3118362,T	TRIM27,85694,	4233	0.91	-0.19	0.04	0.5	8.3E-06
MCH	6,96489123	rs2799633,A	FUT9,81442,	4240	0.52	0.10	0.02	0.5	9.3E-06
MCHC	2,74937383	rs6735303,C	HK2,24094,*	5921	0.79	0.12	0.02	0.5	3.6E-07
MCHC	8,41749562	rs4737009,G	NKX6-3,12980,*	5908	0.75	0.11	0.02	0.5	4.8E-07
MCHC	1,104491594	rs11185384,C	AMY1C,451159,	5927	0.72	0.10	0.02	0.4	1.2E-06
MCHC	22,35800170	rs2413450,C	TMPRSS6,8746,*	5925	0.53	0.09	0.02	0.4	1.4E-06
MCHC	2,11667552	rs3762581,G	GREB1,32811,*	5925	0.51	-0.09	0.02	0.4	1.8E-06
MCHC	7,12797702	rs9719021,G	ARL4A,100619,	5913	0.61	0.09	0.02	0.4	2.8E-06
MCHC	8,2937940	rs17390162,G	MYOM2,857153,	5919	0.85	-0.12	0.03	0.4	4.3E-06
MCHC	8,101843310	rs2935555,G	PABPC1,39819,	5925	0.70	0.09	0.02	0.4	5.7E-06
MCHC	2,37618527	rs6731311,C	CDC42EP3,105719,	5914	0.69	-0.09	0.02	0.4	9.2E-06
RBC	16,53789241	rs12932559,G	IRX6,126730,	4244	0.88	-0.19	0.04	0.8	3.3E-08
RBC	6,135469510	rs9402686,G	HBS1L,51795,	4250	0.73	0.14	0.03	0.7	1.4E-07
RBC	4,13732450	rs3846396,A	FAM44A,494024,	4249	0.87	0.17	0.04	0.7	6.9E-07
RBC	9,135095336	rs9411463,C	OBP2B,20887,	4246	0.94	-0.24	0.05	0.6	1.2E-06
RBC	10,12978760	rs3232,C	CCDC3,130,*	4250	0.71	0.12	0.03	0.6	3.3E-06

RBC	11,80516964	rs1568638,T	FAM181B,1603729,	4228	0.82	-0.14	0.03	0.6	3.9E-06
RBC	2,180421454	rs2219670,C	CWC22,96394,	4248	0.68	0.11	0.03	0.6	4.6E-06
RBC	4,13831732	rs10516275,C	FAM44A,593306,	4248	0.59	-0.11	0.02	0.6	5.4E-06
RBC	3,134768220	rs10433415,T	CDV3,7043,	4250	0.63	0.11	0.02	0.6	6.1E-06
RBC	7,3076972	rs13223548,C	CARD11,26867,	4230	0.65	0.11	0.02	0.5	6.2E-06
RBC	10,128553325	rs10794133,C	DOCK1,30687,	4250	0.80	-0.13	0.03	0.5	8.5E-06
RBC	16,81386902	rs4783277,G	CDH13,168824,*	4247	0.66	-0.11	0.03	0.5	8.5E-06
RBC	10,13710977	rs7088503,G	PRPF18,1897,*	4245	0.62	-0.11	0.02	0.5	8.6E-06
RBC	2,208542722	rs11679492,T	PLEKHM3,55745,*	4250	0.59	-0.11	0.02	0.6	8.6E-06
RBC	16,9297536	rs8048358,A	USP7,359492,	4244	0.70	0.11	0.03	0.5	9.0E-06
RBC	10,24756200	rs16924742,C	KIAA1217,120578,*	4239	0.95	0.23	0.05	0.5	9.1E-06
HT	10,70769894	rs10159477,G	HK1,61749,*	5946	0.86	-0.16	0.03	0.6	5.8E-09
HT	13,76221092	rs7323290,C	KCTD12,132896,	5947	0.65	0.10	0.02	0.4	1.0E-06
HT	9,135102234	rs4246170,A	ABO,18149,	5939	0.94	-0.19	0.04	0.4	1.9E-06
HT	13,76074303	rs9573886,G	KCTD12,279685,	5947	0.83	-0.12	0.03	0.4	4.6E-06
HT	6,153311391	rs9478369,G	FBXO5,21959,	5947	0.74	0.10	0.02	0.4	6.1E-06
HT	3,105901394	rs2633702,C	ALCAM,667008,	5947	0.63	0.09	0.02	0.4	7.5E-06
HT	1,21460436	rs2282714,G	ECE1,29133,*	5947	0.70	0.09	0.02	0.4	8.3E-06
HT	2,22680257	rs936751,T	FLJ14106,958269,	5947	0.80	-0.11	0.02	0.4	9.2E-06
HT	6,165970939	rs12529895,C	PDE10A,24636,*	5937	0.95	-0.20	0.04	0.4	9.7E-06
MCV	6,26212611	rs198851,G	HIST1H4C,67,	5942	0.86	-0.15	0.03	0.6	1.8E-08
MCV	22,49318132	rs140522,C	ODF3B,258,	5945	0.67	0.11	0.02	0.5	8.0E-08
MCV	6,42088644	rs6921368,C	TAF8,37584,	5945	0.65	-0.11	0.02	0.5	1.6E-07
MCV	6,25950930	rs1408272,T	SLC17A3,2376,	5939	0.94	-0.20	0.04	0.5	2.7E-07
MCV	17,19900285	rs3862152,T	CYTSB,30641,	5945	0.58	0.10	0.02	0.5	3.6E-07
MCV	12,67846766	rs10878928,A	CPSF6,72817,	5917	0.89	-0.15	0.03	0.4	1.2E-06
MCV	7,32514815	rs7781196,C	AVL9,13115,*	5939	0.99	-0.41	0.08	0.5	1.2E-06
MCV	4,55102662	rs218262,C	KIT,116189,	5941	0.89	-0.14	0.03	0.4	1.5E-06
MCV	17,19909989	rs7209752,G	CYTSB,20937,	5943	0.94	0.19	0.04	0.4	1.7E-06
MCV	15,53441540	rs7168869,T	PIGB,6402,	5942	0.93	-0.17	0.04	0.4	4.3E-06
MCV	6,108982792	rs9486901,T	FOXO3,4926,	5944	0.84	0.12	0.03	0.4	5.7E-06
MCV	4,122882880	rs6815973,T	TMEM155,16654,	5938	0.70	0.09	0.02	0.4	6.7E-06
MCV	14,44320168	rs1424885,A	KLHL28,143108,	5945	0.87	0.13	0.03	0.4	8.8E-06
MCV	3,24320780	rs1505283,G	THRB,187132,*	5943	0.58	0.09	0.02	0.4	9.5E-06
MCV	6,133862041	rs478907,A	EYA4,32910,*	5941	0.72	0.10	0.02	0.4	9.9E-06
PLT	4,21429230	rs13150985,C	KCNIP4,130242,*	4230	0.98	0.46	0.09	0.7	1.3E-07

PLT	9,106804296	rs11999261,T	ABCA1,74039,	4250	0.91	0.19	0.04	0.6	1.8E-06
PLT	5,24890906	rs10043237,G	CDH10,210238,	4239	0.90	-0.18	0.04	0.6	4.9E-06
PLT	2,156117271	rs11682195,T	KCNJ3,696011,	4241	0.93	-0.22	0.05	0.5	5.5E-06
PLT	15,73098089	rs2289583,C	SCAMP5,2800,*	4250	0.71	-0.12	0.03	0.5	6.5E-06
PLT	1,16206156	rs1763611,G	HSPB7,6953,	4246	0.90	0.18	0.04	0.5	6.7E-06
PLT	6,12628644	rs12212807,G	PHACTR1,196378,	4250	0.69	-0.11	0.03	0.5	8.4E-06
PLT	3,56824789	rs1354034,C	ARHGEF3,88304,*	4249	0.61	0.10	0.02	0.5	8.8E-06

[a] Distance to first base pair of the the first exon or last base pair of the last exon, whichever is smallest. An asterisk (*) indicates that the SNP is located within the gene.

[b] Effect corresponds to standard deviation units for the transformed phenotype, while h^2 represents the proportion of phenotypic variance explained by the SNP.

Hb: hemoglobin; MCH: mean cell hemoglobin; MCHC: mean cell hemoglobin concentration; RBC: red blood cell count; HT: hematocrit; MCV: mean cell volume; PLT: platelet count. SE: standard error.

Table S5 (continued). Loci with less stringent evidence for association ($5.5x10^{-9} < P < 10^{-5}$) with variation in white blood cell indices in the combined analysis of the Australian and Dutch datasets.

Trait	Chromosome, bp position	SNP, allele	Nearest gene, bp distance[a]	Sample size	Allele frequency	Effect[b]	SE	h^2, %	*P*-value
WBC	1,39372236	rs472998,C	MACF1,52532,*	4239	0.99	-0.46	0.09	0.6	5.3E-07
WBC	6,115259991	rs12202473,C	HS3ST5,489758,	4238	0.70	-0.12	0.03	0.6	2.4E-06
WBC	6,30576770	rs3131115,C	HLA-E,7698,	4237	0.64	0.11	0.02	0.6	3.8E-06
WBC	17,35432153	rs3213762,A	MED24,3278,*	4239	0.61	-0.11	0.02	0.6	4.2E-06
WBC	2,17716869	rs4578856,C	SMC6,8308,*	4237	0.82	0.14	0.03	0.6	4.9E-06
WBC	20,15908223	rs6043649,T	LOC613266,56264,	4236	0.99	0.46	0.10	0.6	5.1E-06
WBC	16,47510482	rs12930072,C	N4BP1,308861,	4238	0.73	0.12	0.03	0.6	5.5E-06
WBC	2,232293051	rs11695646,A	PTMA,6557,	4239	0.78	0.12	0.03	0.5	6.3E-06
WBC	8,97405673	rs6468498,T	PTDSS1,10277,*	4236	0.93	-0.20	0.05	0.5	7.0E-06
WBC	18,34019525	rs17552090,T	BRUNOL4,619527,	4201	0.77	0.13	0.03	0.6	7.1E-06
NEUT	17,35425194	rs2227322,C	CSF3,19,	4223	0.61	-0.12	0.02	0.6	9.2E-07
NEUT	1,39408505	rs651694,A	MACF1,88801,*	4223	0.99	-0.42	0.09	0.6	3.9E-06
NEUT	17,16099499	rs11650427,A	PIGL,38266,*	4222	0.52	0.11	0.02	0.6	5.3E-06
NEUT	9,8418988	rs7030220,C	PTPRD,114743,	4223	0.97	0.28	0.06	0.5	6.7E-06
NEUT	7,135128967	rs4732144,C	FAM180A,44980,	4216	0.83	0.14	0.03	0.6	6.9E-06
LYMPH	6,31613459	rs2734583,A	ATP6V1G2,6759,	4209	0.87	0.19	0.03	0.8	3.3E-08
LYMPH	11,121398592	rs17126029,C	BLID,92679,	4224	0.95	-0.25	0.05	0.6	5.0E-06
LYMPH	14,100991643	rs7149416,T	DIO3,105797,	4226	0.57	0.11	0.02	0.6	5.7E-06
LYMPH	6,31573616	rs6915833,C	MCCD1,31101,	4217	0.94	-0.22	0.05	0.5	6.9E-06
LYMPH	4,83717051	rs4693039,T	SCD5,52662,	4198	0.66	-0.11	0.03	0.5	7.8E-06
LYMPH	11,89853841	rs2510566,C	CHORDC1,257987,	4226	0.70	0.11	0.03	0.5	8.6E-06
LYMPH	18,75904738	rs11664633,G	TXNL4A,55218,	4224	0.55	-0.10	0.02	0.5	9.1E-06
MONO	14,103087858	rs10141157,C	BAG5,4783,	4214	0.53	0.13	0.02	0.9	1.6E-08
MONO	2,182016597	rs6740847,G	ITGA4,13266,	4225	0.57	0.13	0.02	0.8	3.6E-08
MONO	7,152402256	rs17173921,A	ACTR3B,218860,	4224	0.76	0.13	0.03	0.6	2.2E-06
MONO	16,84523155	rs524432,T	IRF8,9443,	4219	0.82	-0.14	0.03	0.6	2.7E-06
MONO	10,52236063	rs10821846,G	A1CF,267,	4225	0.52	0.11	0.02	0.6	2.9E-06
MONO	8,97408427	rs11782606,G	PTDSS1,7523,*	4219	0.93	-0.21	0.05	0.5	3.8E-06
MONO	7,25361712	rs1967297,T	NPVF,127082,	4223	0.68	-0.11	0.03	0.6	4.0E-06
MONO	21,38113768	rs2835988,C	KCNJ6,96798,*	4224	0.64	0.11	0.02	0.6	4.7E-06
MONO	16,84537847	rs965773,A	IRF8,24135,	4200	0.50	0.11	0.02	0.6	7.4E-06
MONO	6,31221031	rs3094225,A	PSORS1C1,5215,	4223	0.70	-0.11	0.03	0.5	7.4E-06

EOS	3,4694426	rs4684436,A	ITPR1,169860,*	4214	0.84	0.16	0.03	0.7	6.8E-07
EOS	7,100232939	rs314344,C	ZAN,416,*	4216	0.61	0.12	0.02	0.6	1.1E-06
EOS	11,3701741	rs7931173,G	NUP98,48926,*	4215	0.82	0.15	0.03	0.6	1.8E-06
EOS	11,112161823	rs321118,G	NCAM1,175381,	4216	0.71	0.12	0.03	0.6	3.5E-06
EOS	15,58830670	rs8025324,G	RORA,123646,	4214	0.87	0.16	0.04	0.6	4.3E-06
EOS	18,22516999	rs9945253,G	KCTD1,42693,	4216	0.89	-0.17	0.04	0.6	5.8E-06
EOS	6,7199640	rs2714342,G	RREB1,3446,	4215	0.85	0.15	0.03	0.5	7.2E-06
BASO	12,21993091	rs7954180,C	ABCC9,12196,	4215	0.52	0.11	0.02	0.6	1.1E-06
BASO	16,68068844	rs12445855,G	CYB5B,11176,	4214	0.80	-0.14	0.03	0.6	1.2E-06
BASO	6,123377890	rs9398716,T	RLBP1L2,18610,*	4215	0.77	-0.13	0.03	0.6	2.5E-06
BASO	6,101059869	rs240764,G	ASCC3,3459,	4215	0.53	0.11	0.02	0.6	4.0E-06
BASO	9,97244020	rs357563,C	PTCH1,1064,	4190	0.63	-0.11	0.02	0.6	4.4E-06
BASO	3,15350826	rs17041032,G	SH3BP5,1718,	4205	0.96	0.27	0.06	0.5	9.8E-06

[a] Distance to first base pair of the the first exon or last base pair of the last exon, whichever is smallest. An asterisk (*) indicates that the SNP is located within the gene.

[b] Effect corresponds to standard deviation units for the transformed phenotype, while h^2 represents the proportion of phenotypic variance explained by the SNP.

WBC: white blood cell count; NEUT: neutrophil count; LYMPH: lymphocyte count; MONO: monocyte count; EOS: eosinophil count; BASO: basophil count. SE: standard error.

Table S6. Genes with strongest ($P < 10^{-5}$) overall evidence for association with individual hematology traits in the gene-based analysis performed in a subset of 4,612 unrelated individuals.

Trait	Chromosome, bp range[a]	Gene	Number of SNPs			*P*-value[c]	Associated SNPs
			Tested	P<0.05	P<0.05 & independent[b]		
MCH	6, 135273213-135467715	HBS1L	172	127	1	1E-06	rs9376090
PLT	6, 135273213-135467715	HBS1L	172	126	1	2E-06	rs9376090
MCV	6, 26113946-26214678	HIST1H1C	51	25	1	1E-06	rs198851
MCHC	8, 41572985-41812542	NKX6-3	181	18	1	1E-06	rs4737009
MCHC	8, 41579900-41824297	ANK1	175	19	1	1E-06	rs4737009
MCV	6, 135273213-135467715	HBS1L	172	49	2	4E-06	rs9376090, rs9402683
MCV	6, 26101433-26201864	HIST1H2BB	47	26	1	1E-06	rs1799945
MCV	6, 26103617-26204076	HIST1H3C	44	24	1	2E-06	rs1799945
MCH	6, 26101433-26201864	HIST1H2BB	47	26	1	4E-06	rs1799945
MCH	6, 26103617-26204076	HIST1H3C	44	24	1	4E-06	rs1799945
MCH	6, 26113946-26214678	HIST1H1C	51	25	1	5E-06	rs1799945
EOS	17, 67578755-67684155	SOX9	64	27	1	9E-06	rs9894720
MCH	6, 26021049-26143331	TRIM38	72	45	1	9E-06	rs12216125

[a] Gene coordinates correspond to build 36 transcription start site and end positions -/+ 50 kb. A total of 17,062 genes with at least one available SNP were tested.

[b] Based on a pairwise LD between SNPs of $r^2 < 0.1$.

[c] Gene-based empirical *P*-value for the average test statistic across independently significant SNPs, estimated with PLINK based on 1,000,000 permutations performed while maintaining the original LD structure intact.

MCH: mean cell hemoglobin; MCV: mean cell volume; PLT: platelet count.

Table S7. Loci with $P < 10^{-5}$ in the multivariate association analysis of the thirteen hematology traits in a subset of 4,612 unrelated individuals.

Chromosome, bp position	Nearest gene, bp distance[a]	SNP, allele	Allele Frequency	*P*-value	Most associated traits	h^2, %
6,135460328	HBS1L,42613,	rs7775698,T	0.26	8.78E-20	MCV,MCH,PLT, RBC,MCHC	0.95,0.98,0.91, 0.41,0.26
6,25950930	SLC17A3,2376,	rs1408272,G	0.06	1.24E-10	MCH,MCV,HB, MCHC,HT,LYMPH	1.67,0.67,0.32, 0.25,0.17,0.13
22,35800170	TMPRSS6,8746,*	rs2413450,T	0.47	1.20E-07	MCV,MCH,HB, MCHC,HT,	0.82,0.71,0.20, 0.27,0.12
9,112965355	LPAR1,124008,	rs7023923,C	0.50	2.90E-07	MONO	1.34
6,31237289	TCF19,2682,*	rs7750641,T	0.14	3.16E-07	LYMPH,MCH,WBC, HT,RBC,EOS,HB, MONO,MCHC,NEUT	0.60,0.36,0.30, 0.17,0.05,0.20,0.03, 0.09,0.06,0.12
6,25562994	LRRC16A,165743,*	rs10498725,T	0.19	3.20E-07	MCH,MCV,HB, BASO,MCHC,HT, LYMPH	1.14,0.41,0.17 ,0.30,0.16,0.09, 0.06
3,134956315	TF,24010,*	rs8177220,T	0.03	4.41E-07	HB,PLT,MCV, LYMPH,EOS,HT	0.28,0.28,0.08, 0.16,0.15,0.05
6,26212611	HIST1H4C,67,	rs198851,T	0.14	5.79E-07	MCV,MCH,HB, HT,MCHC	0.60,0.76,0.27, 0.25,0.14
6,34184106	GRM4,2384,	rs2451340,A	0.02	1.08E-06	EOS,LYMPH,MCH, PLT,MCV	0.37,0.14,0.11, 0.11,0.06
2,74943197	HK2,29908,*	rs1545522,C	0.21	1.90E-06	MCHC,BASO,HB, PLT,MCH	0.75,0.37,0.07, 0.07,0.05
3,22397123	ZNF385D,629303,	rs10048943,T	0.01	2.07E-06	MCHC,HB	0.11,0.09
17,22941596	KSR1,33249,*	rs11080226,G	0.11	3.17E-06	WBC,NEUT,HB, HT,LYMPH,BASO	0.50,0.49,0.23, 0.16,0.09,0.07
6,26071945	TRIM38,896,*	rs12210098,T	0.33	3.26E-06	MCH,NEUT,WBC,HB, MCHC,MCV,HT,MONO	0.62,0.58,0.40,0.11, 0.20,0.15,0.09,0.07
4,177476332	SPCS3,1793,	rs1454160,C	0.14	3.35E-06	PLT,RBC,HT, MCHC,NEUT,MONO, WBC,MCH	0.45,0.32,0.15,0.14, 0.15,0.11,0.09,0.05
6,29994143	HLA-A,24161,	rs1611493,T	0.12	3.61E-06	MCHC,EOS,MCH, HB,LYMPH	0.18,0.26,0.15, 0.03,0.11
17,73281006	FLJ45079,105697,	rs4636981,G	0.01	5.55E-06	EOS,MONO	0.26,0.17
4,55089781	KIT,129070,	rs218238,T	0.21	5.62E-06	MCV,RBC,MCH, HB,HT,NEUT, MONO,WBC	0.36,0.24,0.48, 0.11,0.14,0.23, 0.19,0.10
11,94046746	PIWIL4,52512,	rs526187,G	0.10	7.59E-06	NEUT,EOS,WBC, BASO,PLT,HT	0.28,0.32,0.19, 0.23,0.11,0.05
16,50933041	TOX3,96376,	rs11075466,G	0.18	8.00E-06	MCV,MONO,MCH, PLT,HT	0.26,0.49,0.13, 0.12,0.05
14,38451661	SEC23A,119212,	rs12435055,A	0.04	8.22E-06	NEUT,WBC,PLT, MCHC,HT	0.65,0.22,0.16 ,0.10,0.04
10,17171759	CUBN,40063,*	rs7904579,G	0.35	9.61E-06	PLT,BASO,LYMPH, NEUT	0.65,0.34,0.11, 0.05

[a] Distance to the first base pair of the first exon or to the last base pair of the last exon, whichever is

smallest. An asterisk (*) indicates that the SNP is located within the gene.

Loci that were not detected ($P < 10^{-5}$) in the univariate analysis are highlighted in grey. The genomic inflation factor for this analysis (λ) was 1.04.

Hb: hemoglobin; MCH: mean cell hemoglobin; MCHC: mean cell hemoglobin concentration; RBC: red blood cell count; HT: hematocrit; MCV: mean cell volume; PLT: platelet count; WBC: white blood cell count; NEUT: neutrophil count; LYMPH: lymphocyte count; MONO: monocyte count; EOS: eosinophil count; BASO: basophil count.

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