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Supplemental information

Genetic determinants of blood-cell traits influence susceptibility to childhood acute lymphoblastic leukemia

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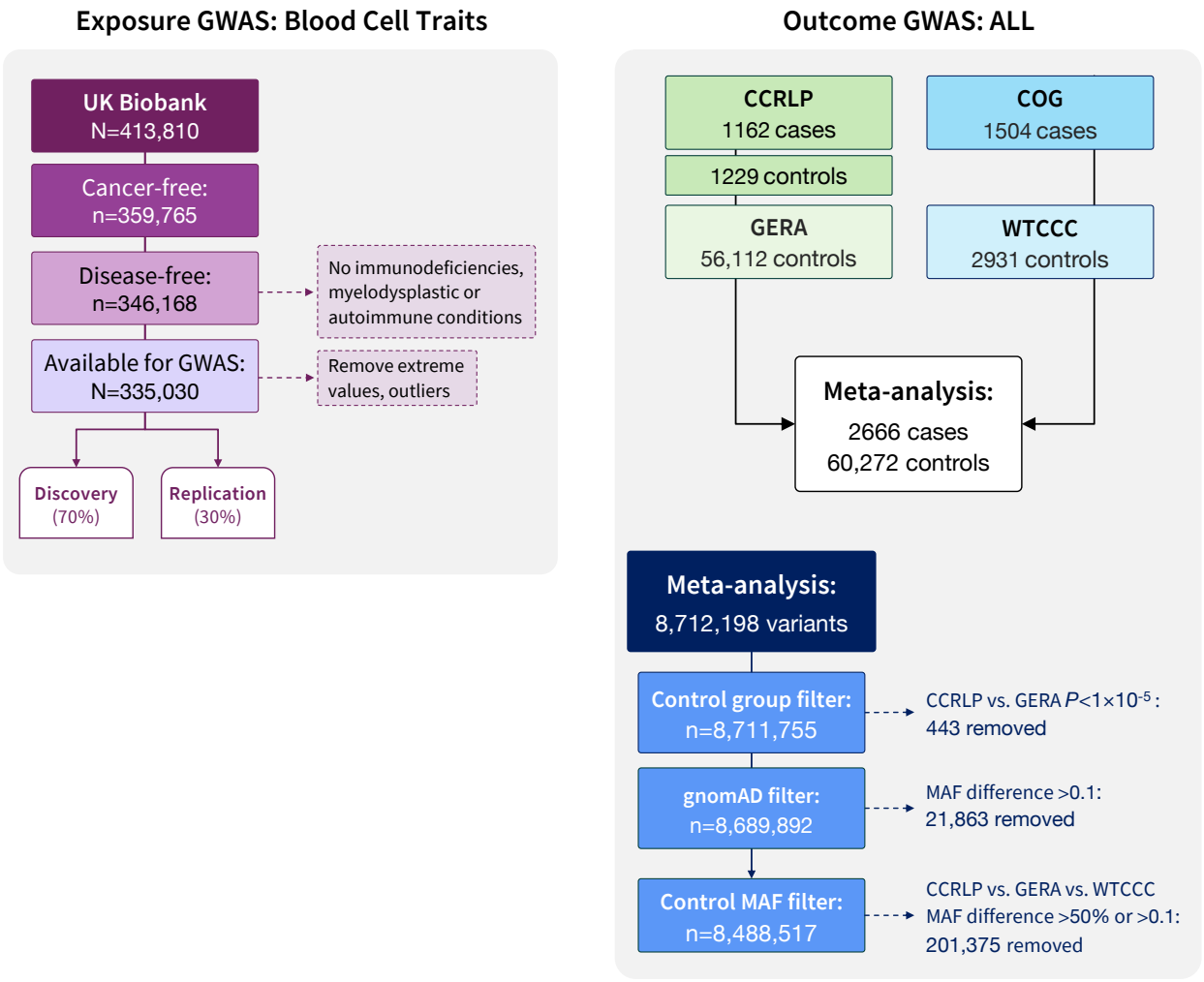

Figure S1: Overview of study populations. Flowchart outlining the inclusion criteria for study participants and l quality control steps. All subjects were restricted to individuals of predominantly European ancestry.

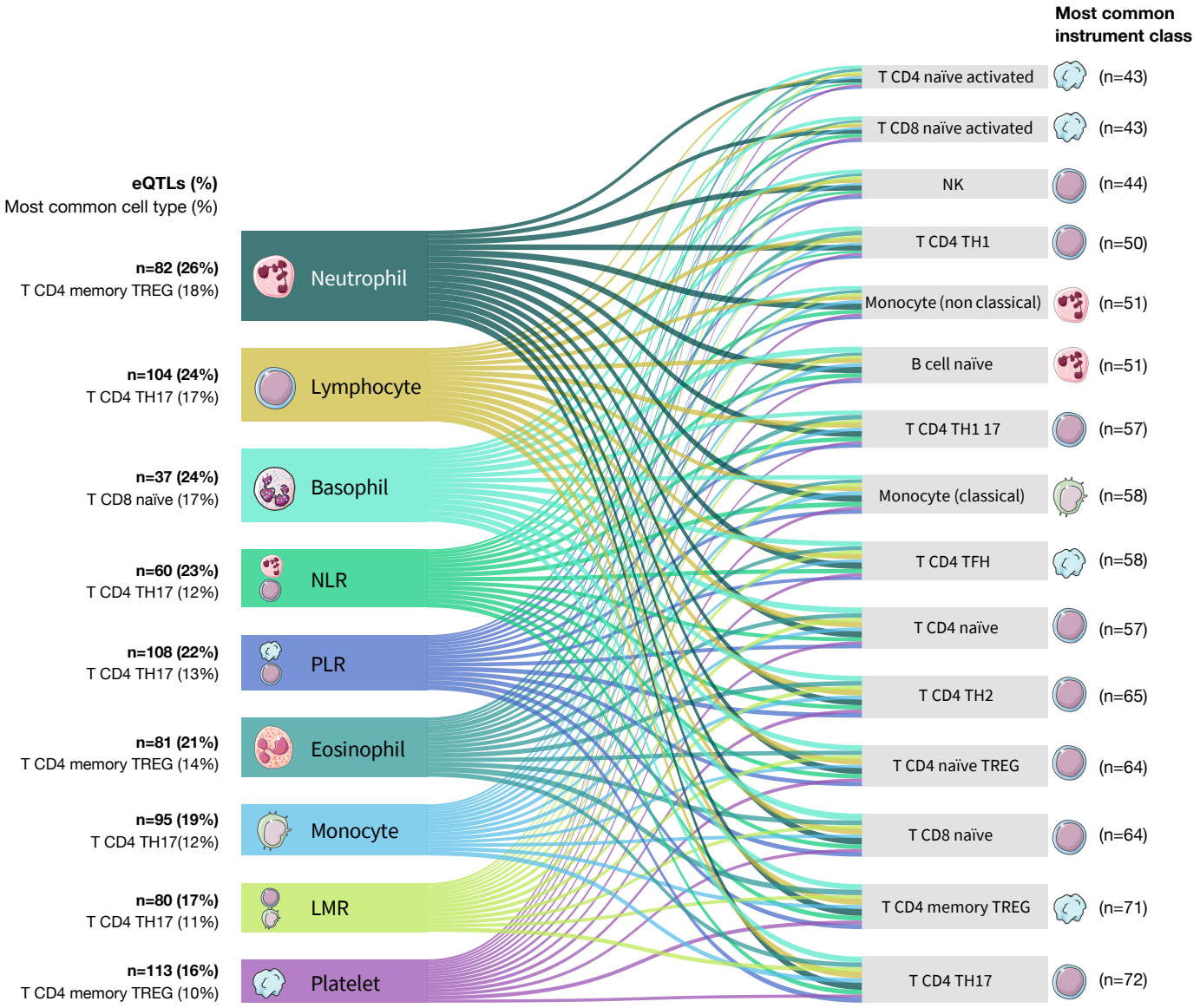

Figure S2: Gene expression in immune cells. Sankey style plot illustrating the pattern of cell-type specific effects on gene expression obtained from DICE (Database of Immune Cell Expression) for blood cell trait genetic instruments. Genetic instruments were considered expression quantitative trait loci (eQTL) if their associations with gene expression were significant at FDR<0.05. The color of each band corresponds to the blood cell type and the width of each band is scaled to reflect the proportion of all eQTL signals accounted for by a specific cell type.

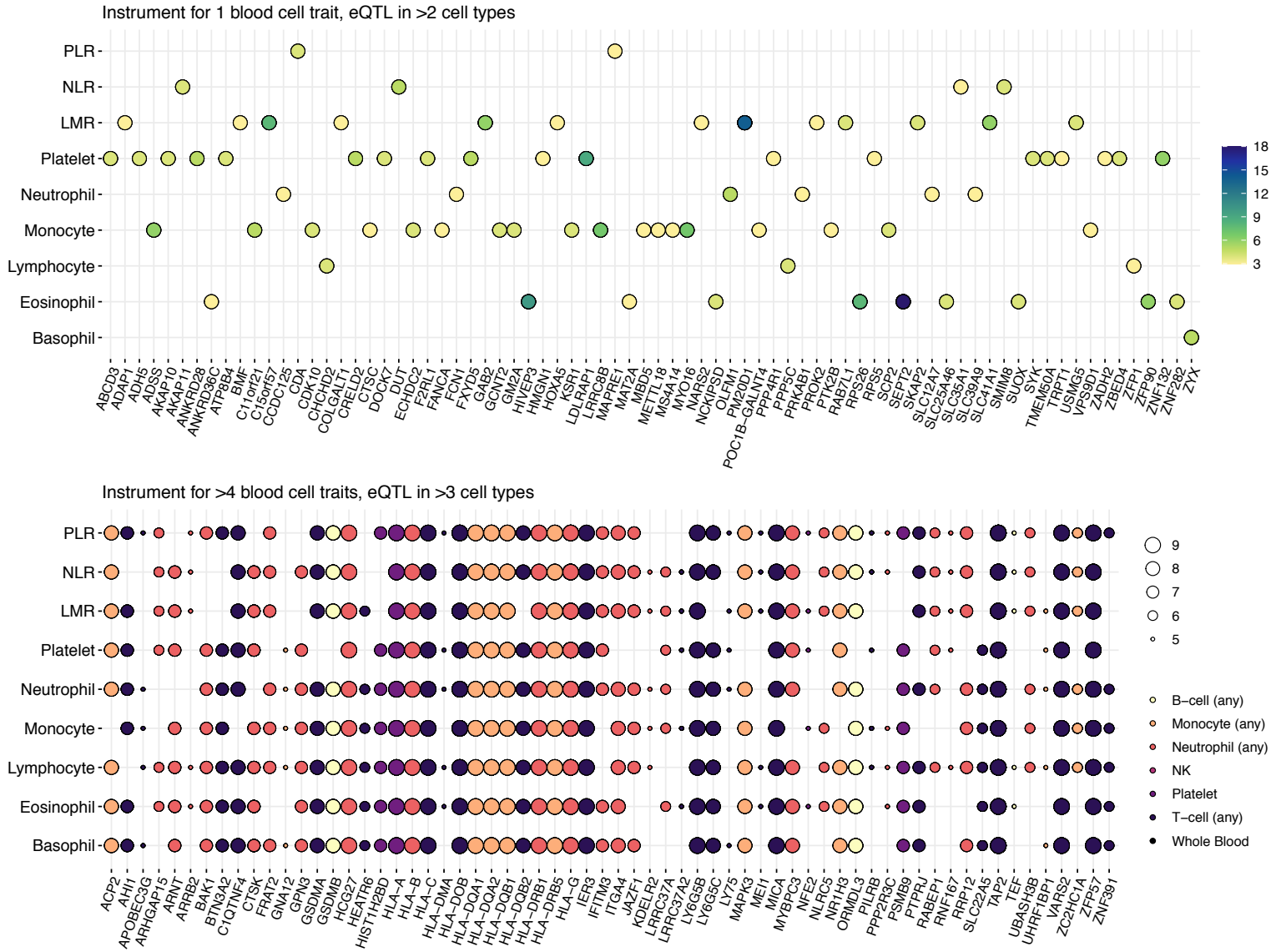

Figure S3: Gene expression targets in multiple tissues and cell types. Genetic instruments were considered expression quantitative trait loci (eQTL) if their associations with gene expression were significant at FDR<0.05. For a given variant, all significant eQTL effects in more than one cell type were retained, but these were not required to be for the same gene. Associations are visualized for each unique eGene-cell group combination. The upper panel shows eGenes for genetic instruments specific to one blood count or ratio trait, with the color of each circle corresponding to the number of cell types in which eQTL effects were observed. The lower panel summarizes eQTL effects for variants that are instruments for multiple blood count or ratio phenotypes (>4), indicated by the size of the circle. The color of the circle corresponds to the eQTL tissue(s) for each eGene.

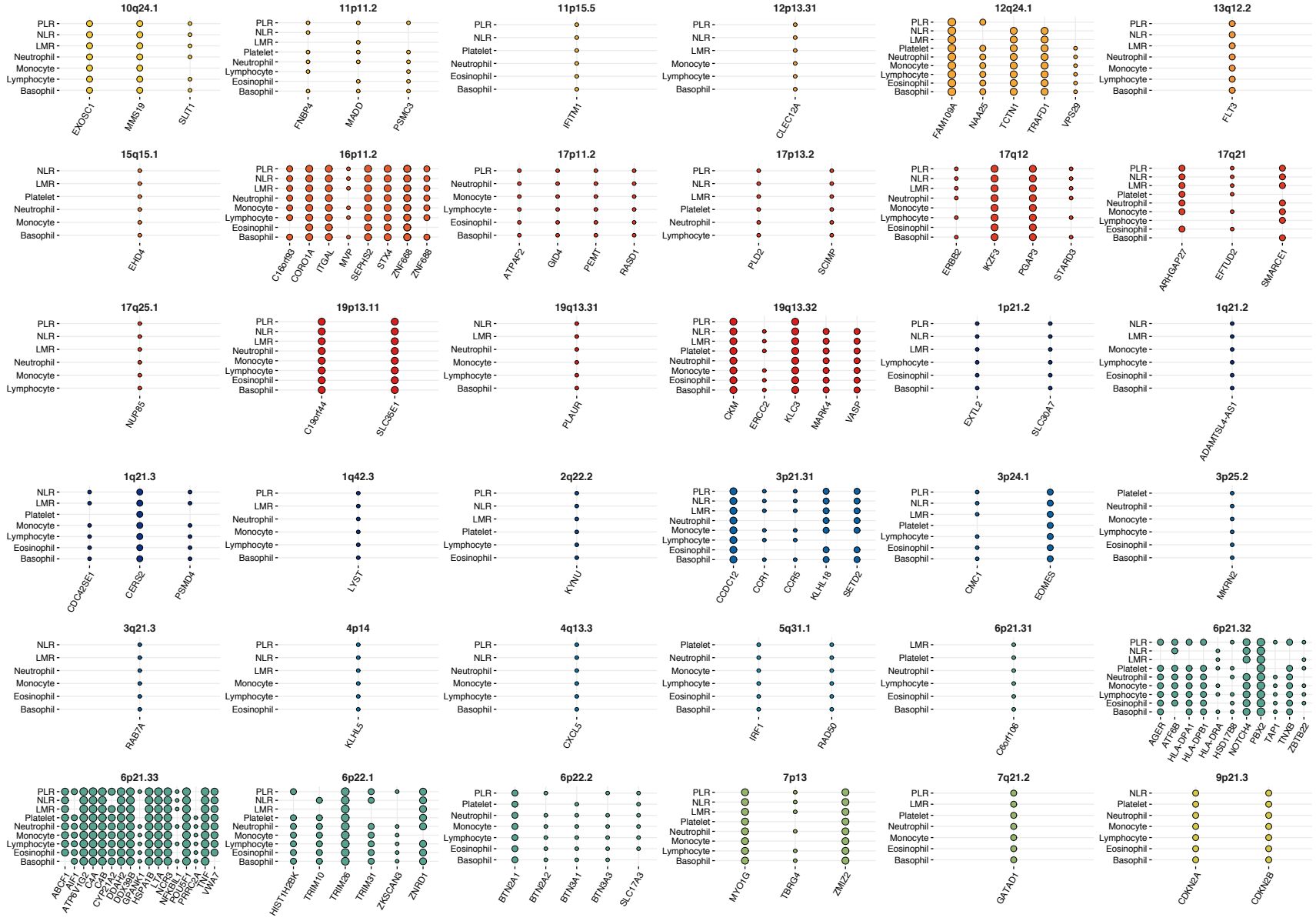

Figure S4: Gene expression targets in whole blood. Genetic instruments were considered expression quantitative trait loci (eQTL) if their associations with gene expression were significant at FDR<0.05. Associations were filtered to retain eGenes (genes with significant eQTLs) among variants that were genetic instruments for >5 blood cell traits with eQTL effects in a single tissue (whole blood). The size of each circle is proportional to the number of phenotypes for each eGene, ranging from 6 to 9. Circles are colored by chromosome.

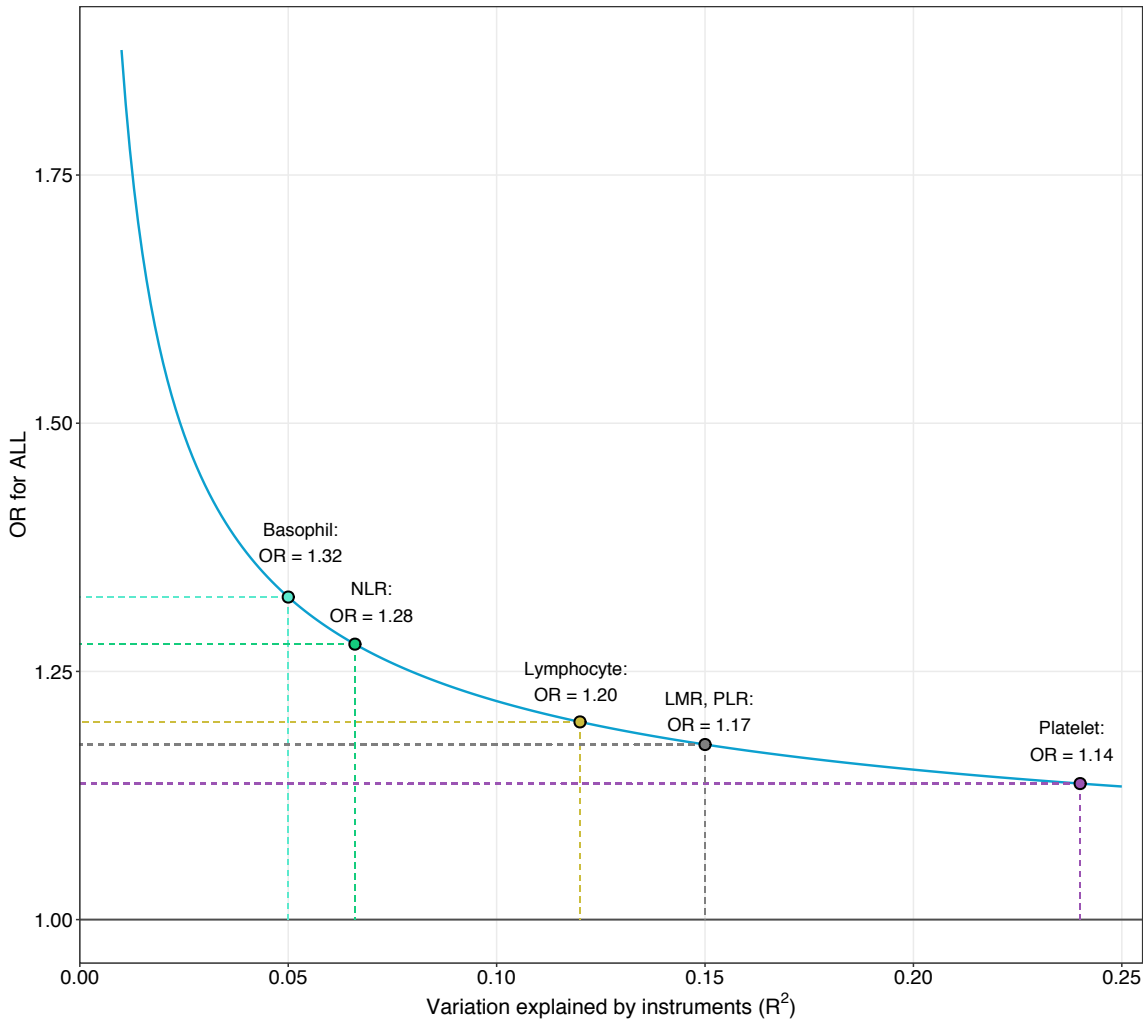

Figure S5: Power calculations for Mendelian randomization analysis. Minimum detectable odds ratio at 80% power for each blood cell trait based on the observed instrument strength and available sample size for the outcome.

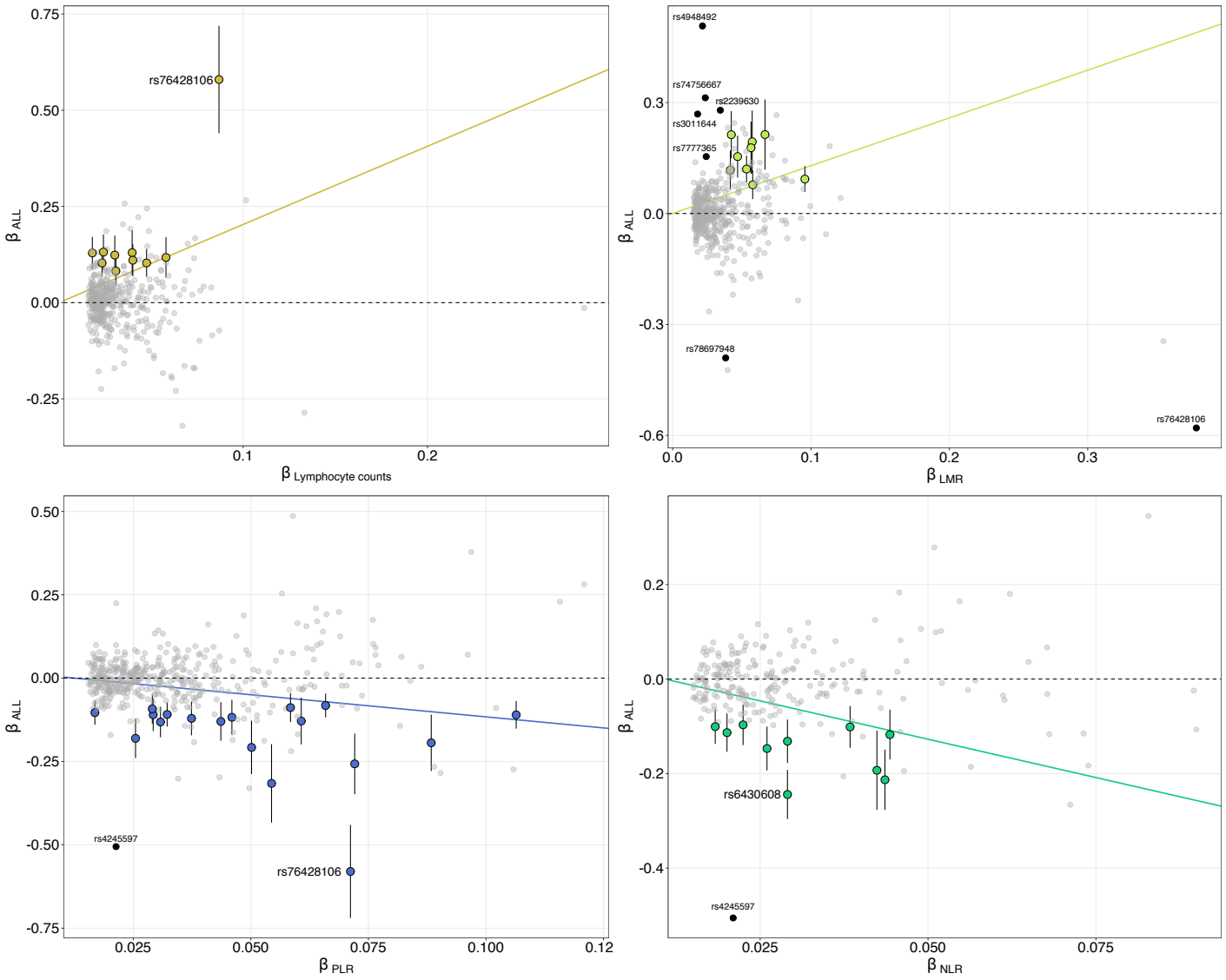

Figure S6: Visualization of MR Clust results. MR Clust was used to identify subgroups of variants with homogenous causal effects and novel ALL risk variants. The slope of the line corresponds to the mean causal effect within each cluster. Substantive clusters included variants with an assignment probability of greater than 50%. Outliers are denoted by solid black circles. Only variants significantly associated with ALL at the Bonferroni-corrected threshold ($P_{ALL}<5\times10^{-5}$) are labeled.

Table S1: Heritability estimates for blood cell traits and acute lymphoblastic leukemia. Array-based heritability (hg) estimates for acute lymphoblastic leukemia (ALL) and blood cell subtypes: lymphocytes, monocytes, neutrophils, basophils, eosinophils, basophils, platelets, lymphocyte to monocyte ratio (LMR), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR) estimated with LD score regression using UKB LD scores from European ancestry participants as the reference panel (7,166,343 variants).

Phenotype		h_g	(SE)
White blood cells		0.141	(0.009)
Lymphocytes		0.165	(0.014)
Monocytes		0.156	(0.017)
Neutrophils		0.122	(0.011)
Eosinophils		0.128	(0.012)
Basophils		0.031	(0.004)
Platelets		0.218	(0.017)
NLR		0.095	(0.006)
LMR		0.117	(0.011)
PLR		0.161	(0.014)
ALL[1]	Lifetime risk: 0.15%	0.181	(0.013)
	Lifetime risk: 0.10%	0.169	(0.012)

[1] For ALL heritability was transformed to the liability scale using SEER estimates of lifetime for non-Hispanic whites (0.15%), with a sensitivity analysis using a lower lifetime risk estimate.

Table S2: Genetic correlation between blood cell phenotypes. Matrix of genetic correlation estimates (r_g) for cell counts and ratios (lymphocyte to monocyte: LMR; neutrophil to lymphocyte: NLR; platelet to lymphocyte ratio: PLR) calculated using LD score regression. Correlations with $p<1.4\times10^{-3}$ were considered statistically significant after Bonferroni correction for 36 pairs tested.

	Lymphocytes	Monocytes	Neutrophils	Eosinophils	Basophils	Platelets	LMR	NLR	PLR
Lymphocytes	1.0	0.405 $p = 1.26\times10^{-8}$	0.384 $p = 1.40\times10^{-51}$	0.255 $p = 5.47\times10^{-21}$	0.378 $p = 1.02\times10^{-26}$	0.224 $p = 3.83\times10^{-35}$	0.468 $p = 2.77\times10^{-48}$	-0.616 $p = 1.34\times10^{-145}$	-0.702 $p = 2.77\times10^{-393}$
Monocytes	0.405 $p = 1.26\times10^{-8}$	1.0	0.449 $p = 1.77\times10^{-83}$	0.265 $p = 1.84\times10^{-26}$	0.267 $p = 8.28\times10^{-17}$	0.213 $p = 6.81\times10^{-26}$	-0.612 $p = 1.88\times10^{-74}$	-0.004 p = 0.89	-0.196 $p = 2.45\times10^{-20}$
Neutrophils	0.384 $p = 1.40\times10^{-51}$	0.449 $p = 1.77\times10^{-83}$	1.0	0.219 $p = 1.52\times10^{-16}$	0.442 $p = 4.00\times10^{-33}$	0.236 $p = 1.65\times10^{-26}$	-0.069 p = 0.017	0.480 $p = 5.89\times10^{-64}$	-0.158 $p = 2.74\times10^{-8}$
Eosinophils	0.255 $p = 5.47\times10^{-21}$	0.265 $p = 1.84\times10^{-26}$	0.219 $p = 1.52\times10^{-16}$	1.0	0.268 $p = 2.43\times10^{-17}$	0.155 $p = 2.24\times10^{-9}$	-0.022 p = 0.32	-0.061 p = 0.017	-0.112 $p = 6.29\times10^{-7}$
Basophils	0.378 $p = 1.02\times10^{-26}$	0.267 $p = 8.28\times10^{-17}$	0.442 $p = 4.00\times10^{-33}$	0.268 $p = 2.43\times10^{-17}$	1.0	0.158 $p = 2.31\times10^{-8}$	0.104 $p = 1.9\times10^{-3}$	0.037 p=0.40	-0.208 $p = 1.12\times10^{-10}$
Platelets	0.224 $p = 3.83\times10^{-35}$	0.213 $p = 6.81\times10^{-26}$	0.236 $p = 1.65\times10^{-26}$	0.155 $p = 2.24\times10^{-9}$	0.158 $p = 2.31\times10^{-8}$	1.0	-0.005 p = 0.74	-0.004 p = 0.82	0.535 $p = 3.08\times10^{-123}$
LMR	0.468 $p = 2.77\times10^{-48}$	-0.612 $p = 1.88\times10^{-74}$	-0.069 p = 0.017	-0.022 p = 0.32	0.104 $P = 1.9\times10^{-3}$	-0.005 p = 0.74	1.0	-0.496 $p = 1.37\times10^{-63}$	-0.408 $p = 9.35\times10^{-39}$
NLR	-0.616 $p = 1.34\times10^{-145}$	-0.004 p = 0.89	0.480 $p = 5.89\times10^{-64}$	-0.061 p = 0.017	0.037 p = 0.40	-0.004 p = 0.82	-0.496 $p = 1.37\times10^{-63}$	1.0	0.532 $p = 4.68\times10^{-80}$
PLR	-0.702 $p = 2.77\times10^{-393}$	-0.196 $p = 2.45\times10^{-20}$	-0.158 $p = 2.74\times10^{-8}$	-0.112 $p = 6.29\times10^{-7}$	-0.208 $p = 1.12\times10^{-10}$	0.535 $p = 3.08\times10^{-123}$	-0.408 $p = 9.35\times10^{-39}$	0.532 $p = 4.68\times10^{-80}$	1.0

Table S4: Overview of the properties of genetic instruments for blood cell traits. Proportion of trait variation explained was estimated in the independent UK Biobank replication sample of over 100,000 individuals. Instruments applied includes available variants and proxies (LD r^2>0.95) in the outcome GWAS meta-analysis of acute lymphoblastic leukemia.

Trait	Instruments Available		Instruments Applied		
	N	Variation (%)	N	Variation (%)	Mean F-statistic[1]
Lymphocytes	429	11.9	406	10.7	71.1
Monocytes	505	16.9	477	16.3	85.6
Neutrophils	313	9.4	301	8.7	69.4
Eosinophils	387	11.1	363	10.4	71.8
Basophils	157	5.1	144	4.5	64.6
Platelets	692	24.4	661	23.4	85.8
NLR	266	6.6	246	6.0	63.8
LMR	464	15.0	432	14.4	83.8
PLR	489	15.1	462	14.0	76.5

[1] F-statistic of 10 from the instrument-exposure regression corresponds to the minimum instrument strength required for avoiding weak instrument bias

Table S6: **Expression quantitative trait loci (eQTL) identified among genetic instruments for blood cell traits.** Number of significant eQTLs and corresponding eGenes detected among 3000 genetic instruments, summarized by broad tissue/cell group and specific cell type.

eQTL Cell Group	eQTL[1]		eQTL (P<5×10^{-8})			eQTL Cell Type	eQTL[1]		eQTL (P<5×10^{-8})			eQTL Study and Sample Size	
	N_{SNP}	(%)	N_{SNP}	%	eGenes		N_{SNP}	(%)	N_{SNP}	(%)	eGenes		
Whole Blood	2405	(80.2)	2253	(75.1)	2981	Whole Blood	2405	(80.2)	2253	(75.1)	2981	Vosa bioRxiv: 447367	31684
Monocytes (any)	810	(27.0)	514	(17.1)	431	Monocyte	559	(18.6)	370	(12.3)	328	Chen PMID: 27863251	197
						Monocyte (CD14 classical)	376	(12.5)	231	(7.7)	148	Momozawa PMID: 29930244	322
						Monocyte (CD14 classical)	228	(7.6)	83	(2.8)	68	Schmiedel PMID: 30449622	91
						Monocyte (non-classical)	206	(6.9)	64	(2.1)	58	Schmiedel PMID: 30449622	91
Neutrophils (any)	633	(21.1)	419	(14)	341	Neutrophil	458	(15.3)	289	(9.6)	274	Chen PMID: 27863251	197
						Neutrophil (CD15)	391	(13)	253	(8.4)	168	Momozawa PMID: 29930244	322
T-cells (any)	708	(23.6)	362	(12.1)	327	T-cell	430	(14.3)	277	(9.2)	233	Chen PMID: 27863251	197
						T CD8 (naïve)	221	(7.4)	87	(2.9)	84	Schmiedel PMID: 30449622	91
						T CD4 TH17	242	(8.1)	78	(2.6)	75	Schmiedel PMID: 30449622	91
						T_CD4 (memory TREG)	230	(7.7)	79	(2.6)	73	Schmiedel PMID: 30449622	91
						T_CD4 (naïve TREG)	228	(7.6)	77	(2.6)	79	Schmiedel PMID: 30449622	91
						T_CD4_TH2	222	(7.4)	74	(2.5)	69	Schmiedel PMID: 30449622	91
						T_CD4 (naïve)	223	(7.4)	69	(2.3)	71	Schmiedel PMID: 30449622	91
						T_CD4_TFH	216	(7.2)	66	(2.2)	65	Schmiedel PMID: 30449622	91
						T_CD4_TH1_17	207	(6.9)	64	(2.1)	61	Schmiedel PMID: 30449622	91
						T_CD4_TH1	182	(6.1)	51	(1.7)	45	Schmiedel PMID: 30449622	91
						T_CD8 (naïve activated)	148	(4.9)	48	(1.6)	39	Schmiedel PMID: 30449622	91
						T_CD4 (naïve activated)	138	(4.6)	45	(1.5)	42	Schmiedel PMID: 30449622	91
B-cells (any)	341	(11.4)	166	(5.5)	119	B-cell (CD19)	233	(7.8)	125	(4.2)	69	Momozawa PMID: 29930244	322
						B-cell (naïve)	185	(6.2)	73	(2.4)	62	Schmiedel PMID: 30449622	91
Platelets	119	(4.0)	72	(2.4)	51	Platelets	119	(4.0)	72	(2.4)	51	Momozawa PMID: 29930244	322
NK cells	154	(5.1)	48	(1.6)	44	NK cells	154	(5.1)	48	(1.6)	44	Schmiedel PMID: 30449622	91

[1] Genetic instruments were considered expression quantitative trait loci (eQTL) if their associations with gene expression were significant at FDR<0.05 within each dataset

Table S7: Mendelian randomization results. Odds ratios (OR) and 95% confidence intervals (CI) for the effect of increasing blood cell counts or cell type ratios on the risk of acute lymphoblastic leukemia (ALL).

Trait	MR Estimator	N_{SNP}	Association Estimates		
			OR	(95% CI)	P
Basophils	IVW (multiplicative random effects)	144	0.95	(0.59 – 1.53)	0.83
	Maximum likelihood		0.95	(0.66 – 1.36)	0.77
	Weighted median		1.31	(0.71 – 2.39)	0.39
	PRESSO (corrected)		0.94	(0.62 – 1.43)	0.78
	RAPS shrinkage		0.97	(0.67 – 1.41)	0.86
Eosinophils	IVW (multiplicative random effects)	363	1.01	(0.84 – 1.22)	0.91
	Maximum likelihood		1.01	(0.86 – 1.18)	0.89
	Weighted median		0.84	(0.64 – 1.09)	0.19
	PRESSO (corrected)		1.00	(0.84 – 1.21)	0.97
	RAPS shrinkage		0.95	(0.81 – 1.12)	0.55
Lymphocytes	IVW (multiplicative random effects)	406	1.15	(0.99 – 1.34)	0.061
	Maximum likelihood		1.16	(1.01 – 1.33)	0.035
	Weighted median		0.96	(0.71 – 1.29)	0.78
	PRESSO (corrected)		1.14	(0.98 – 1.32)	0.087
	RAPS shrinkage		1.16	(1.01 – 1.34)	0.033
Monocytes	IVW (multiplicative random effects)	477	1.01	(0.98 – 1.05)	0.49
	Maximum likelihood		1.01	(0.98 – 1.04)	0.40
	Weighted median		1.02	(0.99 – 1.05)	0.25
	PRESSO (corrected)		1.01	(0.98 – 1.04)	0.52
	RAPS shrinkage		1.01	(0.98 – 1.04)	0.39
Neutrophils	IVW (multiplicative random effects)	301	1.04	(0.85 – 1.27)	0.70
	Maximum likelihood		1.04	(0.87 – 1.25)	0.67
	Weighted median		1.08	(0.80 – 1.46)	0.62
	PRESSO (corrected)		1.00	(0.83 – 1.22)	0.97
	RAPS shrinkage		1.01	(0.84 – 1.22)	0.93
Platelets	IVW (multiplicative random effects)	661	1.02	(0.97 – 1.06)	0.51
	Maximum likelihood		1.02	(0.97 – 1.06)	0.47
	Weighted median		1.02	(0.97 – 1.08)	0.36
	PRESSO (corrected)		1.02	(0.97 – 1.07)	0.40
	RAPS shrinkage		1.02	(0.97 – 1.06)	0.49
LMR	IVW (multiplicative random effects)	432	1.22	(1.00 – 1.50)	0.052
	Maximum likelihood		1.23	(1.07 – 1.41)	4.5×10^{-3}
	Weighted median		1.02	(0.80 – 1.31)	0.86
	PRESSO (corrected)		1.18	(1.01 – 1.38)	0.037
	RAPS shrinkage		1.14	(0.99 – 1.32)	0.070

NLR	IVW (multiplicative random effects)	246	0.67	(0.49 – 0.92)	0.012
	Maximum likelihood		0.67	(0.54 – 0.83)	3.1×10^{-4}
	Weighted median		0.66	(0.47 – 0.93)	0.017
	PRESSO (corrected)		0.77	(0.60 – 0.98)	0.036
	RAPS shrinkage		0.73	(0.58 – 0.91)	5.6×10^{-3}
PLR	IVW (multiplicative random effects)	462	0.80	(0.67 – 0.96)	0.018
	Maximum likelihood		0.80	(0.70 – 0.92)	2.0×10^{-3}
	Weighted median		0.85	(0.67 – 1.08)	0.18
	PRESSO (corrected)		0.82	(0.70 – 0.96)	0.014
	RAPS shrinkage		0.85	(0.73 – 0.98)	0.025

Table S8: Results of diagnostic tests carried out for Mendelian Randomization analyses.

Trait	Heterogeneity[1]			MR Egger[2]		MR PRESSO		I^2_{GX}[5]	$P_{Steiger}$[6]
	Q	DF	$P_{Q\text{-value}}$	β_0	P_{Egger}	P_{Global}[3]	P_{Dist}[4]		
Basophils	262.3	143	4.7×10^{-9}	-0.0099	0.40	$<6.7\times10^{-5}$	0.98	0.985	1.8×10^{-14}
Eosinophils	509.9	360	3.1×10^{-7}	0.0028	0.69	$<6.7\times10^{-5}$	0.04	0.986	1.6×10^{-75}
Lymphocytes	512.1	398	9.4×10^{-5}	0.0082	0.09	$<6.7\times10^{-5}$	0.88	0.986	5.0×10^{-135}
Monocytes	708.8	472	9.0×10^{-12}	-0.0040	0.15	2.7×10^{-4}	0.69	0.988	1.8×10^{-269}
Neutrophils	368.3	299	3.8×10^{-3}	-0.0098	0.16	3.7×10^{-3}	0.03	0.986	3.8×10^{-120}
Platelets	764.5	654	1.8×10^{-3}	-0.0002	0.93	3.1×10^{-3}	0.75	0.988	$<1\times10^{-300}$
LMR	899.0	428	1.2×10^{-35}	0.0097	0.15	$<6.7\times10^{-5}$	0.63	0.988	5.4×10^{-98}
NLR	524.1	242	6.8×10^{-23}	-0.0103	0.39	$<6.7\times10^{-5}$	0.15	0.984	2.1×10^{-10}
PLR	798.9	456	4.1×10^{-21}	-0.0071	0.30	$<6.7\times10^{-5}$	0.83	0.987	1.2×10^{-109}

[1] Cochran's Q based on modified second order weights, p-values<0.05 indicate statistically significant heterogeneity

[2] Presence of statistically significant directional pleiotropy is indicated by non-zero intercept values with p<0.05

[3] Estimated based on 15000 replicates; p-values<0.05 indicate statistically significant pleiotropy

[4] Estimated based on 15000 replicates; p-values<0.05 indicate statistically significant distortion in causal effect estimates

[5] I^2_{GX} <0.90 indicates weak instrument bias due to violations of the no exposure measurement error assumption

[6] P-value for MR Steiger directionality test used to orient the causal effect and confirm that exposure → outcome

Table S9: Sensitivity analyses following manual removal of invalid genetic instruments. Odds ratios (OR) and 95% for acute lymphoblastic leukemia (ALL) were estimated using for selected traits after filtering out instruments that significantly contributed to heterogeneity.

Trait	MR Method	N / N_{SNP}	Association Estimates			Diagnostics	
			OR	(95% CI)	P	$P_{Q\text{-value}}$	P_{Egger}
Lymphocytes	IVW (multiplicative random effects)	356 / 406	1.18	(1.05 – 1.33)	7.4×10^{-3}	1.00	0.17
	Maximum likelihood		1.19	(1.02 – 1.37)	0.023		
LMR	IVW (multiplicative random effects)	403 / 432	1.19	(1.03 – 1.37)	0.016	0.93	0.22
	Maximum likelihood		1.19	(1.02 – 1.38)	0.022		
NLR	IVW (multiplicative random effects)	218 / 246	0.67	(0.55 – 0.82)	1.4×10^{-4}	0.98	0.81
	Maximum likelihood		0.67	(0.53 – 0.84)	6.5×10^{-4}		
PLR	IVW (multiplicative random effects)	429 / 462	0.82	(0.71 – 0.94)	5.8×10^{-3}	0.72	0.72
	Maximum likelihood		0.82	(0.71 – 0.95)	7.3×10^{-3}		

Table S10: Multivariable Mendelian randomization results. Odds ratios (OR) and 95% for acute lymphoblastic leukemia (ALL), estimated using multivariable Mendelian Randomization (MVMR) for traits that were individually associated with ALL or were used to derive associated ratio phenotypes.

Model	Trait	MVMR Method[1]	Association Estimates		
			OR	(95% CI)	P
Cell types	Lymphocytes	IVW	1.18	(1.06 – 1.31)	3.31×10^{-3}
		IVW (instrument specific)	1.43	(1.16 – 1.76)	8.83×10^{-4}
		LASSO	1.05		
	Monocytes	IVW	1.02	(0.92 – 1.13)	0.70
		IVW (instrument specific)	0.94	(0.83 – 1.08)	0.40
		LASSO	-		
	Neutrophils	IVW	0.93	(0.77 – 1.11)	0.41
		IVW (instrument specific)	0.88	(0.68 – 1.14)	0.33
		LASSO	-		
	Platelets	IVW	0.92	(0.85 – 0.99)	0.040
		IVW (instrument specific)	0.95	(0.86 – 1.05)	0.30
		LASSO	-		
Cell type ratios	LMR	IVW	1.00	(0.91 – 1.09)	0.97
		IVW (instrument specific)	1.10	(0.92 – 1.31)	0.28
		LASSO	-		
	NLR	IVW	0.95	(0.81 – 1.12)	0.54
		IVW (instrument specific)	0.83	(0.60 – 1.14)	0.25
		LASSO	-		
	PLR	IVW	0.90	(0.82 – 0.99)	0.034
		IVW (instrument specific)	0.91	(0.77 – 1.09)	0.30
		LASSO	0.82		

[1] For instrument-specific IVW variants were selected for each exposure based on $P<5\times10^{-8}$ and then all exposures for those SNPs are regressed together.

Table S11: Mediation analysis of Mendelian randomization effects. The total effect of blood cell ratios on ALL risk was decomposed into effects mediated by their component cell types. Total effects are based on Mendelian randomization results after filtering out instruments that significantly contributed to heterogeneity, as seen in Table S9.

Trait	Effects	log(OR)	(95% CI)[1]	Mediated (%)	
LMR	Total	0.173	(0.024, 0.322)		
	Indirect (mediated): Lymphocytes	-0.025	(-0.098, 0.053)	14.4	(0, 16.5)
	Indirect (mediated): Monocytes	0.066	(-0.128, 0.264)	38.1	(0, 82.1)
NLR	Total	-0.399	(-0.627, -0.171)		
	Indirect (mediated): Lymphocytes	-0.044	(-0.333, 0.245)	10.9	(0, 53.1)
	Indirect (mediated): Neutrophils	0.008	(-0.046, 0.063)	2.1	(0, 7.3)
PLR	Total	-0.242	(-0.449, -0.034)		
	Indirect (mediated): Lymphocytes	-0.053	(-0.255, 0.138)	21.9	(0, 56.7)
	Indirect (mediated): Platelets	0.043	(-0.100, 0.202)	17.8	(0, 22.3)

[1] Bootstrapped 95% confidence intervals for direct and indirect (mediated) effects were obtained using 1000 replicates.

Table S12: Annotation of blood cell trait instruments assigned to substantive clusters using the MR Clust algorithm. For each blood cell trait, the substantive cluster mean corresponds to the causal effect on ALL, log odds ratio (OR) per 1 unit increase, indicated by the variants comprising that cluster. Clusters were limited to variants with assignment probability of greater than 50%. Published associations with other phenotypes were obtained by querying the PhenoScanner database.

SNP	P_{ALL}	log(OR_{ALL})				PMID	Study	Traits with P <5.0×10^{-8}
		Lymphocyte	LMR	NLR	PLR			
rs76428106	3.2E-05	2.032	-	-	-1.327	27863252	Astle W	Granulocyte count | Granulocyte percentage of myeloid white cells | Monocyte count | Monocyte percentage of white cells | Myeloid white cell count | Sum neutrophil eosinophil counts | White blood cell count
rs1555137	2.0E-03	2.032	-	-	-	27863252	Astle W	Granulocyte count | Myeloid white cell count | Sum basophil neutrophil counts | White blood cell count
rs274555	3.7E-03	2.032	-	-	-	27863252	Astle W	Eosinophil count | Eosinophil percentage of granulocytes | Eosinophil percentage of white cells | Granulocyte count | High light scatter percentage of red cells | High light scatter reticulocyte count | Immature fraction of reticulocytes | Mean platelet volume | Monocyte count | Myeloid white cell count | Neutrophil count | Neutrophil percentage of granulocytes | Platelet count | Sum basophil neutrophil counts | Sum eosinophil basophil counts | Sum neutrophil eosinophil counts | White blood cell count
						26192919	IBDGC	Crohns disease
rs1633043	4.2E-03	2.032	-	-3.240	-1.327	27863252	Astle W	Hemoglobin concentration | High light scatter percentage of red cells | High light scatter reticulocyte count | Immature fraction of reticulocytes | Lymphocyte count | Lymphocyte percentage of white cells | Mean corpuscular hemoglobin | Mean corpuscular hemoglobin concentration | Mean corpuscular volume | Neutrophil percentage of white cells | Red cell distribution width | Reticulocyte count | Reticulocyte fraction of red cells
rs3132571	4.3E-03	2.032	-	-	-	27863252	Astle W	Granulocyte count | Lymphocyte count | Mean platelet volume | Monocyte count | Myeloid white cell count | Neutrophil count | Platelet count | Reticulocyte count | Reticulocyte fraction of red cells | Sum basophil neutrophil counts | Sum eosinophil basophil counts | Sum neutrophil eosinophil counts | White blood cell count
						27723758	Bronson P	IgA deficiency
						21323541	Stanescu HC	Idiopathic membranous nephropathy
						17632545	Hakonarson H	Type 1 diabetes
						27992413	Ji S	Primary sclerosing cholangitis

rs7776054	7.7E-03	2.032	-	-	-1.327	27863252	Astle W	Eosinophil count | Granulocyte count | Hematocrit | Hemoglobin concentration | High light scatter percentage of red cells | Lymphocyte count | Mean corpuscular hemoglobin | Mean corpuscular hemoglobin concentration | Mean corpuscular volume | Monocyte count | Myeloid white cell count | Neutrophil count | Platelet count | Plateletcrit | Red blood cell count | Red cell distribution width | Reticulocyte fraction of red cells | Sum basophil neutrophil counts | Sum eosinophil basophil counts | Sum neutrophil eosinophil counts | White blood cell count
						19862010	Ganesh SK	Erythrocyte count | Hematocrit Hct | Mean corpuscular hemoglobin MCH | Mean corpuscular hemoglobin concentration | Mean corpuscular volume | Mean corpuscular hemoglobin | Erythrocyte indices
rs11757367	0.015	2.032	-	-	-	27863252	Astle W	Eosinophil count | Granulocyte count | Mean corpuscular hemoglobin | Mean corpuscular volume | Mean platelet volume | Monocyte count | Myeloid white cell count | Neutrophil count | Platelet count | Plateletcrit | Red blood cell count | Sum basophil neutrophil counts | Sum eosinophil basophil counts | Sum neutrophil eosinophil counts | White blood cell count
						27723758	Bronson P	IgA deficiency
						20453842	Stahl E	Rheumatoid arthritis
						27992413	Ji S	Primary sclerosing cholangitis
						24390342	Okada Y	Rheumatoid arthritis
rs2872516	0.024	2.032	-	-	-	27863252	Astle W	Basophil count | Eosinophil percentage of granulocytes | Eosinophil percentage of white cells | Granulocyte count | Granulocyte percentage of myeloid white cells | Lymphocyte count | Lymphocyte percentage of white cells | Monocyte percentage of white cells | Myeloid white cell count | Neutrophil count | Neutrophil percentage of granulocytes | Neutrophil percentage of white cells | Sum basophil neutrophil counts | Sum neutrophil eosinophil counts | White blood cell count
						29083406	Ferreira M	Allergic disease
						26192919	IBDGC	Inflammatory bowel disease
rs12722496	0.025	2.032	-	-	-1.327	27863252	Astle W	Lymphocyte count | Lymphocyte percentage of white cells
						29083406	Ferreira M	Allergic disease
rs28447467	0.026	2.032	1.292	-3.240	-1.327	27863252	Astle W	Lymphocyte count | Lymphocyte percentage of white cells | Neutrophil percentage of white cells | White blood cell count
rs61839660	8.6E-04	-	1.292	-3.240	-	27863252	Astle W	Lymphocyte count | Lymphocyte percentage of white cells
						29083406	Ferreira M	Allergic disease | Allergic disease asthma hay fever or eczema
						22293688	Huang J	Type 1 diabetes | Diabetes mellitus type 1
rs4385425	9.7E-04	-	1.292	-	-	27863252	Astle W	Granulocyte percentage of myeloid white cells | Monocyte count | Monocyte percentage of white cells | Neutrophil percentage of white cells

rs62447197	6.5E-03	-	1.292	-	-	27863252	Astle W	Granulocyte percentage of myeloid white cells | Monocyte count | Monocyte percentage of white cells
rs10980797	7.6E-03	-	1.292	-	-	27863252	Astle W	Granulocyte percentage of myeloid white cells | Monocyte count | Monocyte percentage of white cells | Myeloid white cell count | Neutrophil percentage of white cells | White blood cell count
rs57822871	0.012	-	1.292	-	-	27863252	Astle W	Granulocyte percentage of myeloid white cells | Monocyte count | Monocyte percentage of white cells
rs62447173	0.022	-	1.292	-	-	27863252	Astle W	Granulocyte percentage of myeloid white cells | Monocyte count | Monocyte percentage of white cells
rs67483792	0.0242	-	1.292	-	-	27863252	Astle W	Granulocyte percentage of myeloid white cells | Monocyte count | Monocyte percentage of white cells
rs369173	0.04424	-	1.292	-	-	27863252	Astle W	Granulocyte count | Granulocyte percentage of myeloid white cells | Monocyte count | Monocyte percentage of white cells | Neutrophil count | Neutrophil percentage of white cells | Sum basophil neutrophil counts | Sum neutrophil eosinophil counts
rs6430608	2.5E-06	-	-	-3.240	-	-	-	-
rs57153090	1.5E-03	-	-	-3.240	-	27863252	Astle W	Lymphocyte count | Lymphocyte percentage of white cells
rs2415288	5.3E-03	-	-	-3.240	-	27863252	Astle W	Lymphocyte count
rs35045014	6.0E-03	-	-	-3.240	-	27863252	Astle W	Eosinophil count | Eosinophil percentage of granulocytes | Eosinophil percentage of white cells | Granulocyte percentage of myeloid white cells | Monocyte percentage of white cells | Neutrophil percentage of granulocytes | Sum eosinophil basophil counts
rs192665233	0.021	-	-	-3.240	-	27863252	Astle W	Granulocyte count | Lymphocyte percentage of white cells | Neutrophil count | Neutrophil percentage of white cells | Sum basophil neutrophil counts | Sum neutrophil eosinophil counts
rs3132713	0.022	-	-	-3.240	-	27863252	Astle W	Hemoglobin concentration | High light scatter percentage of red cells | High light scatter reticulocyte count | Immature fraction of reticulocytes | Lymphocyte count | Lymphocyte percentage of white cells | Mean corpuscular hemoglobin | Mean corpuscular hemoglobin concentration | Mean corpuscular volume | Neutrophil percentage of white cells | Red cell distribution width | Reticulocyte count | Reticulocyte fraction of red cells
rs9533128	0.024	-	-	-3.240	-	-	-	-
rs1984021	2.2E-03	-	-	-	-1.327	27863252	Astle W	Platelet count | Plateletcrit

rs4795397	2.7E-03	-	-	-	-1.327	27863252	Astle W	Basophil count | Eosinophil percentage of granulocytes | Eosinophil percentage of white cells | Granulocyte count | Granulocyte percentage of myeloid white cells | Lymphocyte count | Lymphocyte percentage of white cells | Monocyte percentage of white cells | Myeloid white cell count | Neutrophil count | Neutrophil percentage of granulocytes | Neutrophil percentage of white cells | Sum basophil neutrophil counts | Sum neutrophil eosinophil counts | White blood cell count
						29083406	Ferreira M	Allergic disease
						24097068	GLGC	High density lipoprotein
						22961000	Liu	Primary biliary cirrhosis
						26192919	IBDGC	Crohns disease | Inflammatory bowel disease | Ulcerative colitis
						24390342	Okada Y	Rheumatoid arthritis
						29273806	TAGC	Asthma
rs7654909	4.4E-03	-	-	-	-1.327	-	-	-
rs72974176	0.005	-	-	-	-1.327	27863252	Astle W	Hematocrit | Mean corpuscular hemoglobin | Mean corpuscular hemoglobin concentration | Mean corpuscular volume | Platelet count | Plateletcrit | Red blood cell count | Red cell distribution width
rs113107801	7.2E-03	-	-	-	-1.327	27863252	Astle W	Lymphocyte count
rs77619009	9.5E-03	-	-	-	-1.327	26192919	IBDGC	Inflammatory bowel disease | Ulcerative colitis
		-	-	-		24390342	Okada Y	Rheumatoid arthritis
rs2428514	0.017	-	-	-	-1.327	27863252	Astle W	White blood cell count
						27992413	Ji S	Primary sclerosing cholangitis
						24390342	Okada Y	Rheumatoid arthritis
rs114694170	0.022	-	-	-	-1.327	27863252	Astle W	Mean corpuscular hemoglobin | Mean corpuscular volume | Mean platelet volume | Platelet count | Platelet distribution width | Plateletcrit | Red blood cell count
rs7098181	0.022	-	-	-	-1.327	27863252	Astle W	Granulocyte count | Granulocyte percentage of myeloid white cells | Mean platelet volume | Monocyte percentage of white cells | Myeloid white cell count | Neutrophil count | Neutrophil percentage of white cells | Platelet count | Platelet distribution width | Sum basophil neutrophil counts | Sum neutrophil eosinophil counts | White blood cell count
rs7098181	0.022				-1.327	27225129	SSGAC	Years of educational attainment in males | Years of educational attainment
rs10066265	0.025	-	-	-	-1.327	27863252	Astle W	Mean platelet volume | Platelet count | Red cell distribution width
rs145125135	0.037	-	-	-	-1.327	27863252	Astle W	Mean corpuscular hemoglobin | Mean corpuscular volume | Platelet count | Plateletcrit | Red blood cell count | Red cell distribution width

rs2523466	0.042	-	-	-	-1.327	27863252	Astle W	Basophil count | Granulocyte count | Hematocrit | Hemoglobin concentration | High light scatter percentage of red cells | High light scatter reticulocyte count | Lymphocyte count | Monocyte count | Myeloid white cell count | Neutrophil count | Reticulocyte count | Reticulocyte fraction of red cells | Sum basophil neutrophil counts | Sum neutrophil eosinophil counts | White blood cell count
rs2523466	0.042	-	-	-	-1.327	27723758 27992413 24390342	Bronson P Ji S Okada Y	IgA deficiency Primary sclerosing cholangitis Rheumatoid arthritis
rs56043070	0.066	-	-	-	-1.327	27863252	Astle W	High light scatter percentage of red cells | High light scatter reticulocyte count | Mean platelet volume | Platelet count | Platelet distribution width | Plateletcrit | Reticulocyte count | Reticulocyte fraction of red cells

Table S13: Mediation analysis of variant-specific effects. For each variant, the total effect on ALL risk was decomposed into direct and indirect effects, mediated via regulation of blood cell profiles. Mediator-outcome effects were obtained from Mendelian randomization analyses excluding outliers (as seen in Table S9).

		OR_{ALL}	P_{ALL}	β_{ALL}	(95% CI)[1]	Mediated (%)	
Mediator: PLR		0.82	5.8×10^{-3}	-0.200			
rs4245597 (*ARID5B*, 10q21.2)	Total	0.60	5.3×10^{-46}	-0.505	(-0.575, -0.436)		
	Direct			-0.500	(-0.571, -0.431)		
	Indirect (mediated)			-0.004	(-0.007, -0.001)	0.84	(0.23, 1.44)
rs76428106 (*FLT3*, 13q12.2)	Total	0.56	3.2×10^{-5}	-0.580	(-0.853, -0.307)		
	Direct			-0.562	(-0.841, -0.291)		
	Indirect (mediated)			-0.014	(-0.024, -0.004)	2.43	(0.68, 4.19)
Mediator: NLR		0.67	1.4×10^{-4}	-0.400			
rs4245597 (*ARID5B*, 10q21.2)	Total	0.60	5.3×10^{-46}	-0.505	(-0.575, -0.436)		
	Direct			-0.496	(-0.567, -0.426)		
	Indirect (mediated)			-0.008	(-0.013, -0.004)	1.65	(0.79, 2.51)
rs6430608 (2q22.1)	Total	0.78	2.5×10^{-6}	-0.244	(-0.346, -0.142)		
	Direct			-0.231	(-0.334, -0.129)		
	Indirect (mediated)			-0.012	(-0.018, -0.006)	4.72	(2.26, 7.20)
Mediator: LMR		1.19	0.016	0.173			
rs4948492 (*ARID5B*, 10q21.2)	Total	1.66	5.1×10^{-46}	0.507	(0.437, 0.577)		
	Direct			0.503	(0.433, 0.574)		
	Indirect (mediated)			0.004	(-0.001, 0.008)	0.75	(0, 1.63)
rs74756667 (8q24.2)	Total	1.37	3.3×10^{-10}	0.313	(0.215, 0.410)		
	Direct			0.310	(0.210, 0.407)		
	Indirect (mediated)			0.004	(0.001, 0.007)	1.31	(0.24, 2.38)
rs2239630 (*CEBPE*, 14q11.2)	Total	1.32	1.2×10^{-13}	0.278	(0.206, 0.353)		
	Direct			0.275	(0.199, 0.348)		
	Indirect (mediated)			0.006	(-0.001, 0.013)	2.16	(0, 4.71)
rs78697948* (*IKZF1*, 7p12.2)	Total	0.68	1.2×10^{-10}	-0.391	(-0.509, -0.272)		
	Direct			-0.395	(-0.516, -0.276)		
	Indirect (mediated)			0.007	(-0.001, 0.015)	1.72	(0, 3.75)
rs76428106* (*FLT3*, 13q12.2)	Total	0.56	3.2×10^{-5}	-0.580	(-0.853, -0.307)		
	Direct			-0.637	(-0.918, -0.368)		
	Indirect (mediated)			0.066	(0.012, 0.120)	11.39	(2.07, 20.7)
Mediator: Lymphocytes		1.18	7.4×10^{-3}	0.166	(0.045, 0.288)		
rs76428106 (*FLT3*, 13q12.2)	Total	1.79	3.2×10^{-5}	0.580	(0.307, 0.853)		
	Direct			0.569	(0.290, 0.840)		
	Indirect (mediated)			0.015	(0.004, 0.025)	2.51	(0.67, 4.35)

[1] Bootstrapped 95% confidence intervals for direct and indirect (mediated) effects were obtained using 1000 replicates.

* Variants had statistically significant effects, and of larger magnitude, on monocyte counts than LMR or lymphocytes