

**Supplementary Table S1: Mendelian randomization results for glioma overall.** Odds ratios (OR) and 95% confidence intervals (CI) for the effect of increasing blood cell counts or cell type ratios on the risk of glioma. MR Egger results are only presented for blood cell traits with statistically significant evidence of directional pleiotropy (MR Egger intercept  $\beta_0 \neq 0$ ,  $p < 0.05$ ).

Blood Cell Trait	MR Estimator	$N_{SNP}$	Explained Variance	Glioma Overall	
				OR	(95% CI)
Basophils	IVW-MRE	146	0.045	0.82	(0.57 – 1.18)
	Maximum likelihood			0.82	(0.58 – 1.16)
	Weighted median			0.81	(0.46 – 1.43)
	RAPS			0.81	(0.56 – 1.19)
	PRESSO			0.82	(0.57 – 1.18)
Eosinophils	IVW-MRE	370	0.105	0.96	(0.82 – 1.12)
	Maximum likelihood			0.96	(0.82 – 1.12)
	Weighted median			0.93	(0.71 – 1.20)
	RAPS			0.98	(0.83 – 1.15)
	MR Egger			0.67	(0.46 – 0.99)
Lymphocytes	PRESSO	414	0.114	0.96	(0.82 – 1.12)
	IVW-MRE			0.98	(0.86 – 1.11)
	Maximum likelihood			0.98	(0.86 – 1.11)
	Weighted median			1.29	(1.01 – 1.65)
	RAPS			0.94	(0.81 – 1.08)
Monocytes	MR Egger	479	0.159	1.23	(0.98 – 1.54)
	PRESSO			0.98	(0.89 – 1.11)
	IVW-MRE			1.01	(0.98 – 1.05)
	Maximum likelihood			1.01	(0.99 – 1.04)
	Weighted median			1.02	(0.99 – 1.05)
Neutrophils	RAPS	296	0.082	1.02	(0.99 – 1.05)
	MR Egger			1.02	(0.99 – 1.06)
	PRESSO			0.99	(0.88 – 1.10)
	IVW-MRE			0.87	(0.70 – 1.10)
	Maximum likelihood			0.87	(0.73 – 1.05)
Platelets	Weighted median	668	0.235	0.77	(0.58 – 1.04)
	RAPS			0.90	(0.73 – 1.11)
	PRESSO			0.83	(0.68 – 1.02)
	IVW-MRE			1.02	(0.97 – 1.07)
	Maximum likelihood			1.02	(0.97 – 1.06)

	PRESSO		1.10	(0.99 – 1.21)	0.074
LMR	IVW-MRE		1.12	(0.95 – 1.31)	0.18
	Maximum likelihood		1.12	(0.98 – 1.28)	0.11
	Weighted median	450	0.147	1.10 (0.86 – 1.40)	0.44
	RAPS			1.05 (0.90 – 1.22)	0.51
	PRESSO			1.07 (0.93 – 1.23)	0.38
	IVW-MRE			0.97 (0.76 – 1.24)	0.82
NLR	Maximum likelihood			0.97 (0.79 – 1.19)	0.78
	Weighted median	249	0.063	1.00 (0.72 – 1.37)	0.98
	RAPS			0.97 (0.76 – 1.25)	0.83
	PRESSO			0.92 (0.73 – 1.15)	0.45
PLR	IVW-MRE			1.25 (1.07 – 1.47)	$4.9 \times 10^{-3}$
	Maximum likelihood			1.25 (1.10 – 1.43)	$9.1 \times 10^{-4}$
	Weighted median	470	0.145	1.18 (0.93 – 1.50)	0.16
	RAPS			1.22 (1.05 – 1.43)	0.011
	PRESSO			1.21 (1.05 – 1.40)	$8.8 \times 10^{-3}$

<sup>1</sup> Out-of-sample trait variance explained by the genetic instruments was previously reported in Kachuri et al. (2021)<sup>22</sup> and estimated for the subset of genetic instruments that were available for this analysis

#### Abbreviations:

IVW-MRE	Inverse variance weighted multiplicative random effect
RAPS	Robust adjusted profile score
PRESSO	Pleiotropy Residual Sum and Outlier
LMR	Lymphocyte to monocyte ratio
NLR	Neutrophil to lymphocyte ratio
PLR	Platelet to lymphocyte ratio

**Supplementary Table S2: Results of Mendelian Randomization diagnostic tests.** Assessment of the robustness of underlying Mendelian randomization assumptions for each set of analyses of glioma susceptibility, overall and stratified by major molecular subtypes.

Blood Cell Trait	$I^2_{GX}$	Glioma						IDH-mutated (IDH <sub>mut</sub> )					
		Heterogeneity <sup>1</sup>			MR Egger <sup>2</sup>		$P_{Global}^3$	Heterogeneity <sup>1</sup>			MR Egger <sup>2</sup>		$P_{Global}^3$
		Q	DF	$P_{Q\text{-value}}$	$\beta_0$	$P_{Egger}$		Q	DF	$P_{Q\text{-value}}$	$\beta_0$	$P_{Egger}$	
Basophils	0.985	162.1	145	0.16	-0.011	0.24	0.15	171.3	145	0.067	-0.008	0.58	0.073
Eosinophils	0.986	406.2	369	0.089	0.012	0.048	0.091	432.7	369	0.012	0.006	0.51	0.011
Lymphocytes	0.986	464.3	413	0.041	-0.010	0.015	0.031	484.7	413	8.5×10 <sup>-3</sup>	-0.009	0.14	8.0×10 <sup>-3</sup>
Monocytes	0.988	639.9	478	9.6×10 <sup>-7</sup>	-0.005	0.048	0.013	765.8	478	1.1×10 <sup>-15</sup>	-0.006	0.19	2.5×10 <sup>-4</sup>
Neutrophils	0.985	476.1	295	1.1×10 <sup>-10</sup>	0.007	0.37	<1.0×10 <sup>-4</sup>	385.2	295	3.2×10 <sup>-4</sup>	0.013	0.23	3.0×10 <sup>-4</sup>
Platelets	0.988	906.6	667	1.6×10 <sup>-9</sup>	0.005	0.031	6.7×10 <sup>-5</sup>	858.6	667	6.8×10 <sup>-7</sup>	0.004	0.24	6.7×10 <sup>-5</sup>
LMR	0.988	631.9	449	2.5×10 <sup>-8</sup>	-0.005	0.33	<6.7×10 <sup>-5</sup>	753.2	449	9.3×10 <sup>-18</sup>	-0.007	0.42	<6.7×10 <sup>-5</sup>
NLR	0.985	355.0	248	9.5×10 <sup>-6</sup>	0.013	0.16	<1e×10 <sup>-4</sup>	306.7	248	6.5×10 <sup>-3</sup>	-0.008	0.54	6.2×10 <sup>-3</sup>
PLR	0.987	658.8	469	1.5×10 <sup>-8</sup>	0.009	0.11	<6.7×10 <sup>-5</sup>	635.5	469	4.3×10 <sup>-7</sup>	0.009	0.30	<6.7×10 <sup>-5</sup>
IDH-mutated 1p/19q co-deleted (IDH <sub>mut-codelet</sub> )													
$I^2_{GX}$		Heterogeneity <sup>1</sup>			MR Egger <sup>2</sup>		$P_{Global}^3$	Heterogeneity <sup>1</sup>			MR Egger <sup>2</sup>		$P_{Global}^3$
		Q	DF	$P_{Q\text{-value}}$	$\beta_0$	$P_{Egger}$		Q	DF	$P_{Q\text{-value}}$	$\beta_0$	$P_{Egger}$	
		162.8	145	0.15	-0.018	0.38	0.14	194.0	145	4.1×10 <sup>-3</sup>	-0.010	0.58	4.3×10 <sup>-3</sup>
Basophils	0.985	162.8	145	0.15	-0.018	0.38	0.14	194.0	145	4.1×10 <sup>-3</sup>	-0.010	0.58	4.3×10 <sup>-3</sup>
Eosinophils	0.986	436.8	369	8.6×10 <sup>-3</sup>	-0.008	0.59	8.1×10 <sup>-3</sup>	468.8	369	3.2×10 <sup>-4</sup>	0.017	0.17	3.6×10 <sup>-4</sup>
Lymphocytes	0.986	502.4	413	1.7×10 <sup>-3</sup>	-0.016	0.086	1.8×10 <sup>-3</sup>	430.1	413	0.27	-0.007	0.34	0.26
Monocytes	0.988	665.9	478	2.6×10 <sup>-8</sup>	-0.005	0.38	1.3×10 <sup>-3</sup>	716.8	478	8.0×10 <sup>-12</sup>	-0.005	0.32	2.8×10 <sup>-3</sup>
Neutrophils	0.985	356.9	295	7.9×10 <sup>-3</sup>	-0.006	0.71	7.7×10 <sup>-3</sup>	367.7	295	2.5×10 <sup>-3</sup>	0.018	0.19	2.4×10 <sup>-3</sup>
Platelets	0.988	931.4	667	4.7×10 <sup>-11</sup>	0.007	0.21	6.7×10 <sup>-5</sup>	752.9	667	0.011	0.004	0.28	0.019
LMR	0.988	645.2	449	3.3×10 <sup>-9</sup>	0.001	0.92	<6.7×10 <sup>-5</sup>	681.6	449	7.8×10 <sup>-12</sup>	-0.014	0.19	<6.7×10 <sup>-5</sup>
NLR	0.985	300.1	248	0.013	0.008	0.66	0.012	283.4	248	0.061	-0.020	0.19	0.055
PLR	0.987	596.8	469	5.5×10 <sup>-5</sup>	0.012	0.35	6.7×10 <sup>-5</sup>	600.0	469	3.8×10 <sup>-12</sup>	0.015	0.15	<6.7×10 <sup>-5</sup>

	$I^2_{GX}$	IDH wildtype ( $IDH_{wt}$ )					
		Heterogeneity <sup>1</sup>			MR Egger <sup>2</sup>		MR PRESSO
		Q	DF	$P_{Q\text{-value}}$	$\beta_0$	$P_{\text{Egger}}$	$P_{\text{Global}}^3$
Basophils	0.985	143.6	145	0.52	-0.014	0.22	0.53
Eosinophils	0.986	387.6	369	0.24	0.006	0.45	0.24
Lymphocytes	0.986	431.3	413	0.26	-0.006	0.36	0.26
Monocytes	0.988	506.5	478	0.18	-0.009	0.082	0.32
Neutrophils	0.985	456.6	295	$4.5 \times 10^{-9}$	-0.005	0.084	$<1.0 \times 10^{-4}$
Platelets	0.988	857.7	667	$7.5 \times 10^{-7}$	0.000	0.98	$1.3 \times 10^{-4}$
LMR	0.988	510.4	449	0.024	0.024	0.029	0.025
NLR	0.985	319.4	248	$1.5 \times 10^{-3}$	0.003	0.26	$1.9 \times 10^{-3}$
PLR	0.987	601.0	469	$3.4 \times 10^{-5}$	0.014	0.059	$<6.7 \times 10^{-5}$

<sup>1</sup> Modified Cochran's Q test for heterogeneity in causal effect estimates (indicative of horizontal pleiotropy), p-values<0.05 are considered statistically significant

<sup>2</sup> Tests for directional horizontal pleiotropy indicated by non-zero in MR Egger intercept ( $\beta_0$ ) values, p-values<0.05 are considered statistically significant

<sup>3</sup> Tests for horizontal pleiotropy, empirical p-values were estimated based on 12000-15000 replicates, p-values<0.05 are considered statistically significant

<sup>4</sup> Values of  $I^2_{GX}<0.90$  indicate potential for regression dilution bias and violation of the NOME (no measurement error assumption)

Abbreviations:

PRESSO Pleiotropy Residual Sum and Outlier

LMR Lymphocyte to monocyte ratio

NLR Neutrophil to lymphocyte ratio

PLR Platelet to lymphocyte ratio

**Supplementary Table S3: Mendelian randomization results for IDH mutant (IDH<sub>mut</sub>) glioma.** Odds ratios (OR) and 95% confidence intervals (CI) estimate the effect of increasing blood cell counts or cell type ratios on disease risk. MR Egger results are only presented for traits with statistically significant evidence of directional pleiotropy (MR Egger intercept  $\beta_0 \neq 0$ ,  $p < 0.05$ ).

Blood Cell Trait	MR Estimator	N <sub>SNP</sub>	IDH <sub>mut</sub>			IDH <sub>mut</sub> 1p/19q co-deleted			IDH <sub>mut</sub> 1p/19q non-codeleted		
			OR	(95% CI)	P	OR	(95% CI)	P	OR	(95% CI)	P
Basophils	IVW-MRE	146	0.67	(0.38 – 1.20)	0.18	0.79	(0.34 – 1.18)	0.57	0.73	(0.34 – 1.57)	0.42
	Maximum likelihood		0.67	(0.39 – 1.15)	0.15	0.79	(0.36 – 1.73)	0.55	0.73	(0.38 – 1.43)	0.36
	Weighted median		0.50	(0.21 – 1.22)	0.13	0.54	(0.14 – 2.02)	0.36	0.29	(0.10 – 0.85)	0.023
	RAPS		0.57	(0.31 – 1.03)	0.064	0.65	(0.28 – 1.53)	0.33	0.65	(0.30 – 1.42)	0.28
	PRESSO		0.67	(0.38 – 1.20)	0.18	0.79	(0.34 – 1.18)	0.57	0.73	(0.34 – 1.57)	0.42
Eosinophils	IVW-MRE	370	0.94	(0.73 – 1.20)	0.60	1.13	(0.78 – 1.64)	0.51	0.83	(0.60 – 1.15)	0.26
	Maximum likelihood		0.93	(0.74 – 1.18)	0.57	1.13	(0.80 – 1.60)	0.48	0.83	(0.62 – 1.11)	0.21
	Weighted median		0.85	(0.57 – 1.25)	0.40	1.12	(0.61 – 2.03)	0.72	0.92	(0.58 – 1.48)	0.74
	RAPS		0.95	(0.73 – 1.22)	0.66	1.16	(0.79 – 1.71)	0.44	0.87	(0.63 – 1.21)	0.40
	PRESSO		0.99	(0.78 – 1.25)	0.91	1.13	(0.78 – 1.64)	0.51	0.87	(0.64 – 1.18)	0.38
Lymphocytes	IVW-MRE	414	0.83	(0.68 – 1.02)	0.079	1.07	(0.79 – 1.45)	0.67	0.70	(0.55 – 0.89)	3.8×10 <sup>-3</sup>
	Maximum likelihood		0.84	(0.69 – 1.02)	0.081	1.07	(0.81 – 1.42)	0.64	0.71	(0.55 – 0.91)	6.5×10 <sup>-3</sup>
	Weighted median		1.25	(0.85 – 1.84)	0.25	1.48	(0.83 – 2.65)	0.19	1.00	(0.62 – 1.62)	0.98
	RAPS		0.75	(0.60 – 0.93)	8.9×10 <sup>-3</sup>	1.05	(0.76 – 1.46)	0.76	0.67	(0.53 – 0.86)	1.9×10 <sup>-3</sup>
	PRESSO		0.83	(0.68 – 1.02)	0.080	1.07	(0.79 – 1.45)	0.67	0.70	(0.55 – 0.89)	3.9×10 <sup>-3</sup>
Monocytes	IVW-MRE	479	0.99	(0.94 – 1.05)	0.85	1.00	(0.93 – 1.07)	0.95	0.98	(0.92 – 1.05)	0.62
	Maximum likelihood		0.99	(0.95 – 1.04)	0.81	1.00	(0.94 – 1.06)	0.95	0.98	(0.93 – 1.04)	0.54
	Weighted median		1.00	(0.96 – 1.04)	0.98	1.00	(0.93 – 1.06)	0.91	0.99	(0.94 – 1.05)	0.82
	RAPS		1.00	(0.96 – 1.05)	0.98	1.01	(0.94 – 1.07)	0.85	0.99	(0.94 – 1.04)	0.66
	PRESSO		1.00	(0.95 – 1.05)	0.96	1.00	(0.94 – 1.07)	0.94	0.91	(0.73 – 1.15)	0.44
Neutrophils	IVW-MRE	296	0.69	(0.50 – 0.94)	0.019	0.80	(0.51 – 1.24)	0.31	0.60	(0.41 – 0.88)	9.1×10 <sup>-3</sup>
	Maximum likelihood		0.69	(0.52 – 0.90)	7.5×10 <sup>-3</sup>	0.79	(0.53 – 1.19)	0.26	0.60	(0.43 – 0.85)	3.9×10 <sup>-3</sup>
	Weighted median		0.54	(0.34 – 0.85)	7.3×10 <sup>-3</sup>	0.70	(0.36 – 1.37)	0.30	0.48	(0.26 – 0.87)	0.016
	RAPS		0.68	(0.49 – 0.95)	0.024	0.87	(0.55 – 1.38)	0.57	0.61	(0.41 – 0.92)	0.017

	PRESSO	0.67	(0.49 – 0.91)	0.011	0.80	(0.51 – 1.24)	0.31	0.60	(0.41 – 0.88)	$9.6 \times 10^{-3}$	
	IVW-MRE	0.98	(0.91 – 1.05)	0.53	0.90	(0.80 – 1.01)	0.071	1.03	(0.94 – 1.12)	0.54	
	Maximum likelihood	0.98	(0.91 – 1.04)	0.48	0.90	(0.81 – 0.99)	0.038	1.03	(0.95 – 1.12)	0.52	
Platelets	Weighted median	668	0.96	(0.89 – 1.04)	0.34	0.89	(0.78 – 1.00)	0.058	1.02	(0.92 – 1.12)	0.74
	RAPS		0.97	(0.90 – 1.06)	0.53	0.90	(0.79 – 1.02)	0.097	1.02	(0.93 – 1.12)	0.66
	PRESSO		0.97	(0.91 – 1.04)	0.45	0.90	(0.80 – 1.00)	0.049	1.02	(0.94 – 1.12)	0.58
	IVW-MRE		1.05	(0.80 – 1.37)	0.73	1.11	(0.77 – 1.60)	0.58	1.02	(0.74 – 1.39)	0.91
	Maximum likelihood		1.05	(0.85 – 1.29)	0.66	1.11	(0.82 – 1.51)	0.51	1.02	(0.79 – 1.32)	0.89
LMR	Weighted median	450	0.98	(0.68 – 1.40)	0.90	0.91	(0.53 – 1.56)	0.74	1.20	(0.75 – 1.94)	0.45
	RAPS		0.94	(0.75 – 1.19)	0.61	0.87	(0.63 – 1.21)	0.41	1.01	(0.75 – 1.36)	0.96
	PRESSO		0.93	(0.75 – 1.15)	0.49	0.95	(0.69 – 1.29)	0.73	0.92	(0.69 – 1.21)	0.54
	IVW-MRE		1.17	(0.83 – 1.66)	0.37	1.06	(0.64 – 1.76)	0.82	1.29	(0.85 – 1.95)	0.24
	Maximum likelihood		1.18	(0.86 – 1.61)	0.32	1.06	(0.66 – 1.69)	0.81	1.29	(0.87 – 1.92)	0.20
NLR	Weighted median	249	1.21	(0.72 – 2.02)	0.47	0.98	(0.46 – 2.07)	0.96	1.62	(0.85 – 3.12)	0.14
	RAPS		1.17	(0.81 – 1.70)	0.39	1.11	(0.64 – 1.90)	0.72	1.26	(0.80 – 1.96)	0.32
	PRESSO		1.17	(0.83 – 1.66)	0.37	1.06	(0.64 – 1.77)	0.82	1.29	(0.85 – 1.95)	0.24
	IVW-MRE		1.38	(1.09 – 1.75)	$7.2 \times 10^{-3}$	1.15	(0.82 – 1.61)	0.43	1.53	(1.15 – 2.03)	$3.7 \times 10^{-3}$
	Maximum likelihood		1.39	(1.13 – 1.71)	$1.7 \times 10^{-3}$	1.15	(0.85 – 1.55)	0.37	1.54	(1.19 – 1.98)	$9.4 \times 10^{-4}$
PLR	Weighted median	470	1.25	(0.88 – 1.78)	0.21	1.17	(0.71 – 1.94)	0.53	1.47	(0.97 – 2.24)	0.072
	RAPS		1.38	(1.08 – 1.76)	0.011	1.19	(0.84 – 1.70)	0.33	1.48	(1.10 – 2.00)	$9.6 \times 10^{-3}$
	PRESSO		1.40	(1.11 – 1.77)	$4.9 \times 10^{-3}$	1.14	(0.82 – 1.61)	0.43	1.55	(1.17 – 2.06)	$2.4 \times 10^{-3}$

Abbreviations:

- IVW-MRE Inverse variance weighted multiplicative random effect
- RAPS Robust adjusted profile score
- PRESSO Pleiotropy Residual Sum and Outlier
- LMR Lymphocyte to monocyte ratio
- NLR Neutrophil to lymphocyte ratio
- PLR Platelet to lymphocyte ratio

**Supplementary Table S4: Mendelian randomization results for IDH wildtype (IDH<sub>wt</sub>) glioma.** Odds ratios (OR) and 95% confidence intervals (CI) for the effect of increasing blood cell counts or cell type ratios on disease risk. MR Egger results are only presented for phenotypes with evidence of directional horizontal pleiotropy (MR Egger intercept  $\beta_0 \neq 0$  ( $p < 0.05$ )).

Blood Trait	MR Estimator	N <sub>SNP</sub>	IDH <sub>wt</sub>		
			OR	(95% CI)	P
Basophils	IVW-MRE	146	0.87	(0.56 – 1.36)	0.54
	Maximum likelihood		0.87	(0.55 – 1.37)	0.54
	Weighted median		0.81	(0.40 – 1.62)	0.55
	RAPS		0.86	(0.54 – 1.38)	0.53
	PRESSO		0.87	(0.56 – 1.36)	0.54
Eosinophils	IVW-MRE	370	0.98	(0.80 – 1.19)	0.81
	Maximum likelihood		0.98	(0.80 – 1.19)	0.81
	Weighted median		1.13	(0.83 – 1.53)	0.45
	RAPS		1.02	(0.82 – 1.25)	0.88
	PRESSO		0.98	(0.80 – 1.19)	0.81
Lymphocytes	IVW-MRE	414	1.05	(0.89 – 1.23)	0.59
	Maximum likelihood		1.05	(0.89 – 1.23)	0.58
	Weighted median		1.19	(0.85 – 1.67)	0.31
	RAPS		1.05	(0.88 – 1.25)	0.57
	PRESSO		1.05	(0.89 – 1.23)	0.59
Monocytes	IVW-MRE	479	1.04	(1.00 – 1.07)	0.058
	Maximum likelihood		1.04	(1.00 – 1.07)	0.052
	Weighted median		1.04	(1.00 – 1.08)	0.036
	RAPS		1.04	(1.00 – 1.08)	0.056
	PRESSO		1.04	(1.00 – 1.07)	0.058
Neutrophils	IVW-MRE	296	1.03	(0.78 – 1.38)	0.82
	Maximum likelihood		1.03	(0.82 – 1.31)	0.78
	Weighted median		0.87	(0.60 – 1.26)	0.45
	RAPS		1.00	(0.76 – 1.30)	0.98
	PRESSO		0.94	(0.74 – 1.21)	0.65
Platelets	IVW-MRE	668	1.03	(0.97 – 1.10)	0.37
	Maximum likelihood		1.03	(0.97 – 1.09)	0.33
	Weighted median		1.00	(0.94 – 1.07)	0.93
	RAPS		1.03	(0.96 – 1.09)	0.42
	PRESSO		1.02	(0.96 – 1.08)	0.49
LMR	IVW-MRE	450	1.08	(0.89 – 1.30)	0.44
	Maximum likelihood		1.08	(0.90 – 1.29)	0.41
	Weighted median		1.01	(0.74 – 1.38)	0.96
	RAPS		1.03	(0.85 – 1.26)	0.76

	PRESSO	1.08	(0.90 – 1.29)	0.44
NLR	IVW-MRE	0.96	(0.71 – 1.30)	0.81
	Maximum likelihood	0.96	(0.74 – 1.26)	0.79
	Weighted median	0.97	(0.64 – 1.48)	0.90
	RAPS	0.93	(0.69 – 1.25)	0.62
	MR Egger	0.42	(0.18 – 0.93)	0.034
	PRESSO	0.89	(0.68 – 1.18)	0.43
PLR	IVW-MRE	1.23	(1.01 – 1.49)	0.036
	Maximum likelihood	1.23	(1.04 – 1.47)	0.017
	Weighted median	1.07	(0.80 – 1.43)	0.64
	RAPS	1.21	(1.00 – 1.47)	0.051
	MR Egger	0.83	(0.53 – 1.30)	0.42
	PRESSO	1.19	(1.00 – 1.42)	0.055

Abbreviations:

- IVW-MRE Inverse variance weighted multiplicative random effect
- RAPS Robust adjusted profile score
- PRESSO Pleiotropy Residual Sum and Outlier
- LMR Lymphocyte to monocyte ratio
- NLR Neutrophil to lymphocyte ratio
- PLR Platelet to lymphocyte ratio

**Supplementary Table S5: Mendelian randomization results following manual removal of invalid genetic instruments.** Odds ratios (OR) and 95% for glioma for selected traits were estimated after filtering instruments that contributed to significant heterogeneity.

Blood Cell Trait	Outcome	N / N <sub>SNP</sub>	IVW-MRE		Diagnostics		
			OR	(95% CI)	P	P <sub>Q-value</sub>	P <sub>Egger</sub>
PLR	Glioma overall	442 / 470	1.27	(1.12 – 1.44)	2.2×10 <sup>-4</sup>	0.98	0.18
PLR	IDH <sub>mut</sub>	425 / 470	1.45	(1.18 – 1.77)	3.1×10 <sup>-4</sup>	0.99	0.40
PLR	1p/19q non-codeleted (IDH <sub>mut-noncodelet</sub> )	434 / 470	1.53	(1.19 – 1.96)	8.1×10 <sup>-4</sup>	0.99	0.11
Lymphocytes	IDH <sub>mut</sub>	388 / 414	0.68	(0.55 – 0.83)	1.8×10 <sup>-4</sup>	0.99	0.52
Lymphocytes	1p/19q non-codeleted (IDH <sub>mut-noncodelet</sub> )	391 / 414	0.69	(0.55 – 0.85)	4.5×10 <sup>-4</sup>	0.99	0.20
Neutrophils	IDH <sub>mut</sub>	271 / 296	0.65	(0.50 – 0.85)	1.4×10 <sup>-3</sup>	0.97	0.16
Neutrophils	1p/19q non-codeleted (IDH <sub>mut-noncodelet</sub> )	278 / 296	0.61	(0.43 – 0.86)	5.2×10 <sup>-3</sup>	0.73	0.51

Abbreviations:

IVW-MRE Inverse variance weighted multiplicative random effect

PLR Platelet to lymphocyte ratio

**Supplementary Table S6: Multivariable (MV) Mendelian randomization results.** Odds ratios (OR) and 95% for glioma, estimated using MVMR for traits that were individually associated with specific glioma subtypes or were used to derive associated ratio phenotypes.

Outcome	Traits Included	MV Method	Association Estimates		
			OR	(95% CI)	P
$IDH_{\text{mut}}$	Lymphocytes	IVW	0.78	(0.58 – 1.06)	0.11
	Neutrophils	IVW	1.08	(0.91 – 1.28)	0.37
	Platelets	IVW	1.09	(0.91 – 1.30)	0.36
	PLR	LASSO	1.11		
	Lymphocytes	LASSO	-		
	Neutrophils	LASSO	0.86		
	Platelets	LASSO	-		
$IDH_{\text{mut-noncodeI}}$	Lymphocytes	IVW	0.70	(0.48 – 1.00)	0.051
	Neutrophils	IVW	1.12	(0.91 – 1.40)	0.27
	Platelets	IVW	1.10	(0.89 – 1.37)	0.36
	PLR	LASSO	1.16		
	Lymphocytes	LASSO	0.89		
	Neutrophils	LASSO	0.90		
	Platelets	LASSO	-		

**Supplementary Table S7: Candidate variants for colocalization.** Genome-wide significant glioma risk variants identified among genetic instruments for blood cell traits. For each variant associations with all blood cell phenotypes and/or leukocyte telomere length that reached genome-wide significance are shown.

Region	SNP <sup>1</sup>	Outcome	OR	P-value	P-values for associated traits	
2q37.3	rs34290285 (G/A)	IDH <sub>mut</sub> 1p/19q non-codel	0.60	5.2×10 <sup>-10</sup>	Eosinophils:	3.9×10 <sup>-37</sup>
		IDH <sub>mut</sub>	0.66	1.6×10 <sup>-9</sup>		
5p15.33	rs7705526 (C/A)	IDH <sub>wt</sub>	0.60	6.7×10 <sup>-25</sup>	Neutrophils:	1.3×10 <sup>-12</sup>
		IDH <sub>wt</sub>	0.60	6.7×10 <sup>-25</sup>	NLR:	1.4×10 <sup>-9</sup>
		Glioma overall	0.68	2.2×10 <sup>-23</sup>	PLR:	2.7×10 <sup>-12</sup>
5p15.33	rs2853677 (G/A)	Glioma overall	1.25	1.2×10 <sup>-9</sup>	Platelets:	9.9×10 <sup>-33</sup>
		IDH <sub>mut</sub>	0.27	2.5×10 <sup>-41</sup>	Neutrophils:	2.2×10 <sup>-11</sup>
		IDH <sub>mut</sub> 1p/19q non-codel	0.27	5.2×10 <sup>-29</sup>	LMR:	5.3×10 <sup>-21</sup>
		Glioma overall	0.47	6.2×10 <sup>-24</sup>	Monocytes:	4.0×10 <sup>-21</sup>
8q24	rs72716319 (A/G)	IDH <sub>mut</sub> 1p/19q co-del	0.26	1.5×10 <sup>-23</sup>		
		IDH <sub>mut</sub>	0.24	3.0×10 <sup>-55</sup>		
		IDH <sub>mut</sub> 1p/19q co-del	0.20	8.9×10 <sup>-37</sup>	LMR:	1.0×10 <sup>-22</sup>
		IDH <sub>mut</sub> 1p/19q non-codel	0.25	2.7×10 <sup>-34</sup>	Monocytes:	1.6×10 <sup>-19</sup>
8q24	rs55705857 (A/G)	Glioma overall	0.44	3.1×10 <sup>-32</sup>		
		IDH <sub>mut</sub>	0.57	1.3×10 <sup>-19</sup>		
		IDH <sub>mut</sub> 1p/19q co-del	0.48	2.0×10 <sup>-17</sup>	LMR:	6.1×10 <sup>-21</sup>
		Glioma overall	0.76	1.5×10 <sup>-10</sup>	Monocytes:	2.2×10 <sup>-17</sup>
8q24	rs16904140 (G/A)	IDH <sub>mut</sub> 1p/19q non-codel	0.64	4.8×10 <sup>-9</sup>	Platelets:	1.1×10 <sup>-8</sup>
		IDH <sub>wt</sub>	0.62	1.3×10 <sup>-14</sup>	Platelets:	1.1×10 <sup>-9</sup>
		Glioma overall	0.71	1.4×10 <sup>-13</sup>	Telomere length:	1.1×10 <sup>-19</sup>

<sup>1</sup> Alleles are listed as effect allele/other allele, where the odds ratio corresponds to the effect allele

**Supplementary Table S8: Colocalization results.** Regions with evidence of colocalization, denoted by posterior probability (PP)>0.90 between signals for glioma susceptibility and putative risk factors.

Locus	Candidate	Colocalized Traits	Dropped Traits	PP <sup>1</sup>	PP <sub>regional</sub> <sup>2</sup>	Fine-mapped <sup>3</sup>	PP <sub>SNP</sub>
2q37.3	rs34290285 ( <i>D2HGDH</i> )	IDH <sub>mut</sub> 1p/19q non-codel, Eosinophils	-	0.939	1	rs34290285	0.944
5p15.33	rs7705526 ( <i>TERT</i> )	IDH <sub>wt</sub> , telomere length, platelets, neutrophils, PLR	-	0.994	1	rs7705526	1
5p15.33	rs2853677 ( <i>TERT</i> )	Glioma, telomere length, platelets	-	0.978	1	rs7705526	1
20q13.33	rs4809319 ( <i>STMN3</i> )	None IDH <sub>wt</sub> , platelets	Telomere length -	0.665 0.952	- 1	rs6011018 ( <i>RTEL1</i> )	0.178

<sup>1</sup> Posterior probability that all traits are colocalized

<sup>2</sup> Posterior probability that one or more SNPs in the region have shared associations across the traits

<sup>3</sup> Candidate variant explaining the shared association

<sup>4</sup> Proportion of the posterior probability explained by the fine-mapped variant

Abbreviations:

PP              Posterior probability

**Supplementary Table S9: Survival analysis of blood cell trait polygenic scores (PGS).** Hazard ratios (HR) and 95% confidence intervals per 1 standard deviation increase in the standardized PGS were estimated using Cox proportional hazards models fit separately in each patient population. Associations of each PGS with all-cause mortality were estimated with adjustment for age, sex, and top 10 genetic ancestry principal components.

Blood Cell PGS	Cases (Events)	UCSF AGS and Mayo Clinic			UCSF AGS			TCGA				
		HR	(95% CI)	P	HR	(95% CI)	P	HR	(95% CI)	P		
Basophils		1.02	(0.97 – 1.08)	0.43	1.01	(0.93 – 1.09)	0.83	1.14	(1.00 – 1.14)	0.042		
Eosinophils		0.99	(0.93 – 1.05)	0.73	1.04	(0.96 – 1.13)	0.30	1.03	(0.92 – 1.16)	0.64		
Lymphocytes		1.02	(0.96 – 1.08)	0.48	1.00	(0.93 – 1.09)	0.94	1.14	(1.01 – 1.29)	0.030		
Monocytes	Glioma	1.00	(0.95 – 1.06)	0.89	Glioma	1.01	(0.93 – 1.10)	0.83	Glioma	0.93	(0.83 – 1.03)	0.17
Neutrophils	1973 (1218)	1.05	(0.99 – 1.11)	0.12	659 (592)	0.97	(0.90 – 1.05)	0.43	786 (310)	1.07	(0.95 – 1.21)	0.26
Platelets		1.01	(0.96 – 1.07)	0.65		1.05	(0.97 – 1.14)	0.23		0.98	(0.88 – 1.09)	0.72
LMR		0.96	(0.91 – 1.02)	0.21		1.00	(0.92 – 1.09)	0.98		1.10	(0.99 – 1.23)	0.090
NLR		1.00	(0.95 – 1.06)	0.94		0.96	(0.88 – 1.04)	0.29		0.87	(0.78 – 0.97)	0.013
PLR		0.97	(0.91 – 1.02)	0.24		1.00	(0.92 – 1.08)	0.97		0.95	(0.85 – 1.06)	0.36
Basophils		1.11	(0.96 – 1.28)	0.18		1.00	(0.78 – 1.29)	0.99		1.70	(1.22 – 2.37)	1.8E-03
Eosinophils		1.17	(1.00 – 1.37)	0.055		0.89	(0.70 – 1.14)	0.36		1.18	(0.86 – 1.61)	0.31
Lymphocytes		1.09	(0.94 – 1.27)	0.26		0.99	(0.78 – 1.25)	0.91		1.42	(1.03 – 1.95)	0.030
Monocytes	IDH <sub>mut</sub> 588 (201)	0.98	(0.85 – 1.13)	0.79	IDH <sub>mut</sub>	0.79	(0.59 – 1.06)	0.11	IDH <sub>mut</sub>	0.86	(0.63 – 1.18)	0.35
Neutrophils		1.12	(0.96 – 1.31)	0.15	111 (74)	0.95	(0.76 – 1.19)	0.66	375 (50)	1.35	(1.00 – 1.82)	0.051
Platelets		1.04	(0.90 – 1.20)	0.58		0.96	(0.76 – 1.21)	0.72		1.09	(0.83 – 1.45)	0.53
LMR		0.93	(0.80 – 1.07)	0.30		1.06	(0.83 – 1.36)	0.64		1.32	(0.96 – 1.81)	0.083
NLR		0.91	(0.80 – 1.05)	0.20		0.95	(0.76 – 1.19)	0.67		0.76	(0.56 – 1.03)	0.073
PLR		0.93	(0.81 – 1.08)	0.34		0.88	(0.70 – 1.10)	0.25		0.84	(0.60 – 1.16)	0.29
Basophils		1.33	(1.00 – 1.77)	0.047		-	-	-		2.59	(1.04 – 6.41)	0.040
Eosinophils		1.56	(1.15 – 2.13)	4.4×10 <sup>-3</sup>		-	-	-		1.94	(0.60 – 6.32)	0.27

Lymphocytes		1.68	(1.24 – 2.27)	$7.4 \times 10^{-4}$		-	-	-		1.38	(0.50 – 3.81)	0.53
Monocytes		1.22	(0.94 – 1.59)	0.13		-	-	-		1.71	(0.65 – 4.48)	0.28
Neutrophils	IDH <sub>mut</sub> 1p/19q	1.37	(1.03 – 1.83)	0.033	IDH <sub>mut</sub> 1p/19q	-	-	-	IDH <sub>mut</sub> 1p/19q	4.82	(1.63 – 14.29)	4.5E-03
platelet	co-del	0.80	(0.61 – 1.05)	0.11	co-del	-	-	-	co-del	1.50	(0.59 – 3.80)	0.39
LMR	244 (64)	0.99	(0.77 – 1.29)	0.97	9 (1)	-	-	-	143 (13)	1.42	(0.58 – 3.46)	0.44
NLR		0.83	(0.64 – 1.07)	0.15		-	-	-		1.78	(0.73 – 4.35)	0.20
PLR		0.83	(0.63 – 1.08)	0.17		-	-	-		0.87	(0.40 – 1.91)	0.73
Basophils		1.13	(0.93 – 1.39)	0.22		1.09	(0.84 – 1.41)	0.51		1.63	(1.08 – 2.45)	0.019
Eosinophils		1.08	(0.88 – 1.32)	0.46		0.97	(0.75 – 1.25)	0.79		1.15	(0.81 – 1.64)	0.43
Lymphocytes		1.02	(0.84 – 1.24)	0.86	IDH <sub>mut</sub> 1p/19q	1.11	(0.87 – 1.41)	0.41	IDH <sub>mut</sub> 1p/19q	1.33	(0.85 – 2.07)	0.21
Monocytes	IDH <sub>mut</sub> 1p/19q	1.04	(0.85 – 1.28)	0.67	1p/19q	0.87	(0.64 – 1.20)	0.41	1p/19q	0.64	(0.42 – 0.99)	0.045
Neutrophils	non-codel	1.03	(0.85 – 1.26)	0.75	non- codel	1.03	(0.83 – 1.28)	0.78	non- codel	1.14	(0.77 – 1.68)	0.51
Platelets	291 (117)	1.04	(0.86 – 1.27)	0.67	94 (69)	0.90	(0.70 – 1.15)	0.41	230 (36)	0.99	(0.70 – 1.39)	0.94
LMR		0.95	(0.79 – 1.14)	0.57		1.11	(0.85 – 1.43)	0.44		1.35	(0.92 – 1.96)	0.12
NLR		0.88	(0.73 – 1.07)	0.19		0.89	(0.71 – 1.11)	0.29		0.70	(0.43 – 1.13)	0.15
PLR		0.96	(0.80 – 1.15)	0.66		0.83	(0.65 – 1.06)	0.13		0.83	(0.53 – 1.30)	0.42
Basophils		1.00	(0.93 – 1.09)	0.91		1.04	(0.94 – 1.14)	0.44		1.11	(0.95 – 1.29)	0.18
Eosinophils		0.95	(0.87 – 1.04)	0.25		1.07	(0.97 – 1.18)	0.18		1.09	(0.95 – 1.25)	0.23
Lymphocytes		1.04	(0.96 – 1.13)	0.32		1.01	(0.91 – 1.11)	0.91		1.09	(0.94 – 1.26)	0.23
Monocytes	IDH <sub>wt</sub>	0.98	(0.91 – 1.06)	0.64	IDH <sub>wt</sub>	1.03	(0.93 – 1.13)	0.57	IDH <sub>wt</sub>	0.89	(0.78 – 1.01)	0.073
Neutrophils	699 (594)	1.02	(0.94 – 1.10)	0.69	416 (402)	0.99	(0.90 – 1.08)	0.81	364 (228)	0.99	(0.86 – 1.15)	0.91
Platelets		1.03	(0.95 – 1.11)	0.53		1.10	(1.00 – 1.22)	0.061		0.90	(0.79 – 1.02)	0.11
LMR		1.00	(0.92 – 1.09)	0.96		0.95	(0.86 – 1.05)	0.33		1.09	(0.96 – 1.24)	0.16
NLR		1.01	(0.93 – 1.10)	0.85		0.99	(0.89 – 1.10)	0.86		0.92	(0.81 – 1.04)	0.16
PLR		0.95	(0.87 – 1.03)	0.20		1.04	(0.94 – 1.15)	0.44		0.92	(0.80 – 1.05)	0.19

**Supplementary Table S10: Meta-analysis of blood cell trait polygenic scores (PGS) associations.** Study specific results in Supplementary Table S9 were combined in a fixed-effects meta-analysis to estimate the overall effect of each blood cell trait PGS on survival. Hazard ratios (HR) correspond to a 1 standard deviation increase in the standardized PGS.

Blood Cell PGS	Cases (Events)	Meta-Analysis Estimates				Heterogeneity <sup>2</sup>	
		HR	(95% CI)	P	FDR <sup>1</sup>	Q P-value	I <sup>2</sup>
Basophils		1.03	(0.99 – 1.08)	0.15	0.47	0.25	0.27
Eosinophils		1.01	(0.97 – 1.06)	0.62	0.79	0.56	0
Lymphocytes		1.03	(0.99 – 1.08)	0.17	0.47	0.19	0.41
Monocytes	Glioma:	0.99	(0.95 – 1.04)	0.75	0.80	0.39	0
Neutrophils	3418 (2120)	1.03	(0.98 – 1.07)	0.26	0.47	0.21	0.36
Platelets		1.02	(0.98 – 1.06)	0.41	0.61	0.57	0
LMR		0.99	(0.95 – 1.04)	0.80	0.80	0.11	0.54
NLR		0.97	(0.93 – 1.01)	0.14	0.47	0.079	0.61
PLR		0.97	(0.93 – 1.02)	0.21	0.47	0.72	0
Basophils		1.14	(1.02 – 1.29)	0.027	0.19	0.035	0.70
Eosinophils		1.09	(0.97 – 1.24)	0.16	0.24	0.17	0.44
Lymphocytes		1.10	(0.98 – 1.24)	0.10	0.19	0.19	0.40
Monocytes	IDH <sub>mut</sub>	0.93	(0.82 – 1.05)	0.22	0.28	0.37	0
Neutrophils	1074 (325)	1.10	(0.98 – 1.24)	0.11	0.19	0.18	0.42
Platelets		1.03	(0.92 – 1.15)	0.60	0.68	0.75	0
LMR		1.00	(0.89 – 1.12)	0.99	1.00	0.11	0.54
NLR		0.90	(0.81 – 1.01)	0.063	0.19	0.46	0
PLR		0.91	(0.81 – 1.02)	0.089	0.19	0.79	0
Basophils		1.42	(1.08 – 1.86)	0.012	0.03	0.17	0.46
Eosinophils		1.59	(1.18 – 2.14)	2.4×10 <sup>-3</sup>	0.011	0.73	0
Lymphocytes		1.65	(1.24 – 2.20)	6.4×10 <sup>-4</sup>	5.8×10 <sup>-3</sup>	0.72	0
Monocytes	IDH <sub>mut-codel</sub>	1.25	(0.97 – 1.61)	0.079	0.14	0.51	0
Neutrophils	396 (78)	1.49	(1.13 – 1.97)	5.2×10 <sup>-3</sup>	0.016	0.029	0.79
platelet		0.84	(0.65 – 1.09)	0.20	0.25	0.20	0.38
LMR		1.02	(0.80 – 1.32)	0.85	0.85	0.45	0
NLR		0.88	(0.69 – 1.13)	0.31	0.34	0.11	0.62
PLR		0.83	(0.64 – 1.07)	0.16	0.23	0.90	0
Basophils		1.17	(1.01 – 1.36)	0.033	0.30	0.23	0.32
Eosinophils		1.05	(0.91 – 1.22)	0.48	0.68	0.68	0

Lymphocytes	IDH <sub>mut-noncodel</sub>	1.08	(0.93 – 1.25)	0.31	0.68	0.55	0
Monocytes	615	0.93	(0.80 – 1.10)	0.41	0.68	0.12	0.52
Neutrophils	(222)	1.04	(0.91 – 1.20)	0.53	0.68	0.90	0
Platelets		0.99	(0.86 – 1.14)	0.84	0.95	0.66	0
LMR		1.00	(0.87 – 1.15)	0.98	0.98	0.10	0.57
NLR		0.90	(0.79 – 1.03)	0.14	0.43	0.49	0
PLR		0.90	(0.78 – 1.04)	0.14	0.43	0.60	0
Basophils		1.03	(0.97 – 1.09)	0.30	0.71	0.52	0
Eosinophils		1.02	(0.96 – 1.08)	0.59	0.76	0.12	0.53
Lymphocytes		1.04	(0.98 – 1.10)	0.21	0.71	0.64	0
Monocytes	IDH <sub>wt</sub>	0.98	(0.93 – 1.03)	0.44	0.71	0.21	0.36
Neutrophils	1479	1.00	(0.95 – 1.06)	0.93	0.93	0.89	0
Platelets	(1224)	1.02	(0.97 – 1.08)	0.44	0.71	0.052	0.66
LMR		1.01	(0.95 – 1.07)	0.81	0.91	0.24	0.31
NLR		0.98	(0.92 – 1.04)	0.47	0.71	0.48	0
PLR		0.97	(0.92 – 1.03)	0.31	0.71	0.24	0.30

<sup>1</sup> False discovery rate (FDR) was calculated for each glioma subtype, FDR<0.05 was considered statistically significant

<sup>2</sup> Heterogeneity in study-specific associations was assessed using the standard Cochran's Q test (p<0.05 were considered statistically significant) and Higgins I<sup>2</sup> statistic, which describes the percentage of variation across studies that is due to heterogeneity rather than chance

**Supplementary Table S11: Mendelian randomization results for survival in *IDH*-mutated 1p19q co-deleted subtype.** Hazard ratios (HR) and 95% confidence intervals (CI) correspond to the effect of increasing blood cell counts or cell type ratios on all-cause mortality. Results are presented for analyses using SNP effects on survival before and after index event bias correction. MR Egger estimates are presented if applicable (Egger intercept test  $p<0.05$ ).

Blood Trait	MR Estimator	$N_{SNP}^1$	Unadjusted			Adjusted for Index Event Bias		
			HR	(95% CI)	P	HR	(95% CI)	P
Basophils	IVW-MRE	143	13.98	(1.63 – 120.3)	0.016	13.18	(1.55 – 112.2)	0.018
	Maximum likelihood		14.00	(2.24 – 87.8)	$4.8 \times 10^{-3}$	13.56	(2.16 – 85.2)	$5.4 \times 10^{-3}$
	Weighted median		46.24	(2.10 – 1018.1)	0.015	32.02	(1.32 – 779.0)	0.033
	RAPS		16.48	(1.72 – 158.1)	0.015	15.05	(1.57 – 144.5)	0.019
Eosinophils	PRESSO	369	13.98	(1.63 – 120.3)	0.017	13.18	(1.55 – 112.2)	0.020
	IVW-MRE		3.83	(1.63 – 9.00)	$2.0 \times 10^{-3}$	3.87	(1.65 – 9.09)	$1.9 \times 10^{-3}$
	Maximum likelihood		3.82	(1.74 – 8.39)	$8.5 \times 10^{-4}$	3.84	(1.74 – 8.45)	$8.4 \times 10^{-4}$
	Weighted median		5.15	(1.35 – 19.68)	0.017	5.27	(1.35 – 20.62)	0.017
Lymphocytes	RAPS	411	3.67	(1.47 – 9.14)	$5.3 \times 10^{-3}$	3.68	(1.47 – 9.20)	$5.4 \times 10^{-3}$
	PRESSO		3.83	(1.63 – 9.00)	$2.2 \times 10^{-3}$	3.87	(1.65 – 9.09)	$2.1 \times 10^{-3}$
	IVW-MRE	411	4.33	(2.16 – 8.65)	$3.4 \times 10^{-5}$	4.36	(2.18 – 8.73)	$3.2 \times 10^{-5}$
	Maximum likelihood		4.40	(2.21 – 8.77)	$2.6 \times 10^{-5}$	4.41	(2.21 – 8.78)	$2.5 \times 10^{-5}$
Monocytes	Weighted median	473	1.27	(0.36 – 4.43)	0.71	1.32	(0.36 – 4.81)	0.68
	RAPS		5.71	(2.68 – 12.17)	$6.6 \times 10^{-6}$	5.56	(2.61 – 11.85)	$9.0 \times 10^{-6}$
	PRESSO		4.32	(2.16 – 8.65)	$4.2 \times 10^{-5}$	4.36	(2.18 – 8.73)	$3.9 \times 10^{-5}$
	IVW-MRE		1.13	(0.97 – 1.32)	0.11	1.13	(0.97 – 1.32)	0.11
Neutrophils	Maximum likelihood	293	1.13	(0.98 – 1.30)	0.087	1.13	(0.98 – 1.30)	0.089
	Weighted median		1.12	(0.96 – 1.29)	0.15	1.12	(0.97 – 1.28)	0.13
	RAPS		1.13	(0.97 – 1.32)	0.12	1.13	(0.97 – 1.32)	0.12
	PRESSO		1.13	(0.97 – 1.32)	0.11	1.13	(0.97 – 1.32)	0.11
Platelets	IVW-MRE	659	4.71	(1.72 – 12.91)	$2.6 \times 10^{-3}$	4.51	(1.66 – 12.26)	$3.2 \times 10^{-3}$
	Maximum likelihood		4.70	(1.85 – 11.96)	$1.2 \times 10^{-3}$	4.50	(1.77 – 11.49)	$1.6 \times 10^{-3}$
	Weighted median		5.33	(1.21 – 23.46)	0.027	4.96	(1.07 – 22.98)	0.041
	RAPS		4.05	(1.37 – 12.02)	0.012	3.87	(1.32 – 11.38)	0.014
	MR Egger		28.45	(2.29 – 353.4)	$9.7 \times 10^{-3}$	26.94	(2.22 – 327.5)	0.010
	PRESSO		4.71	(1.72 – 12.91)	$2.8 \times 10^{-3}$	4.51	(1.66 – 12.26)	$3.5 \times 10^{-3}$
LMR	IVW-MRE	446	0.84	(0.67 – 1.05)	0.13	0.83	(0.66 – 1.04)	0.10
	Maximum likelihood		0.86	(0.69 – 1.06)	0.16	0.84	(0.67 – 1.04)	0.11
	Weighted median		0.77	(0.58 – 1.03)	0.076	0.75	(0.57 – 1.00)	0.052
	RAPS		0.83	(0.65 – 1.07)	0.16	0.82	(0.64 – 1.06)	0.13
LMR	PRESSO		0.84	(0.67 – 1.05)	0.13	0.83	(0.66 – 1.04)	0.10
	IVW-MRE		1.10	(0.53 – 2.30)	0.80	1.13	(0.54 – 2.36)	0.75
	Maximum likelihood		1.10	(0.54 – 2.23)	0.80	1.13	(0.55 – 2.30)	0.74

	Weighted median	0.88	(0.26 – 2.98)	0.83	0.90	(0.26 – 3.04)	0.86	
	RAPS	1.02	(0.48 – 2.20)	0.95	1.06	(0.49 – 2.29)	0.88	
	PRESSO	1.10	(0.53 – 2.30)	0.80	1.13	(0.54 – 2.36)	0.75	
	IVW-MRE	0.50	(0.16 – 1.56)	0.23	0.50	(0.16 – 1.58)	0.24	
	Maximum likelihood	0.50	(0.17 – 1.44)	0.20	0.50	(0.17 – 1.46)	0.20	
NLR	Weighted median	248	0.91	(0.17 – 4.83)	0.91	0.71	(0.13 – 3.90)	0.70
	RAPS		0.47	(0.14 – 1.54)	0.21	0.48	(0.15 – 1.60)	0.23
	PRESSO		0.50	(0.16 – 1.56)	0.23	0.50	(0.16 – 1.58)	0.24
	IVW-MRE	0.50	(0.24 – 1.04)	0.065	0.51	(0.25 – 1.07)	0.074	
	Maximum likelihood	0.51	(0.25 – 1.02)	0.056	0.52	(0.26 – 1.04)	0.063	
PLR	Weighted median	465	0.53	(0.17 – 1.65)	0.27	0.67	(0.22 – 2.06)	0.49
	RAPS		0.50	(0.23 – 1.09)	0.082	0.52	(0.24 – 1.12)	0.10
	PRESSO		0.50	(0.24 – 1.04)	0.066	0.51	(0.25 – 1.07)	0.074

<sup>1</sup> Number of instruments using in the survival analysis is smaller due to the removal of variants with  $\text{abs}(\log(\text{HR})) > 2.5$

#### Abbreviations:

IVW-MRE	Inverse variance weighted multiplicative random effect
RAPS	Robust adjusted profile score
PRESSO	Pleiotropy Residual Sum and Outlier
LMR	Lymphocyte to monocyte ratio
NLR	Neutrophil to lymphocyte ratio
PLR	Platelet to lymphocyte ratio

**Supplementary Table S12: Associations between blood cell trait polygenic scores (PGS) and tumor immune microenvironment (TIME) features in TCGA.** Associations for selected blood cell trait PGS with heritable TIME traits identified in TCGA by Sayaman et al. (2021). Association analyses were conducted stratified by IDH mutation status. Each continuous TME phenotype was analyzed using linear regression with adjustment for age, sex, and genetic ancestry principal components. Heterogeneity in PGS effects by IDH status were assessed using Cochran's Q test.

Module	TME Trait	PGS	IDH mutant				IDH wildtype			P <sub>het</sub>	
			Beta	SE	P	FDR	Beta	SE	P		
Expression Signature (ES)	Bcell mg IGJ	Basophils	-0.008	0.034	0.809	0.839	0.038	0.067	0.572	0.854	0.539
		Eosinophils	-0.005	0.036	0.885	0.991	0.008	0.061	0.896	0.939	0.852
		Lymphocytes	0.032	0.036	0.366	0.528	-0.024	0.064	0.701	0.818	0.437
		Neutrophils	0.062	0.035	0.077	0.197	-0.009	0.072	0.901	0.970	0.372
		Platelets	-0.036	0.032	0.252	0.655	-0.024	0.059	0.688	0.917	0.850
		PLR	-0.046	0.033	0.166	0.307	0.034	0.063	0.587	0.748	0.258
	CD8 CD68 ratio	Basophils	-0.083	0.069	0.232	0.719	0.086	0.077	0.262	0.854	0.101
		Eosinophils	0.080	0.073	0.274	0.991	0.006	0.069	0.936	0.939	0.460
		Lymphocytes	-0.052	0.072	0.472	0.574	0.010	0.073	0.894	0.900	0.547
		Neutrophils	-0.0002	0.072	0.997	0.997	0.022	0.082	0.788	0.964	0.838
	LYMPHS PCA 16704732	Platelets	-0.028	0.064	0.657	0.836	-0.118	0.067	0.077	0.729	0.330
		PLR	0.108	0.067	0.112	0.223	-0.055	0.072	0.442	0.652	0.098
		Basophils	0.027	0.020	0.179	0.719	-0.026	0.040	0.514	0.854	0.235
		Eosinophils	0.018	0.021	0.396	0.991	-0.037	0.036	0.307	0.683	0.189
		Lymphocytes	0.019	0.021	0.377	0.528	-0.066	0.037	0.074	0.209	0.046
Genetic Variation	IDH	Neutrophils	0.026	0.021	0.221	0.428	-0.060	0.042	0.155	0.964	0.068
		Platelets	0.023	0.019	0.217	0.655	0.053	0.034	0.123	0.729	0.449
		PLR	-0.019	0.020	0.349	0.444	0.079	0.036	0.032	0.299	0.019
		Basophils	0.041	0.053	0.443	0.719	-0.057	0.072	0.427	0.854	0.273
		Eosinophils	0.034	0.056	0.542	0.991	-0.044	0.065	0.495	0.769	0.359
	PD1	Lymphocytes	0.054	0.056	0.338	0.525	-0.066	0.067	0.327	0.532	0.170
		Neutrophils	0.129	0.055	0.019	0.090	-0.054	0.075	0.476	0.964	0.049
		Platelets	-0.031	0.050	0.534	0.732	-0.032	0.062	0.599	0.883	0.984

	PLR	-0.069	0.052	0.186	0.307	0.063	0.066	0.344	0.567	0.117
Activated Dendritic Cells (ES)	Basophils	-0.004	0.034	0.903	0.903	-0.019	0.055	0.723	0.854	0.813
	Eosinophils	-0.008	0.036	0.820	0.991	-0.049	0.049	0.319	0.683	0.503
	Lymphocytes	0.057	0.036	0.115	0.354	-0.112	0.050	0.027	0.192	6.4E-03
	Neutrophils	0.043	0.036	0.229	0.428	-0.030	0.057	0.605	0.964	0.282
	Platelets	-0.056	0.032	0.082	0.655	0.004	0.047	0.932	0.988	0.294
	PLR	-0.091	0.033	0.007	0.164	0.109	0.050	0.030	0.299	8.9E-04
Attractor Metagene - IFIT3	Basophils	-0.040	0.053	0.451	0.719	-0.053	0.101	0.600	0.854	0.910
	Eosinophils	-0.034	0.056	0.546	0.991	-0.131	0.091	0.150	0.683	0.362
	Lymphocytes	0.073	0.056	0.189	0.354	-0.162	0.095	0.090	0.228	0.033
	Neutrophils	0.031	0.055	0.572	0.794	0.048	0.107	0.658	0.964	0.892
	Platelets	-0.075	0.049	0.131	0.655	-0.110	0.087	0.209	0.729	0.723
	PLR	-0.103	0.052	0.048	0.164	0.133	0.094	0.158	0.363	0.028
IFN Response	Basophils	-0.005	0.016	0.760	0.828	-0.012	0.024	0.606	0.854	0.796
	Eosinophils	0.003	0.017	0.854	0.991	-0.031	0.022	0.155	0.683	0.217
	GP11 Immune IFN	Lymphocytes	0.029	0.017	0.087	0.354	-0.053	0.022	0.018	0.169
		Neutrophils	0.017	0.017	0.308	0.507	0.0004	0.026	0.986	0.986
	Platelets	-0.017	0.015	0.270	0.655	-0.021	0.021	0.309	0.729	0.856
	PLR	-0.029	0.016	0.069	0.164	0.035	0.022	0.114	0.363	0.019
IFN signature 21978456	Basophils	-0.034	0.038	0.368	0.719	-0.031	0.072	0.664	0.854	0.970
	Eosinophils	-0.026	0.040	0.510	0.991	-0.083	0.064	0.199	0.683	0.455
	Lymphocytes	0.055	0.040	0.167	0.354	-0.123	0.067	0.068	0.209	0.022
		Neutrophils	0.016	0.040	0.693	0.794	0.036	0.076	0.642	0.964
	Platelets	-0.053	0.035	0.136	0.655	-0.080	0.062	0.202	0.729	0.708
	PLR	-0.070	0.037	0.061	0.164	0.093	0.067	0.167	0.363	0.034
IFN Cluster 21214954	Basophils	-0.014	0.029	0.641	0.828	-0.019	0.051	0.706	0.854	0.921
	Eosinophils	-0.015	0.031	0.620	0.991	-0.056	0.046	0.226	0.683	0.461
	Lymphocytes	0.048	0.031	0.114	0.354	-0.094	0.048	0.053	0.209	0.013
	Neutrophils	0.024	0.030	0.425	0.626	0.021	0.055	0.705	0.964	0.957

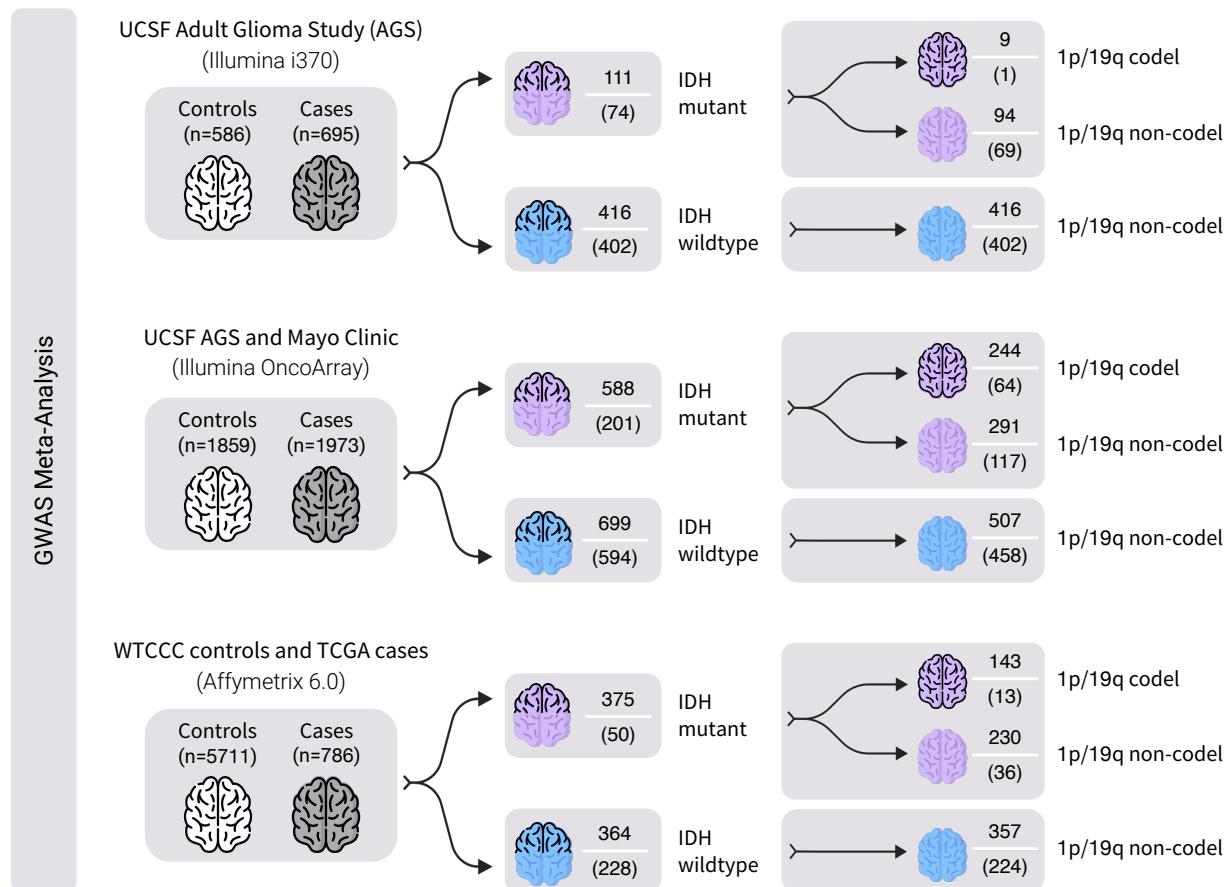
	Platelets	-0.037	0.027	0.170	0.655	-0.044	0.045	0.331	0.729	0.903
	PLR	-0.062	0.028	0.030	0.164	0.069	0.048	0.151	0.363	0.019
	Basophils	-0.036	0.037	0.327	0.719	-0.034	0.069	0.629	0.854	0.974
	Eosinophils	-0.030	0.039	0.447	0.991	-0.081	0.062	0.195	0.683	0.483
IFN signature 19272155	Lymphocytes	0.052	0.039	0.179	0.354	-0.121	0.065	0.065	0.209	0.022
	Neutrophils	0.013	0.038	0.737	0.794	0.031	0.074	0.677	0.964	0.829
	Platelets	-0.053	0.034	0.123	0.655	-0.074	0.060	0.220	0.729	0.759
	PLR	-0.070	0.036	0.055	0.164	0.093	0.065	0.153	0.363	0.028
Module3 IFN score	Basophils	-0.021	0.035	0.540	0.796	-0.034	0.063	0.597	0.854	0.864
	Eosinophils	-0.017	0.037	0.639	0.991	-0.084	0.057	0.142	0.683	0.324
	Lymphocytes	0.055	0.036	0.134	0.354	-0.114	0.060	0.058	0.209	0.016
	Neutrophils	0.030	0.036	0.408	0.626	0.020	0.068	0.764	0.964	0.902
	Platelets	-0.046	0.032	0.155	0.655	-0.053	0.055	0.338	0.729	0.910
	PLR	-0.068	0.034	0.045	0.164	0.098	0.059	0.098	0.363	0.014
NK CD56dim cells (ES)	Basophils	0.005	0.014	0.715	0.828	-0.003	0.032	0.923	0.943	0.813
	Eosinophils	0.006	0.015	0.688	0.991	-0.012	0.029	0.664	0.902	0.568
	Lymphocytes	0.026	0.015	0.078	0.354	-0.056	0.029	0.056	0.209	0.012
	Neutrophils	0.036	0.015	0.015	0.090	-0.034	0.033	0.312	0.964	0.056
	Platelets	-0.017	0.013	0.194	0.655	-0.023	0.027	0.403	0.753	0.852
	PLR	-0.012	0.014	0.369	0.450	0.042	0.029	0.145	0.363	0.088
Leukocyte Subset ES	Basophils	0.016	0.019	0.387	0.719	-0.018	0.035	0.607	0.854	0.391
	Eosinophils	0.005	0.020	0.784	0.991	0.004	0.032	0.901	0.939	0.970
Th17 cells (ES)	Lymphocytes	0.017	0.020	0.398	0.530	-0.006	0.034	0.870	0.900	0.570
	Neutrophils	0.050	0.019	0.010	0.090	-0.037	0.038	0.330	0.964	0.041
	Platelets	-0.017	0.017	0.327	0.655	-0.021	0.031	0.498	0.872	0.912
	PLR	-0.036	0.018	0.047	0.164	0.011	0.033	0.749	0.843	0.215
Th2 cells (ES)	Basophils	-0.006	0.017	0.729	0.828	-0.022	0.030	0.464	0.854	0.637
	Eosinophils	0.011	0.017	0.536	0.991	-0.008	0.027	0.774	0.939	0.563
	Lymphocytes	-0.008	0.018	0.663	0.714	-0.004	0.028	0.900	0.900	0.901

		Neutrophils	-0.004	0.017	0.807	0.837	-0.060	0.031	0.056	0.964	0.117
		Platelets	0.005	0.015	0.768	0.896	-0.029	0.026	0.269	0.729	0.270
		PLR	0.026	0.016	0.106	0.223	0.007	0.028	0.803	0.843	0.544
Macrophage/ Monocyte	Attractor Metagene - G SIGLEC9	Basophils	0.089	0.071	0.215	0.719	0.029	0.104	0.782	0.854	0.634
		Eosinophils	-0.0004	0.075	0.995	0.995	-0.015	0.093	0.876	0.939	0.906
		Lymphocytes	0.116	0.075	0.125	0.354	-0.085	0.097	0.380	0.532	0.101
		Neutrophils	0.147	0.074	0.048	0.151	-0.064	0.109	0.559	0.964	0.110
		Platelets	-0.043	0.067	0.516	0.732	0.043	0.089	0.633	0.886	0.440
		PLR	-0.160	0.070	0.023	0.164	0.140	0.095	0.143	0.363	0.011
	MHC2 signature 21978456	Basophils	0.056	0.064	0.384	0.719	-0.005	0.075	0.943	0.943	0.536
		Eosinophils	0.078	0.067	0.243	0.991	0.055	0.068	0.413	0.723	0.809
		Lymphocytes	0.104	0.067	0.122	0.354	-0.073	0.070	0.303	0.532	0.069
		Neutrophils	0.127	0.066	0.056	0.158	-0.079	0.079	0.319	0.964	0.046
		Platelets	-0.002	0.060	0.967	0.967	0.012	0.065	0.850	0.988	0.867
		PLR	-0.066	0.063	0.293	0.391	0.153	0.069	0.028	0.299	0.019
	CD8 T cells (ES)	Basophils	0.007	0.006	0.237	0.719	-0.028	0.010	0.006	0.109	2.6E-03
		Eosinophils	-0.004	0.006	0.535	0.991	-0.010	0.009	0.266	0.683	0.561
		Lymphocytes	0.007	0.006	0.267	0.440	-0.031	0.009	0.001	0.037	8.3E-04
		Neutrophils	0.007	0.006	0.223	0.428	-0.016	0.011	0.152	0.964	0.064
		Platelets	-0.005	0.005	0.374	0.655	-0.002	0.009	0.837	0.988	0.776
		PLR	-0.010	0.006	0.070	0.164	0.013	0.010	0.160	0.363	0.032
	T-cell/ Cytotoxic	Basophils	0.007	0.015	0.641	0.828	-0.006	0.023	0.793	0.854	0.637
		Eosinophils	0.001	0.016	0.972	0.995	-0.008	0.021	0.700	0.902	0.741
		Cytotoxic cells (ES)	0.022	0.016	0.156	0.354	-0.053	0.021	0.014	0.169	4.4E-03
		Lymphocytes	0.031	0.015	0.043	0.151	0.004	0.025	0.856	0.970	0.357
		Neutrophils	-0.013	0.014	0.357	0.655	-0.006	0.020	0.760	0.967	0.787
		Platelets	-0.019	0.015	0.186	0.307	0.030	0.021	0.168	0.363	0.059
	Eosinophils (ES)	Basophils	0.002	0.007	0.722	0.828	0.008	0.014	0.580	0.854	0.727
		Eosinophils	-0.004	0.007	0.528	0.991	-0.009	0.013	0.489	0.769	0.762

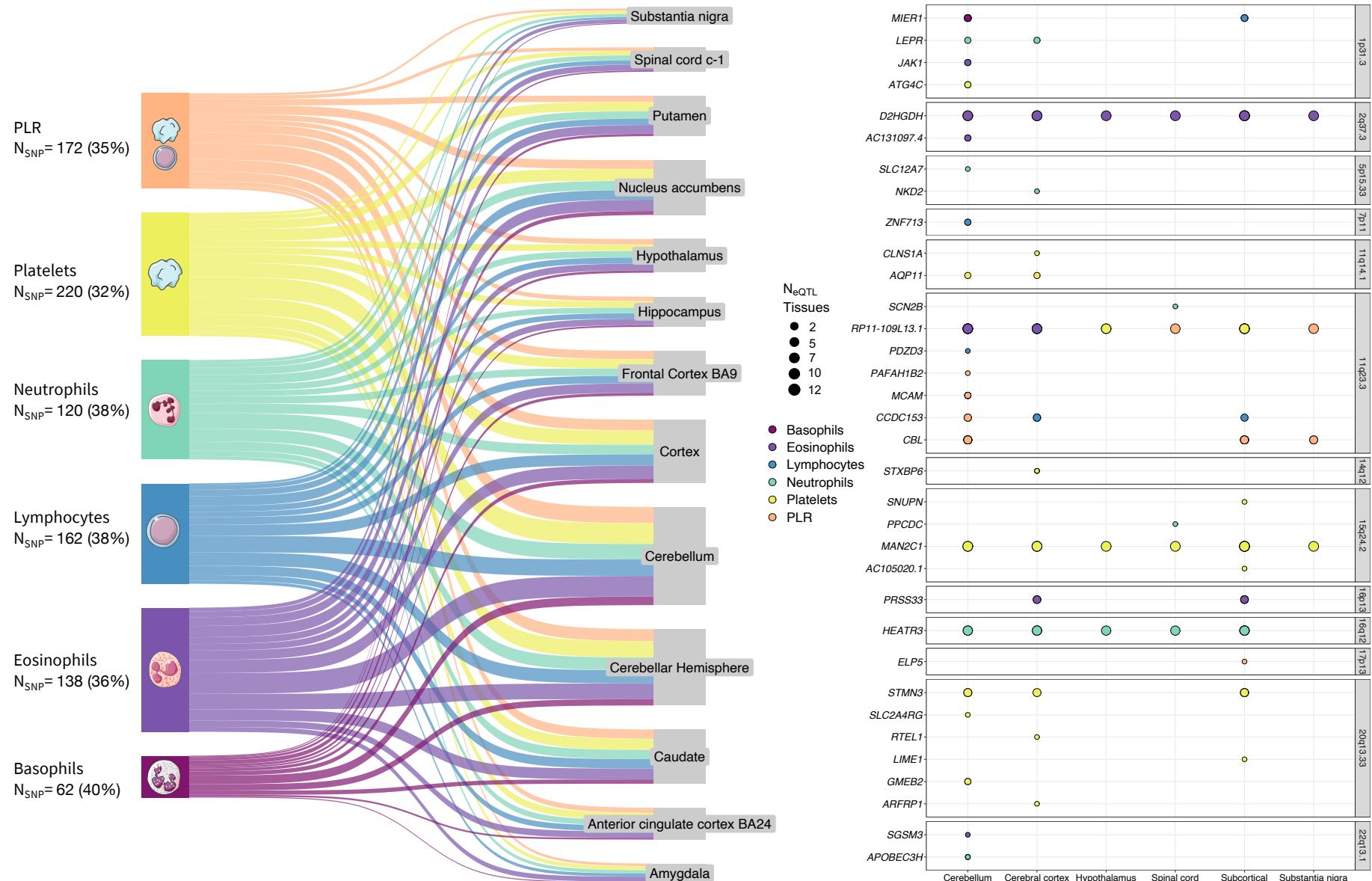
	Lymphocytes	0.002	0.007	0.802	0.832	0.012	0.013	0.371	0.532	0.497
	Neutrophils	0.003	0.007	0.676	0.794	0.010	0.015	0.512	0.964	0.673
	Platelets	-0.007	0.006	0.229	0.655	0.000	0.012	0.973	0.988	0.569
	PLR	-0.003	0.007	0.670	0.734	0.004	0.013	0.749	0.843	0.634
Macrophages (ES)	Basophils	0.019	0.021	0.379	0.719	0.013	0.040	0.739	0.854	0.908
	Eosinophils	-0.005	0.022	0.807	0.991	-0.013	0.036	0.709	0.902	0.850
	Lymphocytes	0.039	0.022	0.080	0.354	-0.030	0.037	0.419	0.533	0.111
	Neutrophils	0.051	0.022	0.019	0.090	-0.023	0.042	0.590	0.964	0.118
	Platelets	-0.004	0.020	0.846	0.911	-0.018	0.034	0.591	0.883	0.712
	PLR	-0.038	0.021	0.067	0.164	0.043	0.037	0.239	0.459	0.053
Neutrophils (ES)	Basophils	0.021	0.016	0.192	0.719	0.021	0.032	0.501	0.854	0.981
	Eosinophils	0.020	0.017	0.233	0.991	-0.002	0.029	0.939	0.939	0.505
	Lymphocytes	0.038	0.016	0.023	0.328	-0.023	0.030	0.446	0.543	0.076
	Neutrophils	0.047	0.016	0.004	0.090	-0.005	0.033	0.875	0.970	0.156
	Platelets	-0.002	0.015	0.905	0.938	0.014	0.027	0.598	0.883	0.602
	PLR	-0.035	0.015	0.024	0.164	0.019	0.029	0.521	0.729	0.104
T-cell/ Cytotoxic	Basophils	0.004	0.006	0.462	0.719	-0.008	0.012	0.484	0.854	0.339
	Eosinophils	-0.001	0.006	0.840	0.991	-0.011	0.010	0.312	0.683	0.440
	Lymphocytes	0.0005	0.006	0.937	0.937	-0.017	0.011	0.109	0.235	0.149
	Neutrophils	0.002	0.006	0.713	0.794	-0.003	0.012	0.792	0.964	0.690
	Platelets	-0.006	0.005	0.282	0.655	-0.009	0.010	0.394	0.753	0.808
	PLR	-0.003	0.006	0.566	0.660	0.009	0.011	0.415	0.646	0.322
T helper cells (ES)	Basophils	0.008	0.008	0.347	0.719	-0.040	0.015	0.008	0.109	5.0E-03
	Eosinophils	-0.004	0.009	0.630	0.991	-0.025	0.013	0.060	0.683	0.183
	Lymphocytes	0.007	0.009	0.428	0.545	-0.012	0.014	0.413	0.533	0.266
	Neutrophils	0.010	0.008	0.253	0.442	-0.024	0.016	0.136	0.964	0.063
	Platelets	-0.002	0.008	0.761	0.896	-0.013	0.013	0.306	0.729	0.463
	PLR	-0.003	0.008	0.682	0.734	0.014	0.014	0.309	0.541	0.276
	Basophils	0.011	0.011	0.318	0.719	-0.045	0.023	0.056	0.519	0.030

T-cell/ Cytotoxic	T-CM cells (ES)	Eosinophils	0.014	0.011	0.218	0.991	-0.031	0.021	0.141	0.683	0.059
		Lymphocytes	0.014	0.011	0.218	0.381	-0.027	0.022	0.236	0.471	0.106
		Neutrophils	0.015	0.011	0.191	0.428	0.002	0.025	0.948	0.983	0.640
		Platelets	0.007	0.010	0.462	0.722	-0.026	0.021	0.218	0.729	0.152
		PLR	-0.002	0.011	0.869	0.869	0.012	0.022	0.588	0.748	0.575
	T-EM cells (ES)	Basophils	0.008	0.007	0.250	0.719	-0.008	0.019	0.657	0.854	0.418
		Eosinophils	0.001	0.007	0.927	0.995	-0.028	0.017	0.101	0.683	0.120
		Lymphocytes	0.019	0.007	0.006	0.178	-0.017	0.018	0.331	0.532	0.055
		Neutrophils	0.018	0.007	0.009	0.090	0.011	0.020	0.584	0.964	0.735
		Platelets	-0.005	0.006	0.464	0.722	-0.026	0.016	0.110	0.729	0.217
Tfh cells (ES)	Tfh cells (ES)	PLR	-0.008	0.007	0.241	0.353	-0.003	0.017	0.843	0.843	0.819
		Basophils	-0.007	0.008	0.402	0.719	-0.020	0.019	0.314	0.854	0.547
		Eosinophils	-0.007	0.009	0.404	0.991	0.017	0.018	0.341	0.683	0.220
		Lymphocytes	-0.005	0.009	0.538	0.602	-0.016	0.018	0.380	0.532	0.594
		Neutrophils	0.003	0.009	0.693	0.794	0.007	0.021	0.723	0.964	0.859
	Th1 cells (ES)	Platelets	0.005	0.008	0.549	0.732	-0.018	0.017	0.297	0.729	0.230
		PLR	0.002	0.008	0.790	0.819	0.004	0.018	0.813	0.843	0.914
		Basophils	-0.003	0.010	0.769	0.828	-0.008	0.017	0.645	0.854	0.797
		Eosinophils	-0.008	0.010	0.455	0.991	-0.013	0.015	0.387	0.723	0.758
		Lymphocytes	0.006	0.010	0.522	0.602	-0.025	0.015	0.104	0.235	0.086
TGF- $\beta$	TGFB PCA 17349583	Neutrophils	0.004	0.010	0.723	0.794	-0.014	0.017	0.412	0.964	0.373
		Platelets	-0.008	0.009	0.353	0.655	-0.001	0.014	0.970	0.988	0.646
		PLR	-0.011	0.009	0.252	0.353	0.003	0.015	0.837	0.843	0.439
		Basophils	0.031	0.033	0.352	0.719	0.029	0.073	0.686	0.854	0.982
		Eosinophils	0.007	0.035	0.833	0.991	-0.035	0.066	0.596	0.879	0.571
		Lymphocytes	0.051	0.035	0.151	0.354	-0.021	0.068	0.755	0.846	0.348
		Neutrophils	0.076	0.035	0.028	0.113	-0.086	0.076	0.261	0.964	0.053
		Platelets	-0.008	0.031	0.802	0.898	-0.001	0.063	0.988	0.988	0.922
		PLR	-0.040	0.033	0.227	0.353	0.078	0.067	0.246	0.459	0.114

**Supplementary Figure S1: Overview of glioma study populations.** For each study analyses were restricted to participants of predominantly European ancestry. Genome-wide association analyses from each study were combined using fixed effects meta-analysis and the results summary statistics were used for all Mendelian randomization analyses. For each molecular subtype, the number of mortality events is reported in brackets. Chromosome 1p/19q co-deletion typically does not occur in IDH wildtype tumors, therefore information on this molecular marker is not always present or assessed for this suptype.



**Supplementary Figure S2: Effects on gene expression in brain tissues.** Prevalence of expression quantitative trait loci (eQTL) in GTEx v8 brain tissues among genetic instruments for blood cell traits and eGenes in regions linked to glioma susceptibility.



**Supplementary Figure S3: Regional association and z-score plots for colocalized signals.** In each plot the LD is calculated with respect to the shared fine-mapped variant, indicated by the black diamond. For chromosome 20q13.33, the lead telomere length variant (rs13038527) is also shown, although the signal for telomere length did not colocalize.

