Genetic analysis of blood cell traits in neurological diseases & psychiatric disorders

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Background

- Epidemiological associations between blood cell traits (BCTs) and a range of neuropsychiatric disorders have been well-established, and blood-based biomarkers have been developed for some neurological diseases (e.g. Alzheimer's disease)[1].
- However, it remains unclear whether BCT-neuropsychiatric associations have a genetic basis, and if so, whether this reflects causality or horizontal pleiotropy.
- Solving this problem is important because it may provide opportunities to improve early and accurate diagnosis, prevention and treatment of common neuropsychiatric disorders.

Study samples

- We obtained publicly-available GWAS summary statistics for 11 neuropsychiatric disorders and 36 BCTs:

Table 1. GWAS Datasets for Neurological and Psychiatric Disorders

Diseases	Abbreviation	No. of Cases	No. of Controls
Attention deficit hyperactivity disorder[2]	ADHD	20,183	35,191
Alzheimer's disease[3]	AD	71,880	383,378
Amyotrophic lateral sclerosis[4]	ALS	20,806	59,804
Autism spectrum disorder[5]	ASD	18,382	27,969
Bipolar disorder[6]	BIP	20,352	31,358
Major depressive disorder[7]	MDD	246,363	561,190
Migraine[8]	Migraine	59,674	316,078
Multiple sclerosis[9]	MS	14,802	26,703
Parkinson's disease[10]	PD	37,688 cases; 18,618 proxy cases	1.4 million
Schizophrenia[11]	SCZ	33,640	43,456
Stroke[12]	Stroke	40,585	406,111

Table 2. GWAS Datasets for BCTs[13]

BCTs	Abbreviation	Total Sample Size
Basophil count	baso	171,846
Basophil percentage of white cells	baso_p	171,996
Basophil percentage of granulocytes	baso_p_gran	170,223
Sum basophil neutrophil counts	baso_neut_sum	170,143
Sum eosinophil basophil counts	eo_baso_sum	171,771
Eosinophil count	eo	172,275
Eosinophil percentage of white cells	eo_p	172,378
Eosinophil percentage of granulocytes	eo_p_gran	170,536
Granulocyte count	gran	169,822
Granulocyte percentage of myeloid white cells	gran_p_myeloid_wbc	169,545
Hematocrit	hct	173,039
Hemoglobin concentration	hgb	172,925
High light scatter percentage of red cells	hlr_p	170,763
High light scatter reticulocyte count	hlr	170,761
Immature fraction of reticulocytes	irf	170,548
Lymphocyte count	lymph	171,643
Lymphocyte percentage of white cells	lymph_p	171,748
Mean corpuscular hemoglobin concentration	mchc	172,851
Mean corpuscular hemoglobin	mch	172,332
Mean corpuscular volume	mcv	172,433
Monocyte count	mono	170,721
Monocyte percentage of white cells	mono_p	170,494
Mean platelet volume	mpv	164,454
Myeloid white cell count	myeloid_wbc	169,219
Sum neutrophil eosinophil counts	neut_eo_sum	170,384
Neutrophil percentage of granulocytes	neut_p_gran	170,672
Neutrophil count	neut	170,702
Neutrophil percentage of white cells	neut_p	171,542
Plateletcrit	pct	164,339
Platelet distribution width	pdw	164,433
Platelet count	plt	166,066
Red blood cell count	rbc	172,952
Red cell distribution width	rdw	171,529
Reticulocyte count	ret	170,641
Reticulocyte fraction of red cells	ret_p	170,690
White blood cell count	wbc	172,435

Statistical analyses

- We used High-Definition Likelihood (HDL)[14] to estimate genetic correlations (r_g) between 36 BCTs and 11 neuropsychiatric disorders.
- For pairs of traits with FDR (<0.05) significant r_g, we performed bi-directional Mendelian randomization (MR) using CAUSE (Causal Analysis Using Summary Effect Estimates)[15] to investigate if genetic overlap was due to causality or horizontal pleiotropy.
- Six alternative MR methods (Latent Causal Variable model (LCV)[16], Generalised Summary-data-based Mendelian Randomisation (GSMR)[17], MR-Egger[18], inverse variance weighting (IVW)[18], weighted median (WMe)[18], and weighted mode (WMo)[18] were used for sensitivity analyses.

Results

Figure 1. Significant genetic correlations between selected BCTs and neuropsychiatric disorders using HDL.

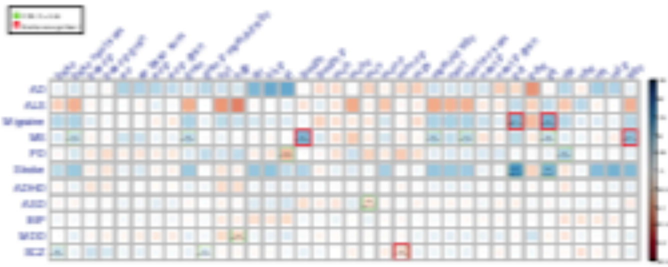
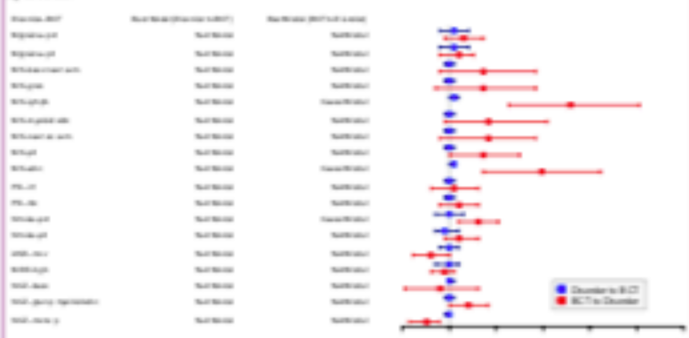


Figure 2. Support for causal relationships between selected pairs of BCTs and neuropsychiatric disorders revealed by CAUSE.



*Best fitted model is selected based on the expected log pointwise posterior density at 5% statistical significance level.

Table 3. Sensitivity MR analyses for significant putative causal associations identified by CAUSE

MR method	lymph → MS	wbc → MS	pct → Stroke
LCV (gcp [p-value])	0.25 (2.47×10^-2)	0.23 (7.92×10^-1)	0.67 (9.97×10^-3)
GSMR (OR [p-value])	1.47 (4.02×10^-11)	0.95 (3.04×10^-2)	1.07 (3.04×10^-5)
MR-Egger (OR [p-value])	0.67 (2.46×10^-1)	3.30 (1.82×10^-1)	1.20 (1.24×10^-4)
IVW (OR [p-value])	1.06 (7.90×10^-1)	1.24 (1.62×10^-1)	1.07 (2.39×10^-3)
Wme (OR [p-value])	1.47 (2.34×10^-6)	0.96 (5.48×10^-2)	1.08 (1.44×10^-2)
Wmo (OR [p-value])	1.95 (5.29×10^-2)	0.95 (6.79×10^-2)	1.06 (1.32×10^-3)

Conclusions

- We identified a significant genetic correlation for 18 pairs of BCT-neuropsychiatric traits, 16 of which have prior evidence for a phenotypic correlation etc. Two novel associations were identified between PD and immature fraction of reticulocytes, and between SCZ and granulocyte percentage of myeloid white cells.
- A causal effect of elevated plateletcrit level on increased susceptibility to stroke was consistently identified by all MR methods except for Wmo (which only utilises a subset of SNP instruments and thus is often less powerful than other models). Our results suggest that plateletcrit level may be a potential biomarker for early detection of stroke.
- Conversely, MR analyses of the effect of lymphocyte count and white blood cell count on MS were highly inconsistent, and thus we could not determine if the identified genetic correlations were due to causality or pleiotropy.
- MR analyses with neuropsychiatric disorders as exposures for BCTs were universally non-significant.
- Our results indicate that for some neuropsychiatric disorders (e.g. stroke), correction for differences in blood cell type proportions in DNA methylation analyses may dilute true disease signals.

References

1. Hampel et al., Nat Rev Neurol 2018; 2. Demontis et al., Nat Genet 2019; 3. Jansen et al., Nat Genet 2019; 4. Nicolas et al., Neuron 2018; 5. Grove et al., Nat Genet 2019; 6. Stahl et al., Nat Genet 2019; 7. Wray et al., Nat Genet 2018; 8. Gormley et al., Nat Genet 2016; 9. IMSGC Science 2019; 10. Nalls et al., Lancet Neurol 2019; 11. Ripke et al., Nature 2014; 12. Malik et al., Nat Genet 2018; 13. Astle et al., Cell 2016; 14. Ning et al., Nat Genet 2020; 15. Morrison et al., Nat Genet 2020; 16. O'Connor et al., Nat Genet 2018; 17. Zhu et al., Nat Commun 2018; 18. Hemani et al., Elife 2018.

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