UCLA QCBio

Metabolome-Wide Association Study of Cerebral Spinal Fluid

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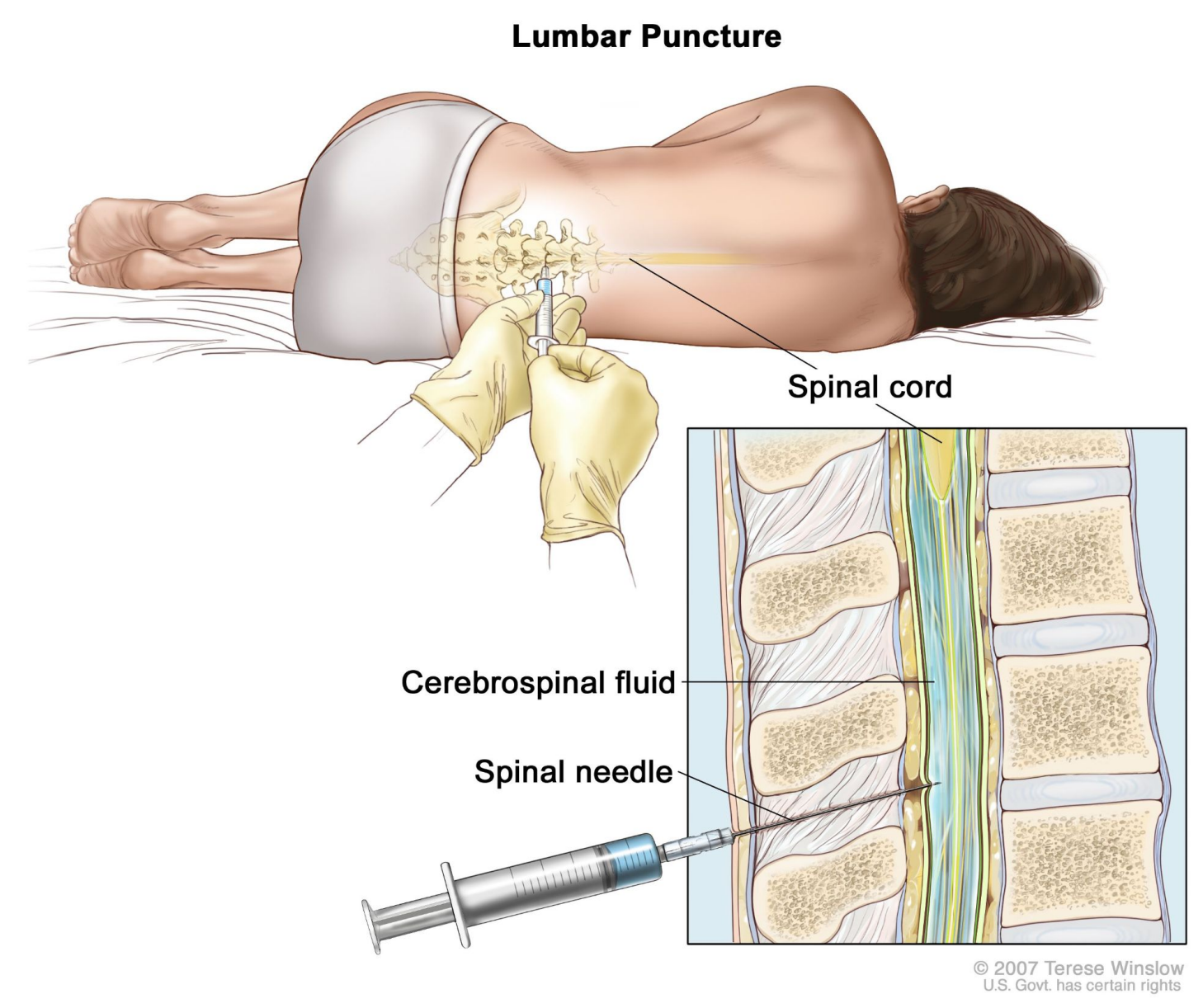
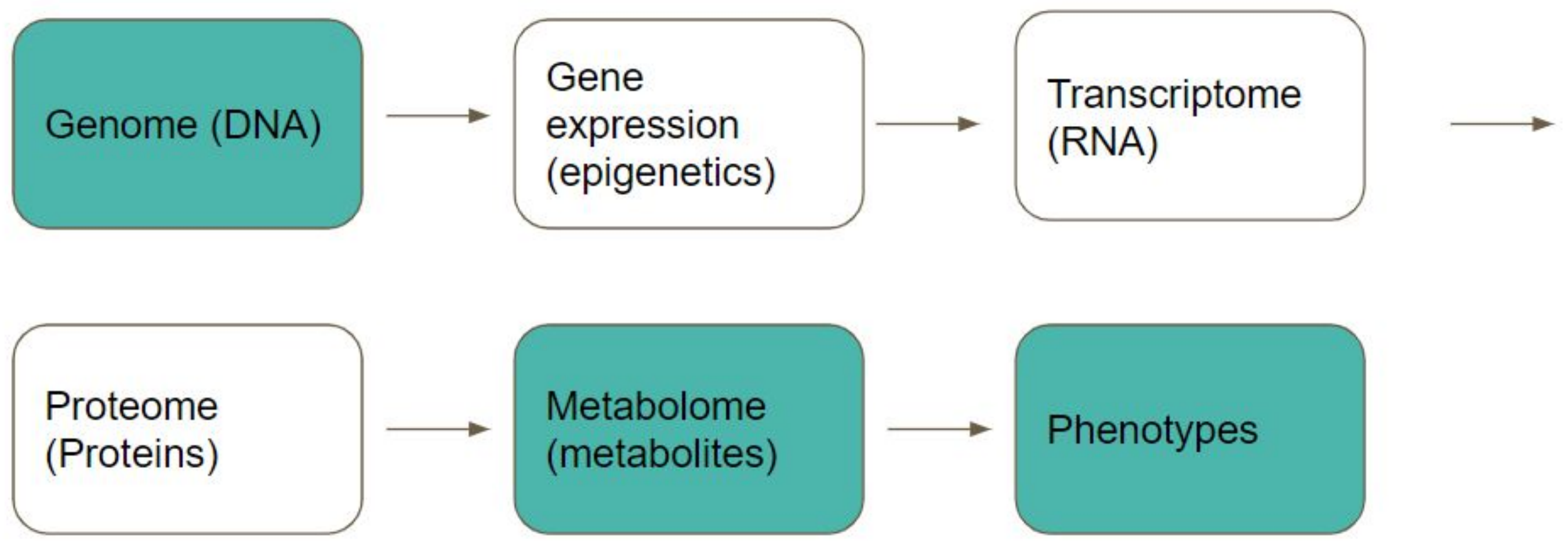
Background:

- Neuropsychiatric traits are caused by both environmental and genetic factors.
- Cerebrospinal Fluid (CSF) is in direct contact with the brain, likely to provide valuable insights into biological pathways related to psychiatric traits.
- Difficult to collect CSF, very limited sample sizes
- GWAS have much larger sample sizes



A metabolome wide association study (MWAS) was conducted.

Functional phenotypes were imputed on genome wide association study (GWAS) traits



Genome (DNA) → Gene expression (epigenetics) → Transcriptome (RNA) →

Proteome (Proteins) → Metabolome (metabolites) → Phenotypes

CSH QTOF	HILIC QTOF	GCTOF
ceramides	acylcarnitines	carbohydrates and sugar phosphates
sphingomyelins	TMAO	amino acids
cholesteryl esters	cholines	hydroxyl acids
lyso- and phospholipids	betaines	free fatty acids
mono-, di- and triacylglycerols	SAM	purines
galactosyl- and glucuronyllipids	methylated and acetylated amines	pyrimidines
	di- and oligopeptides	aromatics
	SAH	exposome-derived chemicals

Winslow, T. (2007). *Lumbar Puncture*. cancer.gov. NIH. Retrieved August 8, 2022, fromhttps://nci-media.cancer.gov/pdq/media/images/503953.jpg.

Phenotype data:

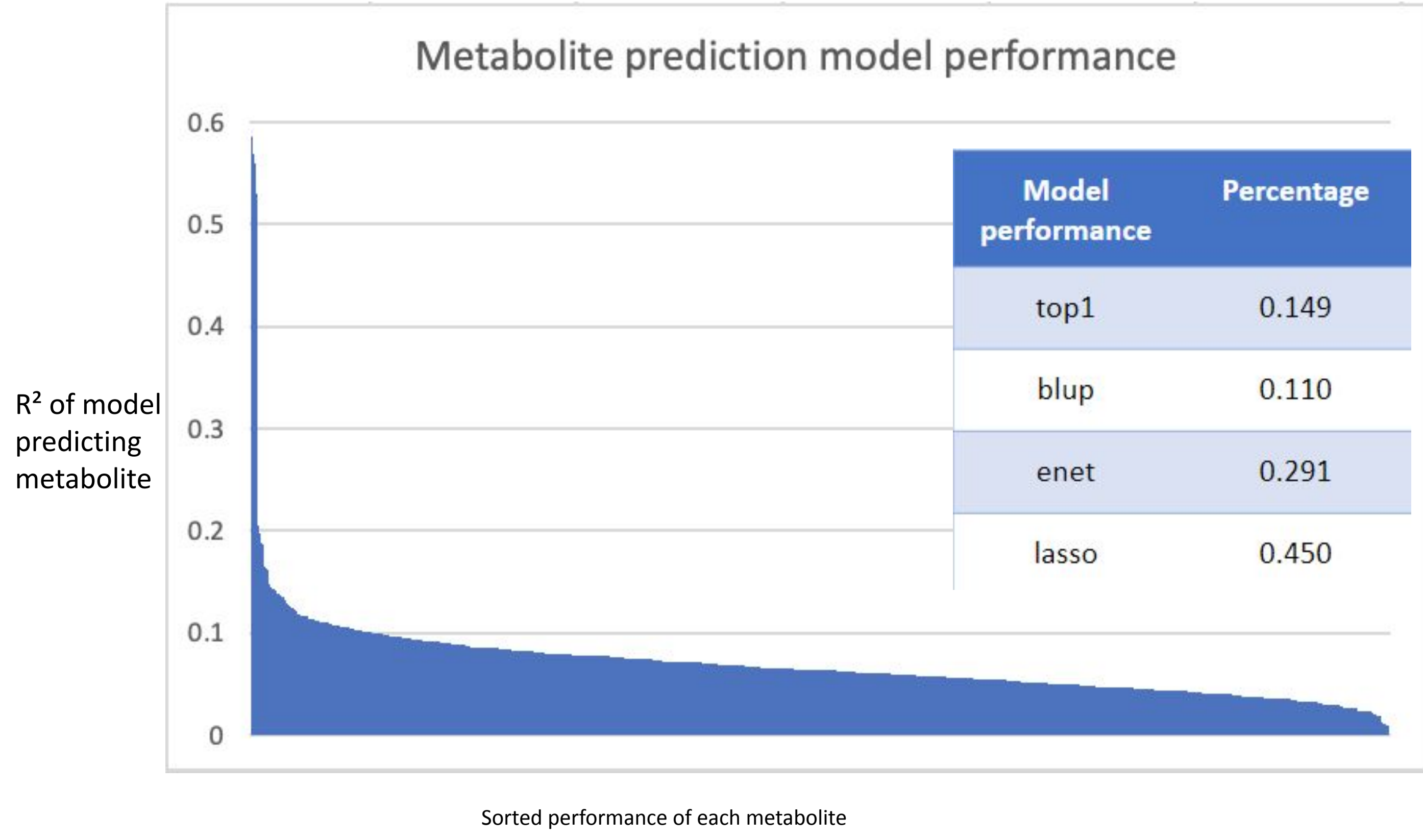
Trait	Sample Size	Number of Sig. Loci	SNP-heritability
Bipolar Disorder	101,963	64	0.18
Schizophrenia	161,405	270	0.24
Major Depressive Disorder	107,171	44	0.25
ADHD	55,374	12	0.10 - 0.28
Alcohol Dependence	16,931	10	0.12
Cannabis Use Disorder	334,955	2	0.06 - 0.12
Insomnia	385,506	202	0.07
Migraine	289,307	14	0.17
Alzheimer's	380,883	29	0.28

This data was acquired from previous GWA studies

The CSF dataset was composed of 450 controls (none of the neuropsychiatric traits) from the Netherlands

Methods:

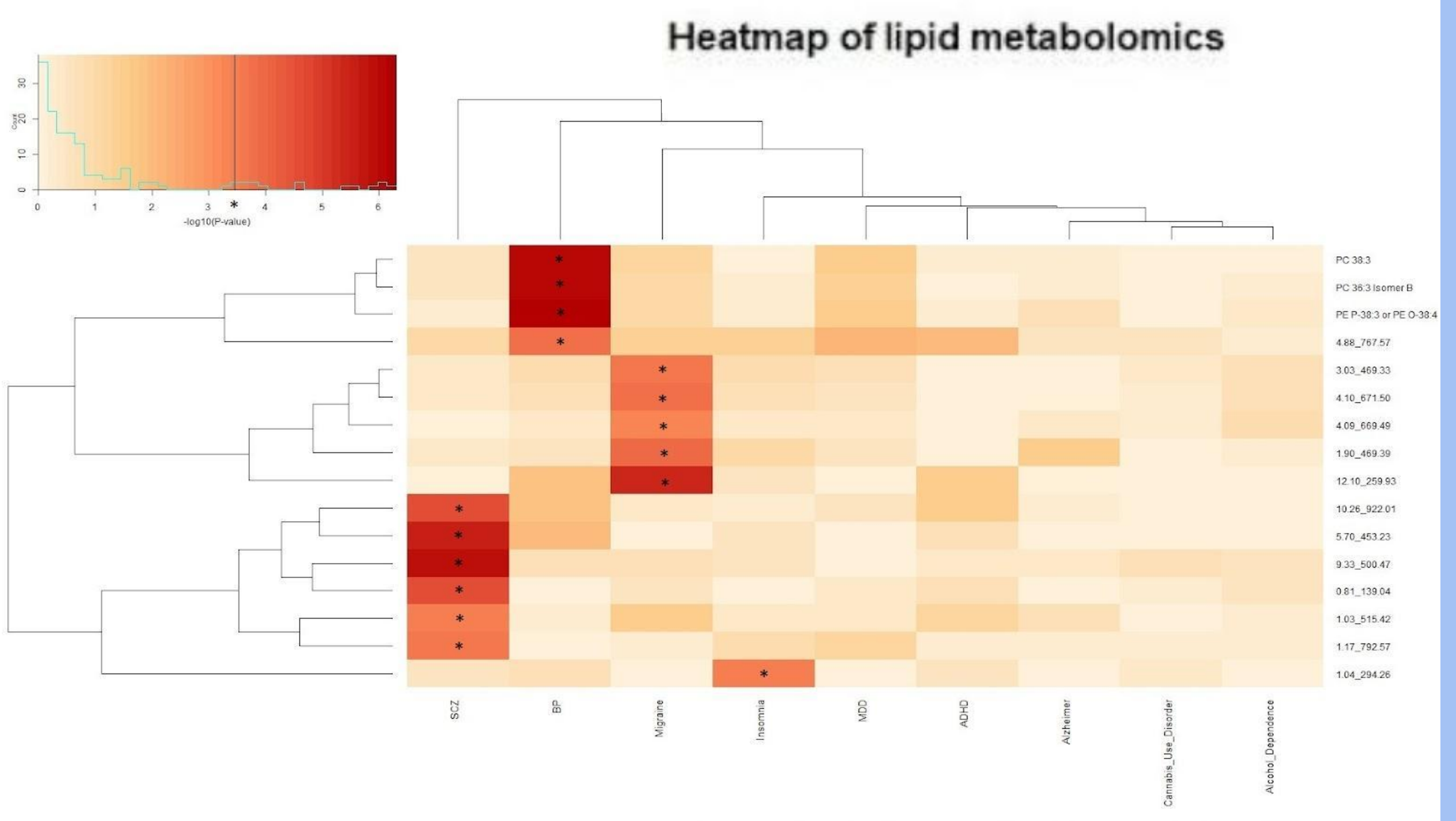
1. Started with 5544 metabolites
2. GWAS of metabolites through FUSION software
3. Checked for heritability
4. Investigated associated regions in genome (±500kb)
5. Using top 3 regions we then used metabolites to predict phenotypes
6. Only 780 were significant
7. Created metabolite prediction weights

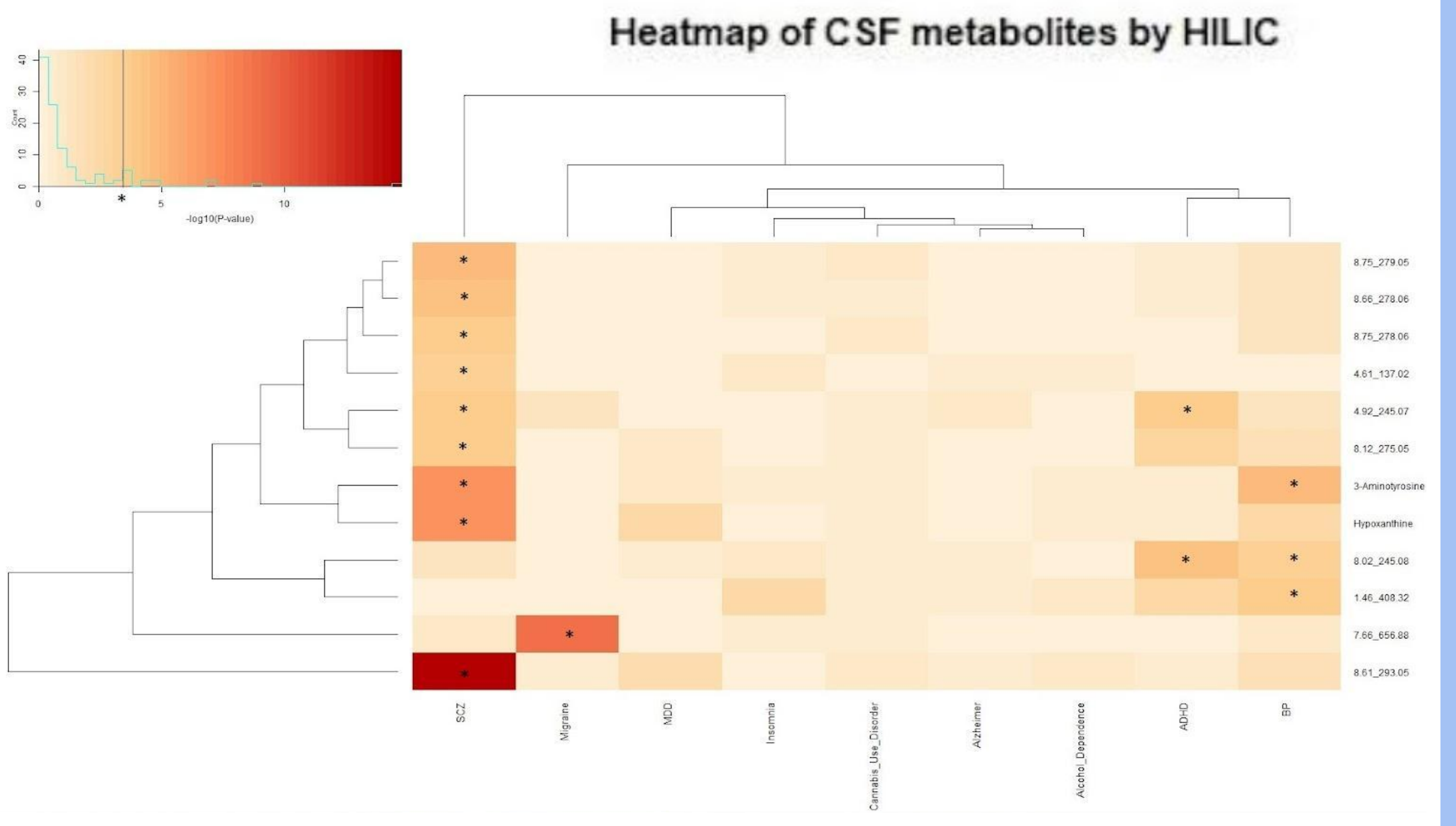


Model performance	Percentage
top1	0.149
blup	0.110
enet	0.291
lasso	0.450

Results:

FDR of 10% we ran associations for each of the phenotypes
In the end there were 30 significant metabolites:


Heatmap of lipid metabolomics


Heatmap of CSF metabolites by HILIC

Conclusions:

- Novel metabolite interactions with the neuropsychiatric disorders
- Overlap between associated metabolite
- Genetic factors of neuropsychiatric traits are associated with metabolites in CSF

Future Directions:

- New pathways could be investigated
- Future studies with different datasets could reveal more metabolites
- Potential drug targeting for metabolites

Acknowledgements:

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