Heritability of Psychiatric Disorders and their Genetic Correlation with Cardiovascular Disease Risk Factors

Vignesh Rajagopalan

Abstract

Psychiatric disorders are a leading cause of disability and mortality worldwide. Such disorders are influenced by genetic variants that act in conjunction with environmental factors. There is evidence that patients with Coronary Artery Disease (CAD) are at a high risk to develop Major Depressive Disorder (MDD). There is a dire need to understand the underlying genetic relationships among psychiatric disorders and Cardiovascular disease risk factors.

The aim of this project was to compare two statistical regression techniques, LDSC and HDL on GWAS datasets to estimate heritability (genetic influence) of the above disorders/traits and evaluate genetic correlation among them. This data was used for gene pathway analysis of the mapped genes.

The Psychiatric disorders considered were Major Depressive Disorder (MDD), Bipolar Disorder (BiP), Schizophrenia (ScZ) and major CVD risk factors were Coronary Artery Disease(CAD), Type-2 diabetes.

The results from LDSC and HDL showed that all three psychiatric disorders were highly heritable(0.5-0.75) and highly genetically correlated (0.3-0.74). MDD showed moderate correlation with CAD (0.29) and Diabetes (0.18). HDL showed more precise estimations for genetic correlation with 40% lower standard error than LDSC. The gene pathway analysis showed that the genes involved in MDD, CAD and Diabetes are enriched for the following pathways: Immune system, Developmental Biology, Metabolism, Signal Transduction, Neuronal System, Cellular responses to stimuli and Metabolism of proteins.

Statistical genetics and gene pathway analysis can give us insights into complex genetic relationships among diseases/traits. Future genetic research will lead us to better diagnostic accuracy and precision medicine discovery.

Introduction

Psychiatric disorders are devastating conditions that disrupt normal functioning and are a leading cause of mortality world wide. Individuals with severe mental illness typically have a life expectancy around 10 years shorter than the general population [5]. This reduced lifespan is largely due to physical health conditions, mental health issues like suicide, and cardiovascular diseases. The World Health Organization has stressed the urgent need to improve both the care and prevention of mental illness.

Psychiatric disorders are influenced by a mix of genetic and environmental factors. Research has found associations among cardiovascular disease (CVD) risk factors, such as body mass index, Type 2 Diabetes, hypertension, and psychiatric disorders. Meta-analyses reveal that depression affects between 45% and 51% of individuals with coronary artery disease (CAD) [5]. Furthermore, depression has been linked to a 1.5 to 2.7 times greater risk of future cardiac events and overall

mortality in CAD patients. However, the genetic factors contributing to these associations are not yet fully understood. [5]

It is therefore important to understand the genetic influence of psychiatric disorders and their genetic overlap with cardiovascular risk factors. By delving into genetic research, we can uncover valuable insights and understand how genes interact with environmental influences. This can lead to improved risk assessment, earlier detection, and the development of more targeted and personalized treatment strategies.

Recent advancements in Genome-Wide Association Studies (GWAS) have led to the development of statistical techniques for estimating heritability through single nucleotide polymorphisms (SNPs) and assessing genetic correlations between traits. The availability and efficiency of using GWAS summary statistics have made these methods increasingly preferred over those requiring individual-level genotype data. In the last two decades, many GWAS have been conducted, identifying a vast number of SNPs related to various complex human traits and diseases.

This study aimed to show that statistical genetic methods can reveal significant heritability and genetic links between psychiatric disorders and cardiovascular risk factors. By analyzing these connections, we can uncover shared genetic features and pathways related to both types of conditions. Two statistical techniques, LDSC and HDL, were used on GWAS data to assess the heritability of three major psychiatric disorders: Major Depressive Disorder (MDD), Bipolar Disorder (BiP) and Schizophrenia (SCZ). We also evaluated the genetic relationships between these psychiatric disorders and various cardiovascular risk factors like Coronary Artery Disease (CAD), Hypertension, Triglycerides, Type-2 Diabetes, Body Mass Index, LDL, systolic and diastolic blood pressure, using datasets from the UK Biobank and the GWAS catalog. The results from LDSC and HDL regression techniques were compared and their performance was evaluated. Additionally, gene/loci/pathway analysis was done to find the overlapping genes and pathways.

Background

Table 1: Glossary of Genetic Terms

SNP (Single Nucleotide Polymorphism)	A Single Nucleotide Polymorphism (SNP) is a kind of genetic variation where a single nucleotide differs at a specific position in the DNA sequence. This means that one of the codes (A/C/T/G) is changed to a different letter.
Linkage disequilibrium (LD)	Patterns of correlation between genetic variants that are near one another are referred to as Linkage disequilibrium.

Genome-wide association studies (GWAS)	GWAS identifies genes related to specific diseases or traits by analyzing the complete genome of a large population, particularly minor variations known as SNPs or single nucleotide polymorphisms. GWAS statistical methods enable us to estimate heritability captured by single nucleotide polymorphisms (SNPs) and genetic correlation between traits.
Manhattan plot	A Manhattan plot represents statistical significance by plotting –log10(p-value) on the vertical axis and chromosomes on the horizontal axis. This visualization effectively displays a large number of genetic variants in a single chart.
Heritability	Heritability measures how genetic factors contribute to variation in a trait or disease within a specific population. A high heritability suggests that genetics have a major impact on that trait or condition.
Genetic correlation	Genetic correlation measures how genetic variations that affect one trait are related to variations affecting another trait. A strong genetic correlation suggests that the traits share some of the same genetic influences, leading to a higher probability that the traits might occur together.
Gene pathway	A gene pathway refers to a network of genes that collaborate to achieve a specific biological function or contribute to a particular physiological process.

LDSC vs HDL

LDSC(Linkage Disequilibrium Score Regression) and HDL (High Definition Likelihood) are two statistical regression methods that make use of GWAS summary statistics and can be used for computing SNP heritability and Genetic correlation. The differences and similarities between the two techniques have been captured below:

Table 2: Comparison between LDSC and HDL Regression techniques

	LDSC (Linkage Disequilibrium Score) Regression	HDL Regression

Key Concept	Estimates Heritability and Genetic Correlation using GWAS summary statistics instead of individual-level genotype data	Uses GWAS summary statistics but considers non-diagonal elements of the matrix
SNP Heritability (h^2)	Standard Linear Model with N individuals and M genotypes $\boldsymbol{y} = \boldsymbol{X} * \boldsymbol{\beta} + \boldsymbol{\epsilon}, \boldsymbol{y}, \boldsymbol{\epsilon} \mathbb{R}^{N\times 1}, \boldsymbol{X} \in \mathbb{R}^{N\times M}, \boldsymbol{\beta} \in \mathbb{R}^{M\times 1}$ $\boldsymbol{X} = (\boldsymbol{x}_1, \boldsymbol{x}_2, \ldots\ldots, \boldsymbol{x}_{\boldsymbol{M}})$ A Z-score is a measure of the effect allele in relation to the phenotype. $z_j = \frac{\boldsymbol{x}_j^T \boldsymbol{\beta}}{\sqrt{N}}, \boldsymbol{x}_{\boldsymbol{j}} \in \mathbb{R}^{N\times 1}$ $\boldsymbol{z} = \{z_1, z_2, \ldots\ldots, z_M\}$ $Cov(\boldsymbol{z}) = E(\boldsymbol{z}\boldsymbol{z}^T)$ Linkage Disequilibrium (LD) is the non-random association of alleles at different loci in a given population, and LD-matrix (R) is defined as $\boldsymbol{R} = \{r_{jk}\}, r_{jk} = E(\boldsymbol{x}_{\boldsymbol{j}}^T \boldsymbol{x}_{\boldsymbol{k}}), \{r_{jj}\} = 1$ LD Score is a measure of how well each SNP can tag other local SNPs. LD score for a SNP is defined as$\boldsymbol{L} = \{l_{jk}\} = \boldsymbol{R}^T \boldsymbol{R}, l_{jk} = E(\boldsymbol{r}_{\boldsymbol{j}}^T \boldsymbol{r}_{\boldsymbol{k}})$	
	$diag(E(\boldsymbol{z}\boldsymbol{z}^T)) = \frac{Nh^2}{M}\boldsymbol{diag}(\boldsymbol{L}) + \boldsymbol{diag}(\boldsymbol{R})$ $\sigma_j^2 = \frac{Nh^2}{M} l_{jj} + 1$	$Cov(z) = E(\boldsymbol{z}\boldsymbol{z}^T) = \frac{Nh^2}{M}\boldsymbol{L} + \boldsymbol{R}$
Genetic correlation	Standard Linear Model for 2 Phenotype vectors $\{\boldsymbol{y}_1, \boldsymbol{y}_2\}$, 2 genotype matrices$\{\boldsymbol{X}^{(1)}, \boldsymbol{X}^{(2)}\}$, and 2 test-statistics $\{\boldsymbol{z}^{(1)}, \boldsymbol{z}^{(2)}\}$ are used. N_1= Number of Individuals for Phenotype 1 N_2= Number of Individuals for Phenotype 2 N_0= Overlapping number of Individuals	
	$diag\{Cov(\boldsymbol{z}^{(1)}, \boldsymbol{z}^{(2)})\}$ $= \frac{\sqrt{N_1 N_2} h_{12}}{M} diag(\boldsymbol{L})$ $+ \frac{N_0(h_{12} + \rho_{12})}{\sqrt{N_1 N_2}} diag(\boldsymbol{R}) E\left(z_j^{(1)} z_j^{(2)}\right)$ $= \frac{\sqrt{N_1 N_2} h_{12}}{M} l_{jj} + \frac{N_0(h_{12} + \rho_{12})}{\sqrt{N_1 N_2}}$	$Cov(\boldsymbol{z}^{(1)}, \boldsymbol{z}^{(2)})$ $= \frac{\sqrt{N_1 N_2} h_{12}\boldsymbol{L}}{M}$ $+ \frac{N_0(h_{12} + \rho_{12})}{\sqrt{N_1 N_2}}\boldsymbol{R}$
Pros/Cons	Computationally Simpler	Computationally Intensive Higher precision than LDSC Reduced variance of genetic correlation Lower standard deviation

Methods

GWAS summary statistics for Major Depressive Disorder, Bipolar Disorder, and Schizophrenia were obtained from the Psychiatric Genomics Consortium. Summary statistics for cardiovascular risk factors—including Coronary Artery Disease, Type-2 Diabetes, Body Mass Index, Cholesterol, Diastolic Blood Pressure, Systolic Blood Pressure, Hypertension, High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), Smoking, Alcohol Consumption, and Atrial Fibrillation—were accessed from the GWAS Catalog. SNP heritability and genetic correlation were estimated using the LDSC package (available at https://github.com/bulik/ldsc). The GWAS summary statistics and LD Scores from the various datasets were downloaded and converted to LDSC recognized format for each dataset.

SNP heritability and genetic correlation were assessed with the HDL R package. For traits and diseases with significant genetic correlations, Manhattan plots were created and analyzed using the topr package. The topr package enables visualization of association results across the whole genome or in specific regions, including detailed gene information.The genetic pathways for the mapped genes was determined using Reactome database and tool that helps with visualization, interpretation and analysis of genetic pathways.

Results

SNP-Heritability

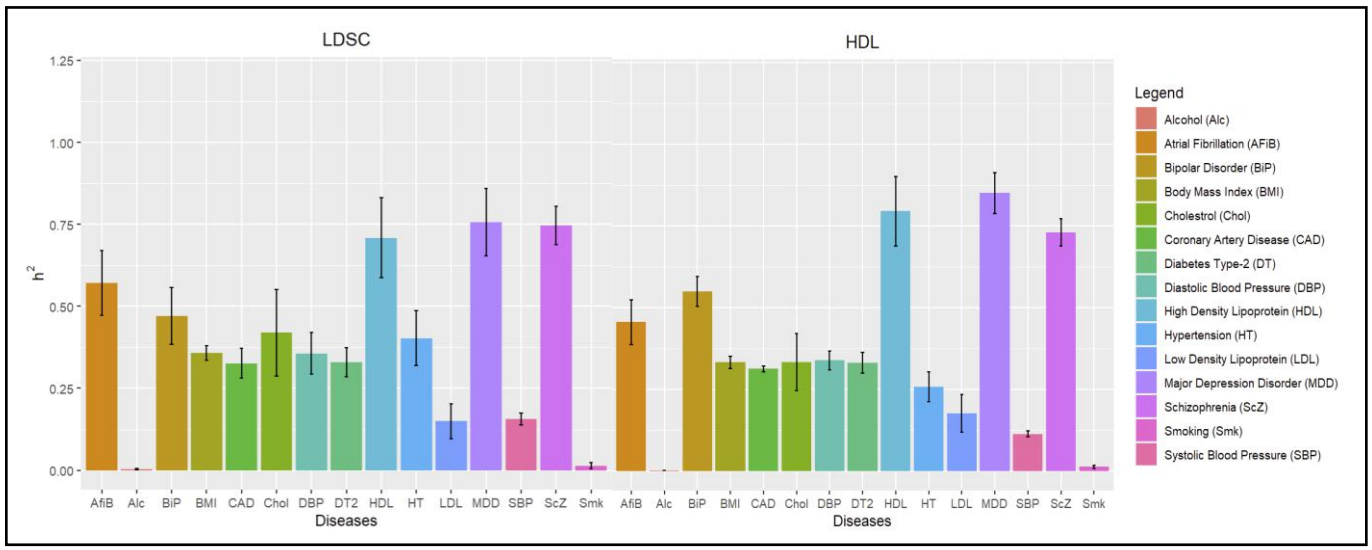


Figure 1: SNP-Heritability of Psychiatric disorders and cardiovascular traits.

The SNP-Heritability results from LDSC and HDL showed that all three psychiatric disorders are highly heritable(0.5-0.75). CAD and Type2 Diabetes are moderately heritable (0.2-0.5). Acquired traits like Smoking and Alcohol consumption are not heritable (<0.1)

Genetic Correlation

The Genetic correlation results for LDSC and HDL from Figure 2, showed that all three psychiatric disorders have moderate to high genetic correlation (0.3-0.74). MDD was moderately correlated with CAD and Type2-Diabetes (0.1-0.3). Schizophrenia showed the highest genetic correlation with bipolar disorder (≥ 0.7). Schizophrenia also showed high genetic correlation with Smoking and Alcohol consumption (≥ 0.3).

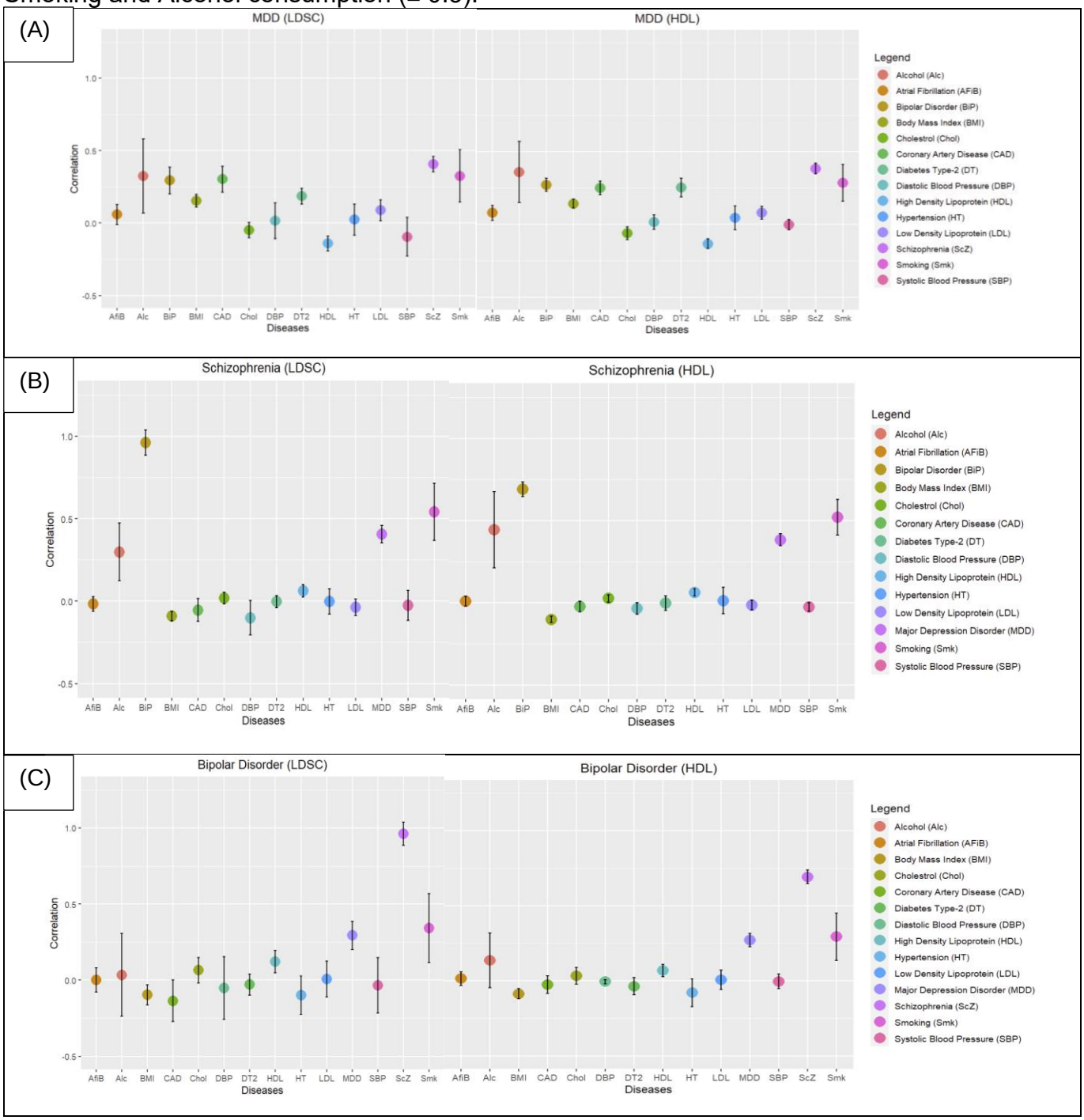
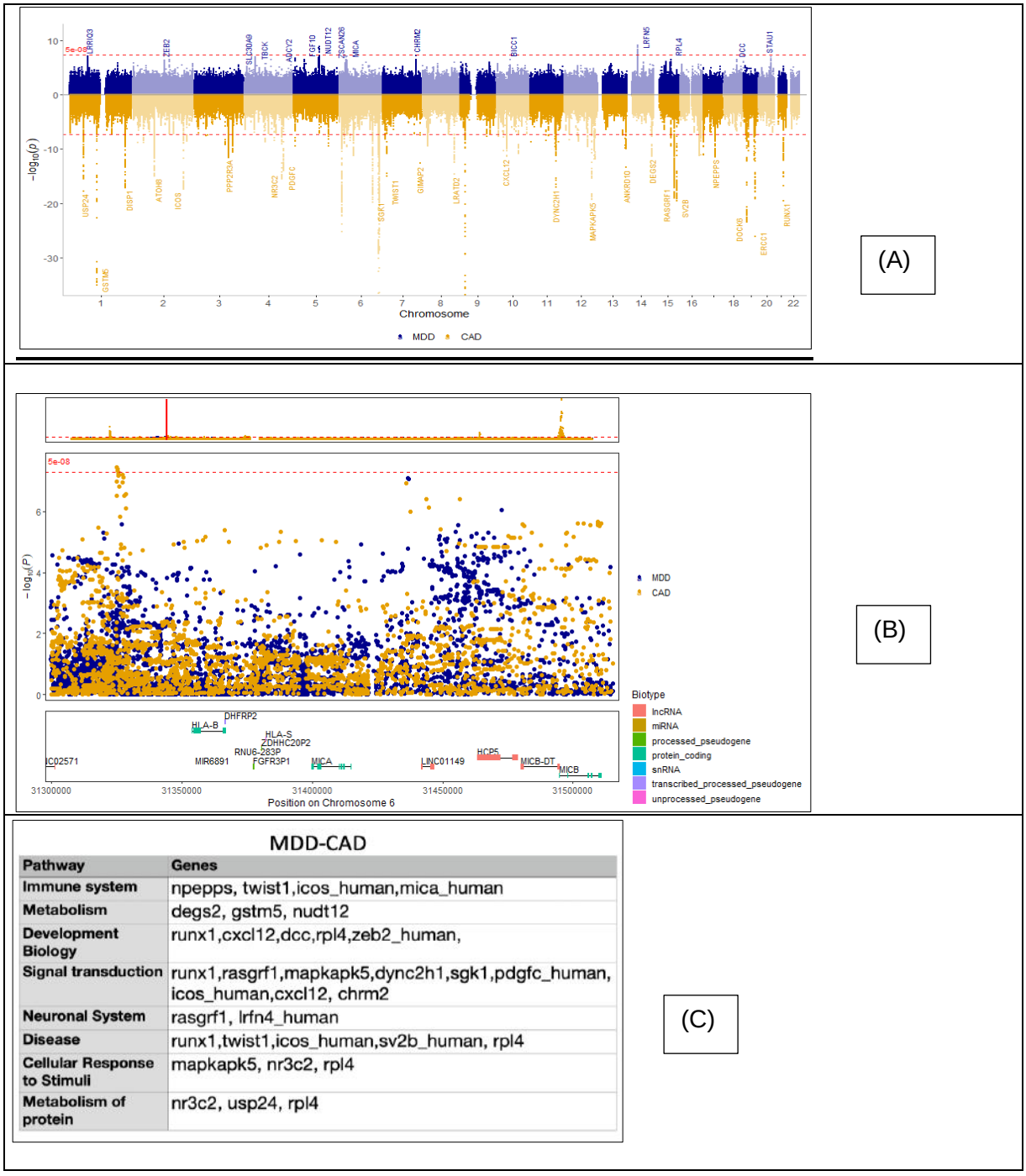


Figure 2: Genetic Correlation of (A) MDD, (B) Schizophrenia (C) Bipolar Disorder with other diseases

Gene/Loci/Pathway Analysis (MDD- CAD)



MDD-CAD

Pathway	Genes
Immune system	npepps, twist1,icos_human,mica_human
Metabolism	degs2, gstm5, nudt12
Development Biology	runx1,cxcl12,dcc,rpl4,zeb2_human,
Signal transduction	runx1,rasgrf1,mapkapk5,dync2h1,sgk1,pdgfc_human, icos_human,cxcl12, chrm2
Neuronal System	rasgrf1, lrfn4_human
Disease	runx1,twist1,icos_human,sv2b_human, rpl4
Cellular Response to Stimuli	mapkapk5, nr3c2, rpl4
Metabolism of protein	nr3c2, usp24, rpl4

(C)

Figure 3: (A) Manhattan Plot (MDD-CAD), (B) Region Plot around genes MICA/B, (C) Gene Pathways (MDD-CAD)

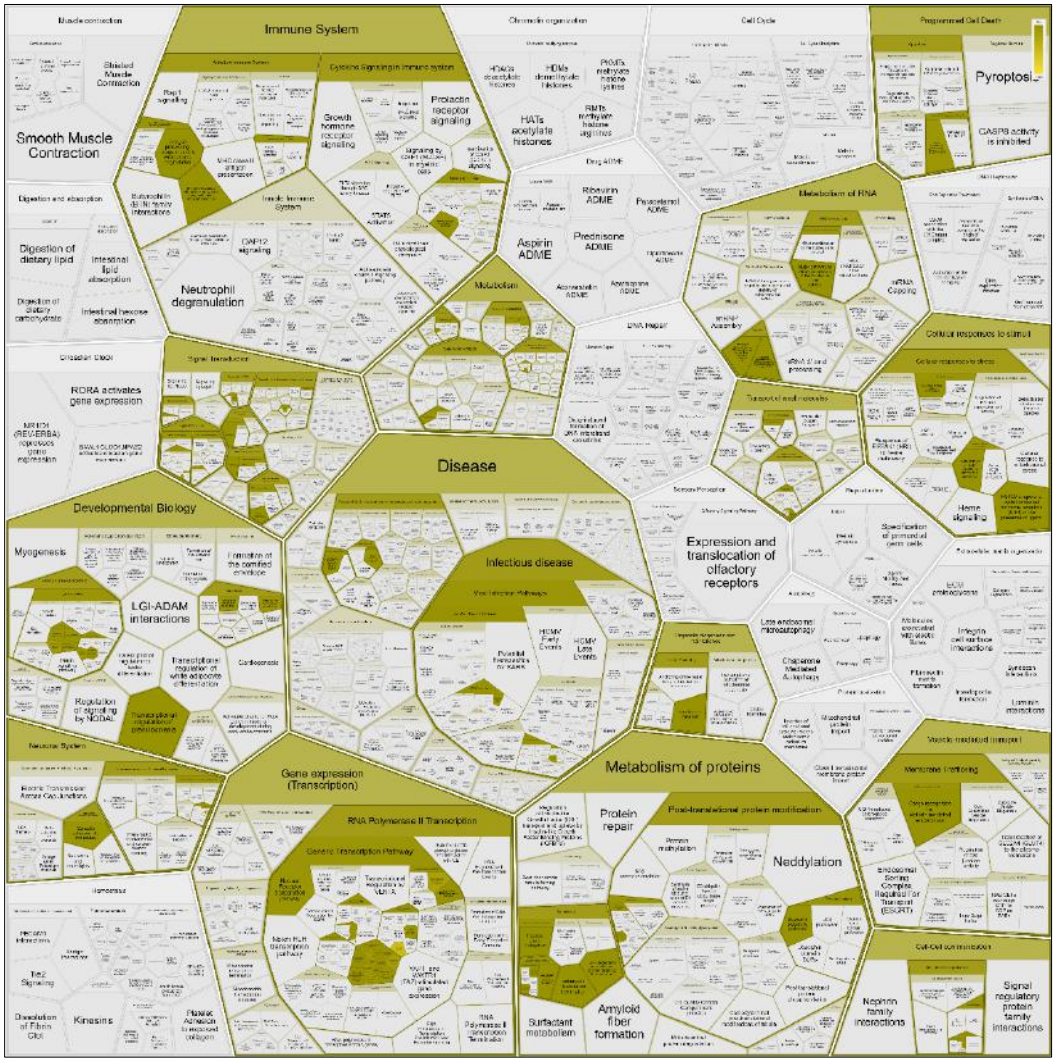
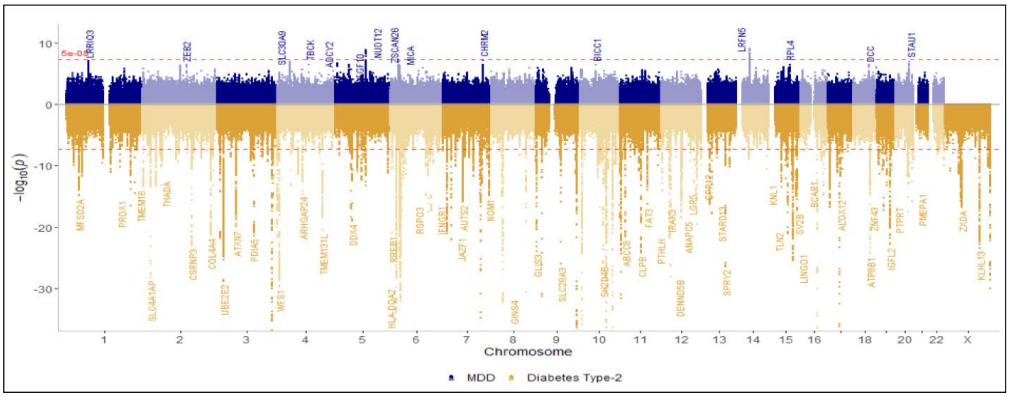


Figure 4: Visualization of pathways of mapped genes for MDD and CAD

Manhattan plot for MDD versus CAD showed lead genes that crossed the threshold and the pathway analysis showed gene enrichment of the mapped genes for the following pathways: Immune system, Developmental Biology, Metabolism, Signal Transduction, Neuronal System, Cellular responses to stimuli and Metabolism of proteins.

Gene/Loci/Pathway Analysis (MDD- Type-2 Diabetes)

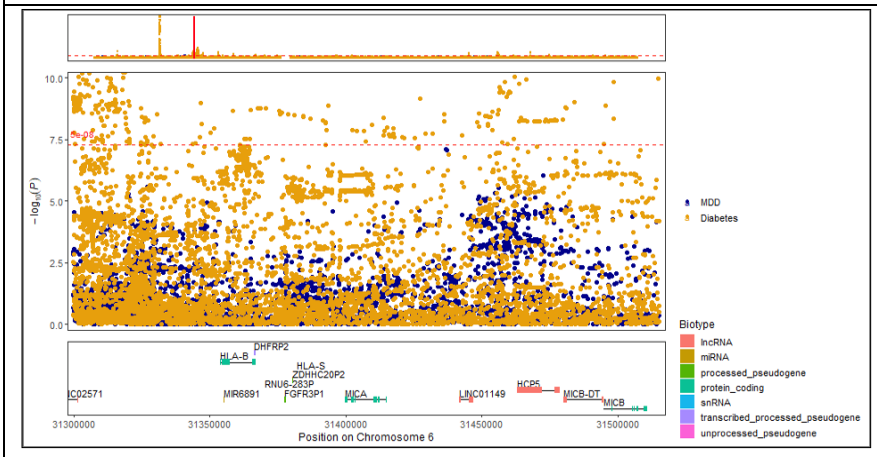


(A)

MDD-DT

Pathway	Genes
Immune System	Klhl13, Anapc5, Ifngr1, Hla-dqa2, Ube2e2, mica_human
Metabolism	Alox12, Abcc8, Mfsd2a, Rpl4, Nudt12
Metabolism of RNA	thada_human, Rpl4
Development of Biology	Col4a4, Dcc, Rpl4, Zeb2_human
Signal Transduction	Pmepa1, Bcar1, Knl1, Lgr5, Pthlh, Rspo3, Arhgap24, Col4a4, Chrm2
Neuronal System	Abcc8, Irfn4_human
Cellular Response to Stimuli	Anapc5, wfs1_human, pdia5_human, Rpl4
Metabolism of Proteins	Klhl13, wfs1_human, Atxn7, Rpl4

(B)



(C)

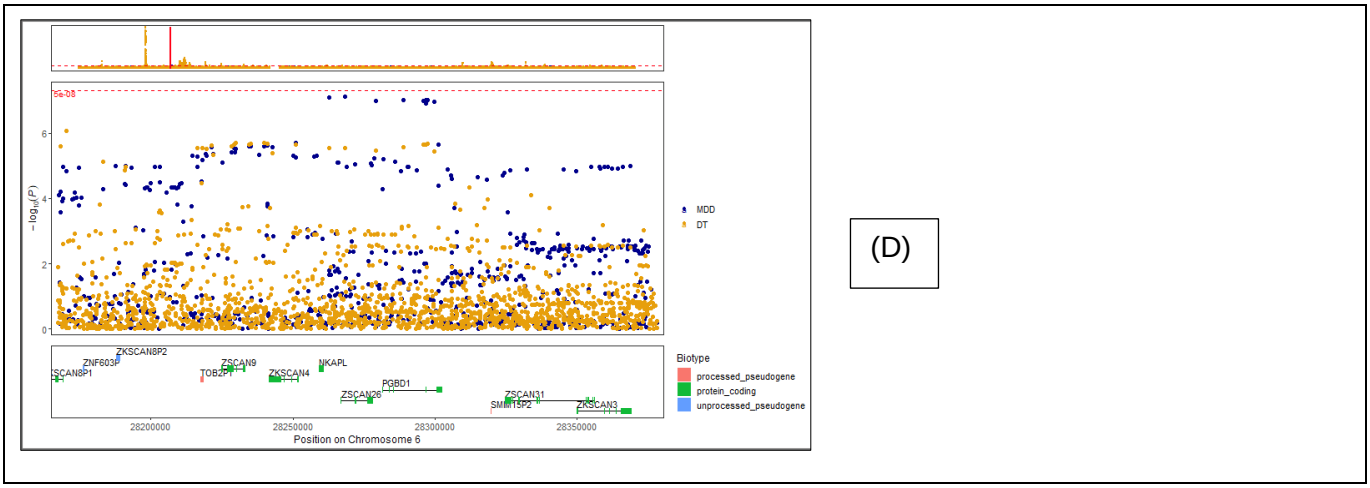


Figure 5: (A) Manhattan plot (MDD-Type2 Diabetes), (B) Gene pathways MDD-Type2 diabetes, (C) Region plot around genes MICA/B, (D) Region plot around gene ZSCAN26

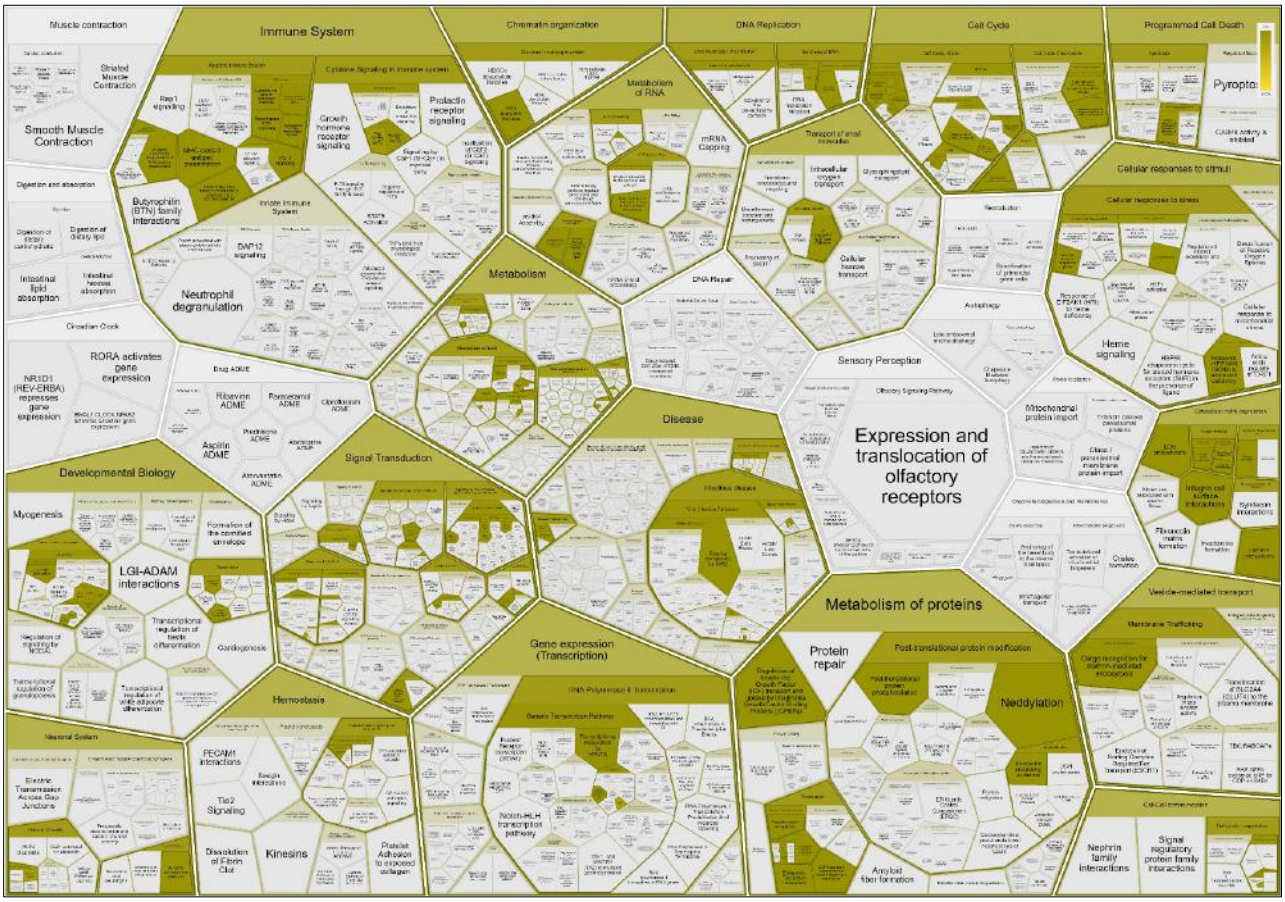
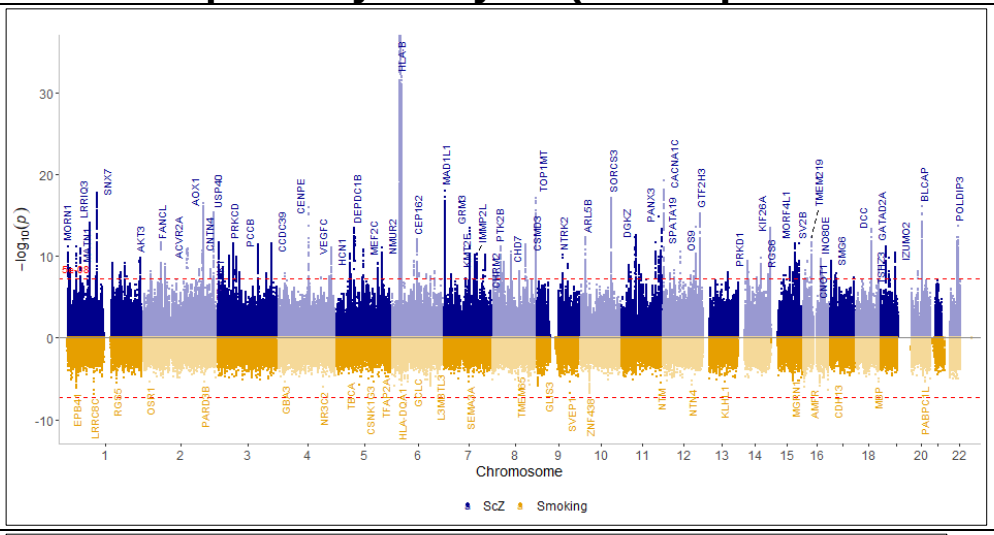


Figure 6: Visualization of pathways of mapped genes for MDD-Type 2 Diabetes

Manhattan plot for MDD versus Type2 Diabetes showed genes that crossed the threshold and the pathway analysis showed gene enrichment of the mapped genes for the following pathways: Immune System, Metabolism, Metabolism of RNA, Developmental Biology, Signal Transduction, Neuronal System, Cellular Response to Stimuli, Metabolism of Proteins.

Gene/Loci/pathway analysis (Schizophrenia – Smoking)

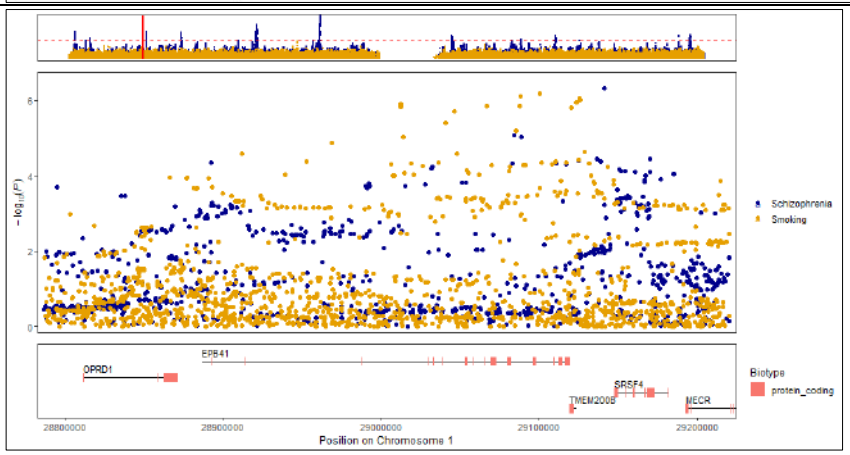


(A)

SCZ-SMK

Pathway	Genes
Immune System	kif26a, hla-b, mef2c, fancl_human, prkcd, hla-dqa1, svep1l, mgrn1_human
Metabolism	CACNA1C, pccb_human, aox1, gba3, gclc,
Gene Expression	Poldip3, gatad2a, gtf2h3, chd3_human, mef2c, akt3_human, nr3c2, tfap2a
Development of Biology	Gatf2h3, dgkz, chd3_human, mef2c, acvr2a, akt3_human, osr1_human, tfap2a, sema3a, mbp_human, ntn4
Signal Transduction	Gatad2a, cacna1c, dgkz, ntrk2, sorcs3, gm3_human, mad1l1, nmur-2, mef2c, depdc1b, vegfc, prkcd, acvr2a, akt3_human, rgs5_human,
Neuronal System	Hcn1, epb41
Cellular response to stimuli	Mef2c, prkcd, akt3_human, nr3c2, gclc
Metabolism of Proteins	top1_human, ched3_human, hla-b, pccb_human, cntn4, nr3c2, tfap2a, amfr
Disease	Gatad2a, gtf2h3, chd3_human, hla-b, pccb_human, akt3_human, gclc,
Cell Cycle	Dcc1, akt3_human, amfr
Extracellular Matrix Organization	matn1_human, ntn4

(B)



(C)

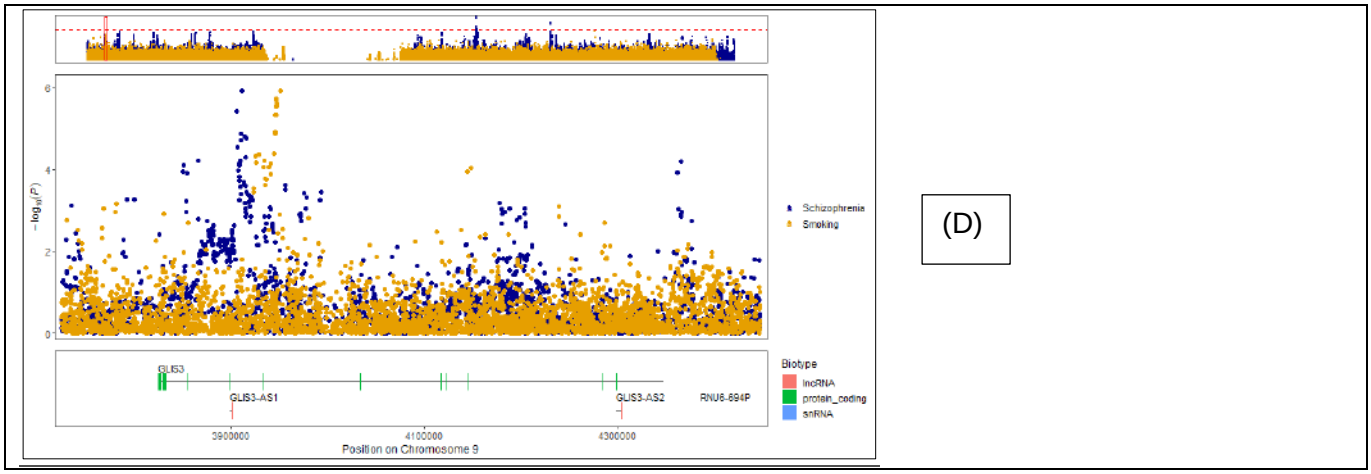


Figure 7: (A) Manhattan plot, (B) Genetic Pathways, (C) Region plot around gene EPB41, (D) Region plot around gene GLIS3

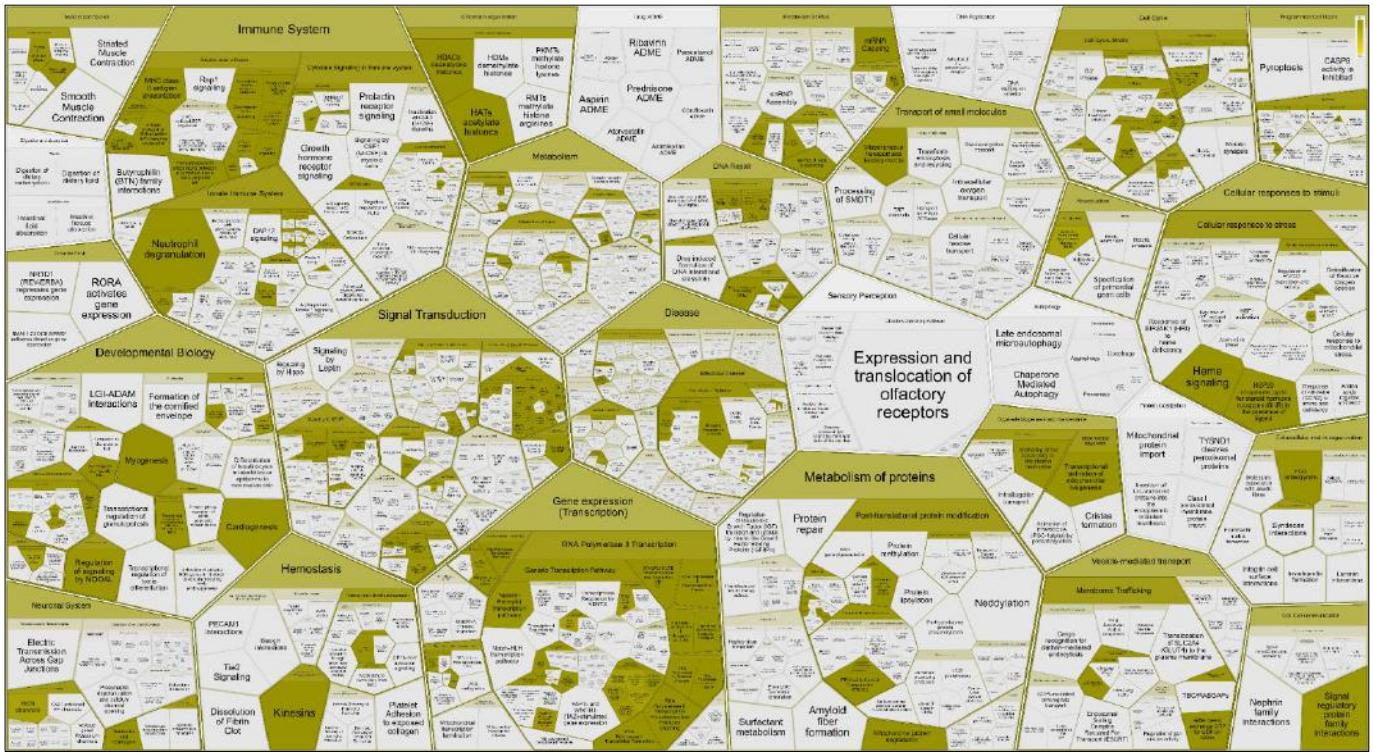


Figure 8: Visualization of pathways of mapped genes for Schizophrenia and Smoking

Manhattan plot for Schizophrenia versus Smoking showed genes that crossed the threshold and the pathway analysis showed gene enrichment of the mapped genes for the following pathways: Immune System, Metabolism, Gene Expression, Developmental Biology, Signal Transduction, Neuronal System, Cellular Response to Stimuli, Metabolism of Proteins, Diseases, Cell Cycle, Extracellular Matrix Organization.

Discussion

The high SNP-heritability of ~75-80% for psychiatric disorders, Major Depressive Disorder and Schizophrenia indicate that genetic factors play a strong role in these diseases and affected individuals carry a greater risk to pass on the disease to family members. The high genetic correlation among these psychiatric diseases also indicates significant genetic overlap. The Manhattan plots revealed top overlapping genes: ANK3 ,CACNA1C and MAD1LI for Bipolar Disorder, Major Depressive Disorder and Schizophrenia. ANK3 gene expression levels in blood are significantly elevated in individuals with Bipolar Disorder and Schizophrenia compared to healthy individuals, resulting in varied tissue expression and function, especially in relation to neuronal development. [12,13] The CACNA1C gene is responsible for producing a particular type of calcium channel, which transports calcium ions into cells to generate electrical signals. This also affects the nervous system and can lead to schizophrenia [14]. MAD1L1 is associated with both Bipolar Disorder and Schizophrenia. In schizophrenia, differential DNA methylation in the brain spans across the genome and is connected to the MAD1L1 locus. This locus reveals a shared genetic variation between DNA methylation, gene expression changes, and susceptibility to schizophrenia. [15,16]

Coronary Artery Disease and Type2 Diabetes showed a moderate heritability of ~25-40%. Coronary artery calcification (CAC) is significantly influenced by genetic factors. People with a family history of CAD are more likely to develop noncalcified plaque (NCP). Additionally, NCP is more frequent in younger individuals with a family history of CAD compared to those without any [11]. A number of individuals with Type 2 diabetes have a close family member, like a parent or sibling, who also suffers from the disease. The risk to develop Type 2 diabetes goes up with more affected family members, due to a combination of shared genetic factors and lifestyle habits, such as diet and physical activity.

The results showed that there was a moderate correlation between Major Depressive Disorder and CAD and similarly, between MDD and Type2 Diabetes. The Manhattan plot for Major Depressive Disorder (MDD) and Coronary Artery Disease (CAD) identified the overlapping gene MICA/B. This gene produces stress-related proteins and is associated with inflammatory and autoimmune disorders, including atherosclerosis, which can lead up to CAD. CAD is considered to be an autoimmune disease, and atherosclerosis is the buildup of plaque in the coronary artery which ends up leading to CAD. Stress is also associated with MDD, and MICA/B codes for stress-induced proteins associating both MDD and CAD with each other[17]. Type 2 Diabetes is a metabolic condition, so issues with the gene expression of the genes that contribute to Metabolism, Metabolism of RNA, Metabolism of proteins may lead to Diabetes. An overlapping gene between MDD and Type 2 Diabetes happens to also be MICA/B. Type 2 Diabetes has been shown to be an independent risk factor for accelerated atherosclerosis development which MICA/B is associated with. Another overlapping gene between MDD and Type 2 Diabetes is ZSCAN26 that regulates the production of insulin which has a direct correlation with diabetes [17].

The top overlapping genes found for Schizophrenia and Smoking are EPB41 and GLIS3. EPB41 is a gene that influences peripheral blood leukocyte RNA leading to abnormal psychomotor behavioral characteristics. EPB41 is also a cytoskeleton-related gene and its impairment is linked to cigarette smoking. GLIS3 gene is a member of the GLI-similar zinc finger protein family and abnormalities with GLIS3 mutations have impacts on psychological development. [21,22,23,24].

Finally, the GWAS statistical methods, LDSC and HDL were compared for their computation times, precision and standard error. As expected, HDL showed more precise estimations for genetic correlation with 40% lower standard error than LDSC. HDL was however computationally more intensive and took several minutes to complete while LDSC completed in ~5seconds.

Conclusion

Recently, there has been growing interest in exploring the potential relationship between psychiatric disorders and cardiovascular diseases (CVDs).

This study focused on applying GWAS-based statistical genetics methods to determine the SNP-heritability of psychiatric disorders and examine their genetic connections with cardiovascular diseases, particularly Coronary Artery Disease (CAD). This data was then used to determine the overlap in the genetic architecture among these diseases/traits by identifying mapped genes/loci and pathways.

The study revealed significant heritability for the three psychiatric disorders and a moderate genetic correlation between MDD-CAD and MDD-Type 2 Diabetes. It also identified several genes that contribute to the genetic overlap between MDD-CAD and MDD-Type 2 Diabetes, through various genetic pathways linking these conditions.

Therefore, screening could likely be recommended for individuals with family history of psychiatric disorders. People who are diagnosed with MDD could preferably be screened for CAD.

Statistical genetics and gene pathway analysis offer valuable insights into the intricate genetic relationships between diseases and traits. However, the biological impacts of these genetic risk variants are still under investigation. Genetic research has the potential to enhance mental health care by refining diagnostic accuracy and advancing precision medicine.

Acknowledgements

Special thanks to my mentor, Connor Duffy, PhD candidate at Stanford University, who provided guidance for my research project.

References

1. Sun, Ning and Zhao, Hongyu, Statistical Methods in Genome-Wide Association Studies (July 1, 2020). Annual Review of Biomedical Data Science, Vol. 3, pp. 265-288, 2020, Available at SSRN: https://ssrn.com/abstract=3658968 or http://dx.doi.org/10.1146/annurev-biodatasci-030320-041026

2. Srivastava AK, Williams SM, Zhang G. Heritability Estimation Approaches Utilizing Genome-Wide Data. Curr Protoc. 2023 Apr;3(4):e734. https://doi.org/10.1002/cpz1.734. PMID: 37068172; PMCID: PMC10923601.

3. Zhang Y, Cheng Y, Jiang W, Ye Y, Lu Q, Zhao H. Comparison of methods for estimating genetic correlation between complex traits using GWAS summary statistics. Brief Bioinform. 2021 Sep 2;22(5):bbaa442. https://doi.org/10.1093/bib/bbaa442. PMID: 33497438; PMCID: PMC8425307.

4. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR; ReproGen Consortium; Psychiatric Genomics Consortium; Genetic Consortium for Anorexia Nervosa of the Wellcome Trust Case Control Consortium 3; Duncan L, Perry JR, Patterson N, Robinson EB, Daly MJ, Price AL, Neale BM. An atlas of genetic correlations across human diseases and traits. Nat Genet. 2015 Nov;47(11):1236-41. https://doi.org/10.1038/ng.3406. Epub 2015 Sep 28. PMID: 26414676; PMCID: PMC4797329.

5. Torgersen, K., Rahman, Z., Bahrami, S., Hindley, G. F. L., Parker, N., Frei, O., Shadrin, A., O'Connell, K. S., Tesli, M., Smeland, O. B., Munkhaugen, J., Djurovic, S., Dammen, T., & Andreassen, O. A. (2022). Shared genetic loci between depression and cardiometabolic traits. PLoS genetics, 18(5), e1010161. https://doi.org/10.1371/journal.pgen.1010161

6. Chen, C. J., Liao, W. Y., Chattopadhyay, A., & Lu, T. P. (2023). Exploring the genetic correlation of cardiovascular diseases and mood disorders in the UK Biobank. Epidemiology and psychiatric sciences, 32, e31. https://doi.org/10.1017/S2045796023000252

7. Zhang, F., Cao, H., & Baranova, A. (2021). Shared Genetic Liability and Causal Associations Between Major Depressive Disorder and Cardiovascular Diseases. Frontiers in cardiovascular medicine, 8, 735136. https://pubmed.ncbi.nlm.nih.gov/34859065/

8. Andreassen OA, Hindley GFL, Frei O, Smeland OB. New insights from the last decade of research in psychiatric genetics: discoveries, challenges and clinical implications. World Psychiatry. 2023 Feb;22(1):4-24. https://doi.org/10.1002/wps.21034. PMID: 36640404; PMCID: PMC9840515.

9. Roelfs, D., van der Meer, D., Alnæs, D. *et al.* Genetic overlap between multivariate measures of human functional brain connectivity and psychiatric disorders. *Nat. Mental Health* **2**, 189–199 (2024). https://doi.org/10.1038/s44220-023-00190-1

10. Solmi, M., Radua, J., Olivola, M. *et al.* Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. *Mol Psychiatry* **27**, 281–295 (2022). https://doi.org/10.1038/s41380-021-01161-7

11. Drobni, Zsofia D., et al. "Heritability of coronary artery disease: Insights from a classical twin study." *Circulation: Cardiovascular Imaging*, vol. 15, no. 3, Mar. 2022, https://doi.org/10.1161/circimaging.121.013348.

12. Zhou, Young, et al. "Genetic animal models for psychiatric disorders." Psychiatric Genomics, 2022, pp. 241–267, https://doi.org/10.1016/b978-0-12-819602-1.00015-2.

13. Wirgenes, Katrine Verena et al. "ANK3 gene expression in bipolar disorder and schizophrenia." The British journal of psychiatry : the journal of mental science vol. 205,3 (2014): 244-5. https://doi.org/10.1192/bjp.bp.114.145433

14. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US); [updated 2020 Jun 24]. Noonan syndrome; [updated 2020 Jun 18; reviewed 2018 Jun 01; cited 2020 Jul 1]; [about 5 p.]. Available from: https://medlineplus.gov/genetics/condition/noonan-syndrome//.

15. Trost, Sarah et al. "Investigating the Impact of a Genome-Wide Supported Bipolar Risk Variant of MAD1L1 on the Human Reward System." Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology vol. 41,11 (2016): 2679-87. https://doi.org/10.1038/npp.2016.70

16. McKinney, Brandon C et al. "Schizophrenia-associated differential DNA methylation in brain is distributed across the genome and annotated to MAD1L1, a locus at which DNA methylation and transcription phenotypes share genetic variation with schizophrenia risk." Translational psychiatry vol. 12,1 340. 20 Aug. 2022, http://doi.org/10.1038/s41398-022-02071-0

17. Haohan, Songpol et al. "Association of Major Histocompatibility Complex Class I Related Chain A/B Positive Microparticles with Acute Myocardial Infarction and Disease Severity." Diagnostics (Basel, Switzerland) vol. 10,10 766. 29 Sep. 2020, https://doi.org/10.3390/diagnostics10100766

18. James, Lisa M et al. "Schizophrenia, Human Leukocyte Antigen (HLA), and Herpes Viruses: Immunogenetic Associations at the Population Level." Neuroscience insights vol. 18 26331055231166411. 14 Apr. 2023, https://doi.org/10.1177/26331055231166411

19. Yang, Yang et al. "Association of NKAPL rs1635 With Cognitive Function in Early-Onset Schizophrenia." Frontiers in genetics vol. 13 941171. 21 Jun. 2022, https://doi.org/10.3389/fgene.2022.941171

20. Lehrer, S, and P H Rheinstein. "Diabetes, cigarette smoking and transcription factor 7-like 2 (Tcf7L2) in the UK Biobank cohort." Bulletin de l'Academie nationale de medecine vol. 205,9 (2021): 1146-1150. https://doi.org/10.1016/j.banm.2021.09.001

21. Dimitri, P et al. “Expanding the Clinical Spectrum Associated With GLIS3 Mutations.” The Journal of clinical endocrinology and metabolism vol. 100,10 (2015): E1362-9. https://doi.org/10.1210/jc.2015-1827

22. Myles-Worsley, Marina et al. “Deletion at the SLC1A1 glutamate transporter gene co-segregates with schizophrenia and bipolar schizoaffective disorder in a 5-generation family.” American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics vol. 162B,2 (2013): 87-95. https://doi.org/10.1002/ajmg.b.32125

23. Zhang, Yunqiao et al. “Peripheral Blood Leukocyte RNA-Seq Identifies a Set of Genes Related to Abnormal Psychomotor Behavior Characteristics in Patients with Schizophrenia.” Medical science monitor : international medical journal of experimental and clinical research vol. 26 e922426. 10 Feb. 2020, https://doi.org/10.12659/MSM.922426

24. Kim, Soo-Jeong et al. “Effects of smoking cessation on gene expression in human leukocytes of chronic smoker.” Psychiatry investigation vol. 11,3 (2014): 290-6. https://doi.org/10.4306/pi.2014.11.3.290