HIGH SCHOOL EDITION
Journal of Student Research
Volume 13 Issue 1 (2024)

Spatio-Functional Annotation of ADHD Risk Loci in Human Brain

Jeremy Nashid[1] and Tereza Clarence[#]

[1]Icahn School of Medicine at Mount Sinai, New York, USA
[#]Advisor

ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental condition characterized by inattention, hyperactivity, and impulsivity. Recent genomic advances have identified genetic loci[*1] associated with an increased risk of ADHD. While these loci offer insights into ADHD's genetic underpinnings, understanding their implications in the human brain remains a challenge. This study presents a comprehensive spatio-functional annotation of the recently proposed 27 ADHD risk loci within the human brain.

By utilizing gene enrichment analysis, a method to identify and analyze gene functions and interactions, we can deepen our understanding of the molecular pathways and functional roles of genes linked to ADHD. This analysis uncovers diverse functions among genes associated with ADHD, spanning neuronal activities, transcriptional regulation, receptor signaling, immune responses, and more. Additionally, we explore the spatial context of these genes through the available Hi-C datasets. By examining their spatial localization and potential regulatory interactions, we gain insights into how these risk loci might contribute to ADHD etiology at the chromatin and gene regulation levels.

These findings not only enhance our comprehension of ADHD's genetic basis but may also hold promise for potential future targeted therapeutic strategies. By unraveling the intricate interplay between genetics, brain function, and ADHD, this research opens avenues for precise interventions that could benefit individuals affected by this disorder. Ultimately, this study bridges the gap between genetic discoveries and spatial organization or genome, offering insights into the complexity of ADHD and potential directions for future research.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by persistent patterns of inattention, impulsivity, and hyperactivity that can significantly impact daily functioning and quality of life. It is one of the most common psychiatric conditions affecting children, adolescents, and even persists into adulthood [1]. While the etiology of ADHD is complex and multifactorial, substantial evidence suggests that genetic factors largely contribute to its development in people. Unraveling the intricate genetic basis of ADHD holds immense promise for advancing our understanding of its underlying mechanisms, potential biomarkers, and targeted therapeutic interventions.

Genetic studies have consistently demonstrated the heritability of ADHD, with estimates ranging from 60% to 90% [2,3] . The advent of advanced genetic techniques, including genome-wide association studies (GWAS), whole-exome sequencing, and polygenic risk scoring, has facilitated the identification of multiple genetic risk factors associated with ADHD susceptibility [3,4,5,6]. These findings have highlighted the involvement of various neurodevelopmental pathways, neurotransmitter systems, and synaptic processes in contributing to the disorder's pathophysiology.

[1] Genetic loci are specific positions on a chromosome where certain genes or genetic markers are located.

Building upon this increased understanding of genetic factors contributing to ADHD development, challenges remain in comprehensively understanding of the genetic architecture of ADHD. The polygenic nature of the disorder suggests that hundreds or even thousands of genetic variants with small effect sizes collectively contribute to its development. Integrating these findings is not only complex but also crucial to fully understanding the pathology of ADHD.

This research investigates the spatio-functional features of newly identified ADHD risk loci and their spatial co-regulation. We employ gene enrichment analysis and explore Hi-C datasets to uncover insights into these loci's roles. Our study aims to provide a deeper understanding of ADHD genetic risk factors and their regulatory relationships.

Methods

In this study, we employed a multi-faceted approach to comprehensively explore the genetic and functional aspects of newly identified ADHD risk loci within the human brain. Our research methodology involved data collection and compilation, functional annotation and pathway enrichment analysis, spatial context analysis, data visualization, and statistical analysis. To begin, we gathered a list of 27 genetic loci associated with an increased risk of ADHD from a recent genomic study [6], which established these loci as the primary genetic markers of interest in causing ADHD.

We collected important gene information, including gene symbols and Ensembl IDs, from publicly available databases and resources, ensuring that we had the necessary genetic data to conduct our analyses.

To annotate and classify the genes associated with the ADHD risk loci, we utilized the Shiny Gene Ontology (GO) tool, which involves inputting gene symbols and Ensembl IDs into the tool for analysis. The tool leverages the Gene Ontology database to categorize genes based on their involvement in biological processes, cellular components, and molecular functions. This annotation and classification process provides insights into the functional roles of these genes, such as their contribution to neuronal activities, transcriptional regulation, receptor signaling, immune responses, and more. Subsequent gene enrichment analysis further identifies enriched pathways and functional categories, highlighting the overrepresented biological processes within the set of genes related to ADHD risk loci. This tool enabled us to annotate and classify these genes based on their biological functions and molecular pathways, providing crucial insights into their potential roles in ADHD etiology. Gene enrichment analysis was performed, revealing significantly enriched pathways and functional categories, further enhancing our understanding of these genes' roles in the context of ADHD.

Moreover, we went beyond functional annotation by categorizing these genes into similarity groups, based on shared characteristics such as chromosomal localization, gene function, and gene length. This classification allowed us to discern potential functional relationships and shared biological processes among these genes, shedding light on the genes' collective contribution to ADHD risk. Simultaneously, we delved into the spatial context of these genes using Hi-C datasets, which provide valuable information on chromatin interactions and 3D genome structures. These datasets were thoughtfully selected based on their relevance to the human brain and the genes under investigation. Leveraging 3D genome modeling techniques, we gained insights into the spatial coordination of the ADHD risk loci within the human brain, offering a deeper understanding of how these loci are positioned in relation to each other and to other genomic elements. To perform such analysis, we prepared a python code which performs text analysis and similarity comparison on a collection of PDF files in a specified folder. It utilizes the NLTK library for text preprocessing tasks like tokenization, removing stopwords, and stemming. The script calculates the cosine similarity between the TF-IDF (Term Frequency-Inverse Document Frequency) representations of the text content within the PDF files. The similarity scores are then visualized as a heatmap using the Matplotlib library. The main function reads PDF files from the provided folder path, preprocesses the text, calculates similarity, and finally displays the similarity matrix heatmap. The

script helps to identify the textual similarity between different PDF documents, which can be useful for tasks such as PDF formatted heatmaps similarity charts.

Our research methodology also encompassed data visualization to facilitate the interpretation of our findings. We generated various visual representations, including lollipop/dotplots, and genome plots, to illustrate key results from functional annotation, pathway enrichment analysis, and spatial context analysis. To ensure the statistical robustness of our findings, we conducted rigorous statistical analyses to assess the significance of pathway enrichments and functional annotations. Fold enrichment values were calculated, providing insights into the relative importance of specific pathways within gene categories.

In summary, our multifaceted approach combined genetic, functional, and spatial analyses to provide a comprehensive understanding of the ADHD risk loci. This research methodology allowed us to bridge the gap between genetic discoveries and clinical understanding, offering valuable insights into the complexity of ADHD genetics and potential directions for future research in the realm of neurodevelopmental disorders.

Results

Functional Annotation and Similarity Grouping of ADHD-Associated Genes

In this study, we performed functional annotation and pathway enrichment analysis on genes associated with the 27 ADHD risk loci. We utilized the Shiny Gene Ontology (GO) tool (version 0.77) [7] to annotate and classify these genes based on their biological functions and molecular pathways. Genes examined are taken from a very recent study where they were identified as being associated with ADHD risk loci [6], (Supplementary Table 1).

To further expand on gene enrichment analysis, we categorized genes associated with ADHD risk loci into similarity groups based on shared characteristics, including chromosomal localization, gene function, and gene length. This classification revealed diverse functional roles among these genes (Table1).

Table 1. Gene classification into similarity groups [7]

Phosphates and Kinases:	**Enzymes and Ion Channel:**	**Trafficking and Signaling:**	**Motif Containing Proteins:**	**Transcription Factors:**
PTPRF	KDM4A	TRAIP	IQCF1	FOXP2
SNRK	ANO10	MON1A	IQCF2	VGLL3
CAMKV			IQCF3	NKX2-4
C8orf82			IQCF5	
Receptor Tyrosine Kinase and Lipid Metabolism:	**RNA and mRNA Degradation:**	**GTPase Activating Proteins and Receptors:**	**Miscellaneous Proteins:**	**Cell Adhesion and Extracellular Matrix Proteins:**
ABHD5	LSM6	ARHGAP39	METTL15	CDH8
MST1R	SLC10A7	SORCS3	POC1B	COL19A1
		DCC		

To better understand the functional roles of these genes, we classified them into similarity groups based on shared characteristics such as chromosomal localization, gene function, and gene length. This classification provides insights into potential functional relationships and shared biological processes among these genes, shedding light on their collective contribution to ADHD risk.

The fold enrichment values across different pathways were utilized to provide insights into the relative significance of each pathway within its respective gene category. While some pathways exhibited higher fold enrichments (e.g., Thyroid Cancer, VEGF signaling), others showed more modest enrichments (e.g., Breast Cancer, Pentose Phosphate Pathway). These trends could indicate the prominence of specific pathways in certain gene categories and guide future studies on their functional relevance.

Description of Functional Groups

Phosphates and Kinases

Genes: PTPRF, SNRK, CAMKV, C8orf82

This group encompasses a diverse set of phosphates and kinases with potential implications in cellular signaling and regulation. PTPRF, known for its involvement in neuropsychiatric disorders, showcases the intricate relationship between phosphatases and neurological processes [8] . SNRK, though less explored, holds promise as a kinase with potential roles in cellular functions [9] . CAMKV, on the other hand, is positioned at the intersection of neurodevelopment and kinase activity, underscoring its significance in shaping neural processes [10].

A) B)

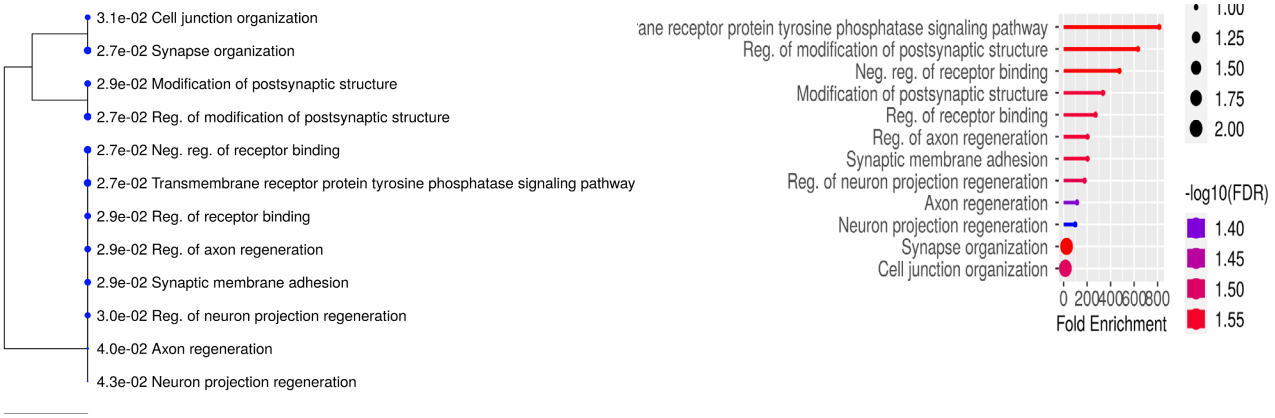

Figure 1. Summary information from gene enrichment analysis for genes relating to Phosphates and Kinases. A) Dendrogram of similarities for GO biological processes. B) Dotplot depicting enriched biological processes.

Enzymes and Ion Channel

Genes: KDM4A, ANO10

This group comprises enzymes and ion channels that play crucial roles in cellular processes, with potential implications in neuropsychiatric and neurodevelopmental contexts. KDM4A, an enzyme involved in histone demethylation, has garnered attention for its influence on gene expression and, by extension, neurodevelopment [11]. However, ANO10's association with neuropsychiatric or neurodevelopmental processes has not been heavily researched to discover its functions.

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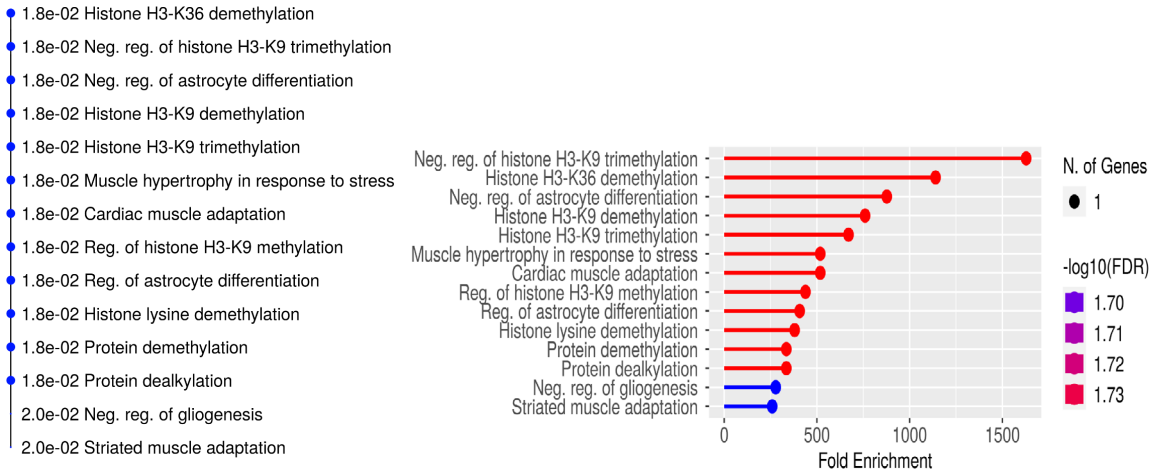

Figure 2. Summary information from gene enrichment analysis for a group of genes related to Enzymes and Ion Channels. A) Dendrogram of similarities for GO biological processes. B) Dotplot depicting enriched biological processes.

Trafficking and Signaling

Genes: TRAIP, MON1A

The group focusing on trafficking and signaling encompasses genes crucial for cellular processes, providing insights into their potential relevance to neuropsychiatric and neurodevelopmental contexts. TRAIP, involved in DNA damage response and cell cycle regulation, has recently gained attention for its potential contributions to neuronal functions [12] . MON1A, associated with endosomal trafficking, adds an intriguing dimension to this group, with studies suggesting its role in specific cellular functions or signaling pathways relevant to neurodevelopment.

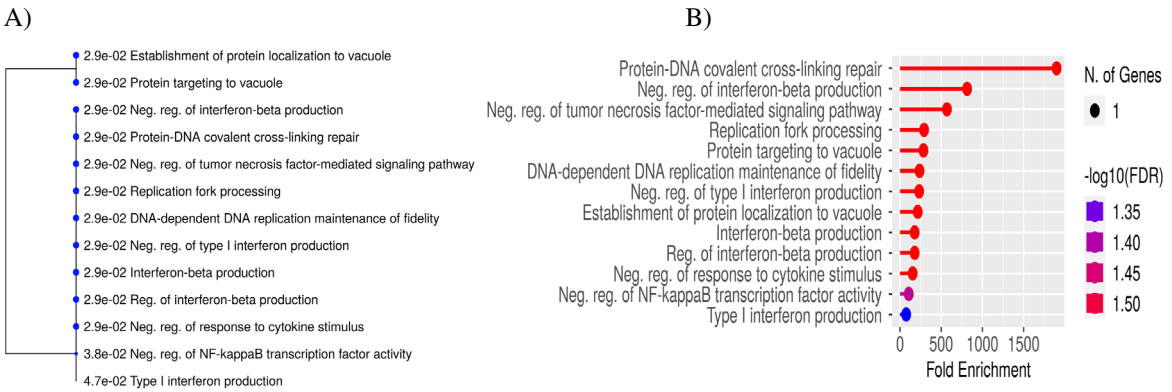

Figure 3. Summary information from gene enrichment analysis for a group of genes involved in Trafficking and Signaling. A) Dendrogram of similarities for GO biological processes. B) Dotplot depicting enriched biological processes.

Motif Containing Proteins

Genes: IQCF1, IQCF2, IQCF3, IQCF5

Motif-containing proteins within this group represent a set of intriguing players in cellular processes, with potential implications in neuropsychiatric and neurodevelopmental realms. IQCF1, IQCF2, IQCF3, and IQCF5, each harboring distinct motifs, contribute to the complexity of this group. While specific information about the association of IQCF1, IQCF2, IQCF3, and IQCF5 with neuropsychiatric or neurodevelopmental processes is less researched, their presence in the Motif Containing Proteins group indicates their potential involvement in intricate cellular processes.

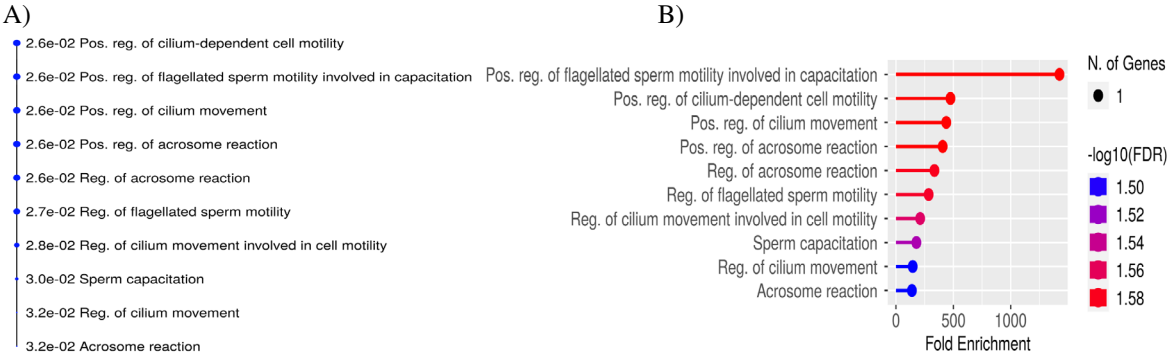

Figure 4. Summary information from gene enrichment analysis for a group of genes containing Motif's. A) Dendrogram of similarities for GO biological processes. B) Dotplot depicting enriched biological processes.

Transcription Factors

Genes: FOXP2, VGLL3, NKX2-4

This group of transcription factors constitutes key regulators in gene expression, offering crucial insights into their potential implications in neuropsychiatric and neurodevelopmental processes. FOXP2, recognized for its significance in language development, extends its influence to broader neurodevelopmental pathways [13]. Specific information about the association of VGLL3 and NKX2-4 with neuropsychiatric or neurodevelopmental processes has not been heavily researched.

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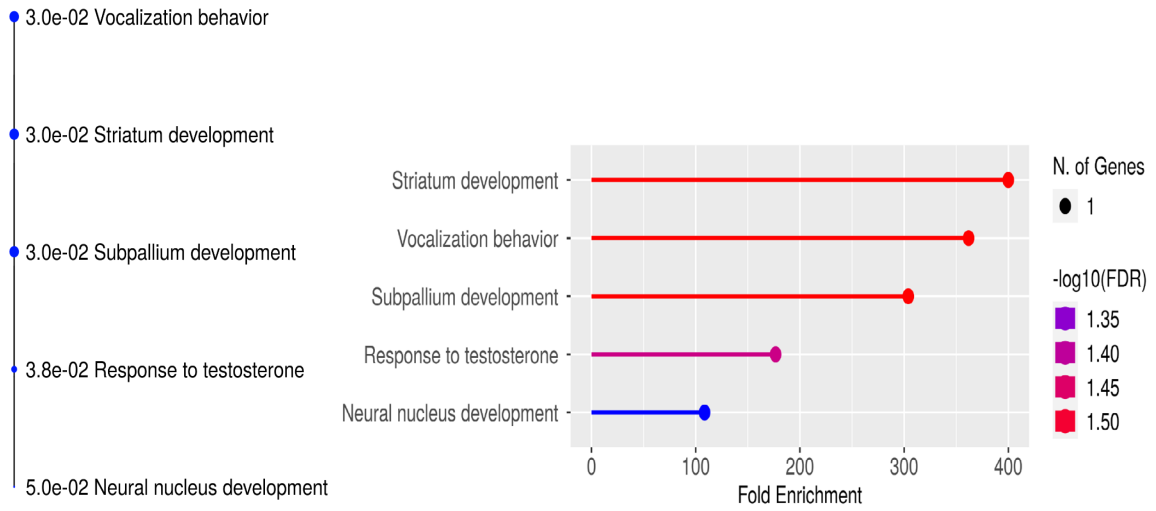


Figure 5. Summary information from gene enrichment analysis for a group of genes with Transcription Factors. A) Dendrogram of similarities for GO biological processes. B) Dotplot depicting enriched biological processes.

Receptor Tyrosine Kinase and Lipid Metabolism

Genes: ABHD5, MST1R

Within this group, the intersection of receptor tyrosine kinase activity and lipid metabolism unveils potential links to neuropsychiatric and neurodevelopmental processes. The convergence of receptor tyrosine kinase activity and lipid metabolism in this group presents an intriguing avenue for understanding how these processes collectively influence neural development and function. ABHD5 (CGI-58) is a key activator of adipose triglyceride lipase (ATGL), playing a crucial role in lipid metabolism by facilitating the breakdown of triglycerides into fatty acids [14]. MST1R (Macrophage Stimulating 1 Receptor) functions as a receptor for macrophage-stimulating protein (MSP), activating signaling pathways involved in cell survival, migration, and differentiation, with implications in tissue repair, inflammation, and cancer progression [15,16].

A) B)

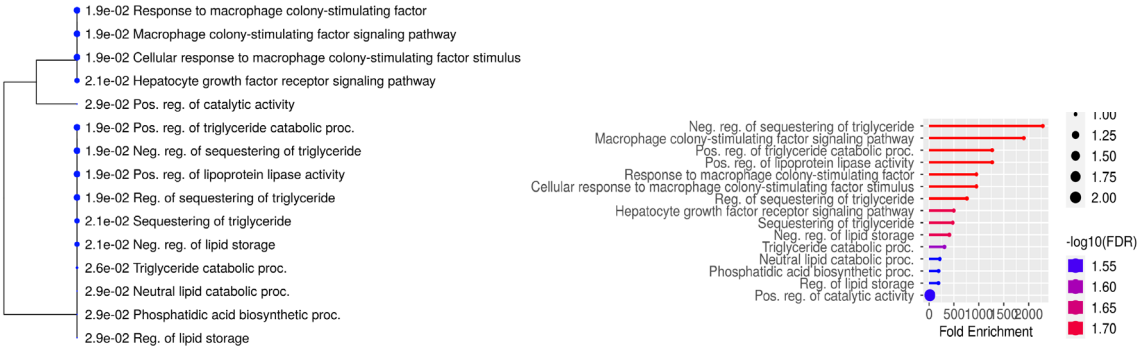


Figure 6. Summary information from gene enrichment analysis for a group of genes with Receptor Tyrosine Kinase and Lipid Metabolism relations. A) Dendrogram of similarities for GO biological processes. B) Dotplot depicting enriched biological processes.

RNA and mRNA Degradation

Genes: LSM6, SLC10A7

This group focuses on genes involved in RNA and mRNA degradation, shedding light on their potential significance in neuropsychiatric and neurodevelopmental contexts. LSM6 is involved in RNA degradation, contributing to the regulation of gene expression by facilitating the degradation of RNA molecules [17]. SLC10A7 plays a role in mRNA degradation, suggesting its involvement in controlling the levels of specific messenger RNA molecules within the cell. The intricate regulation of RNA and mRNA degradation by LSM6 and SLC10A7 underscores the importance of these processes in shaping neural functions.

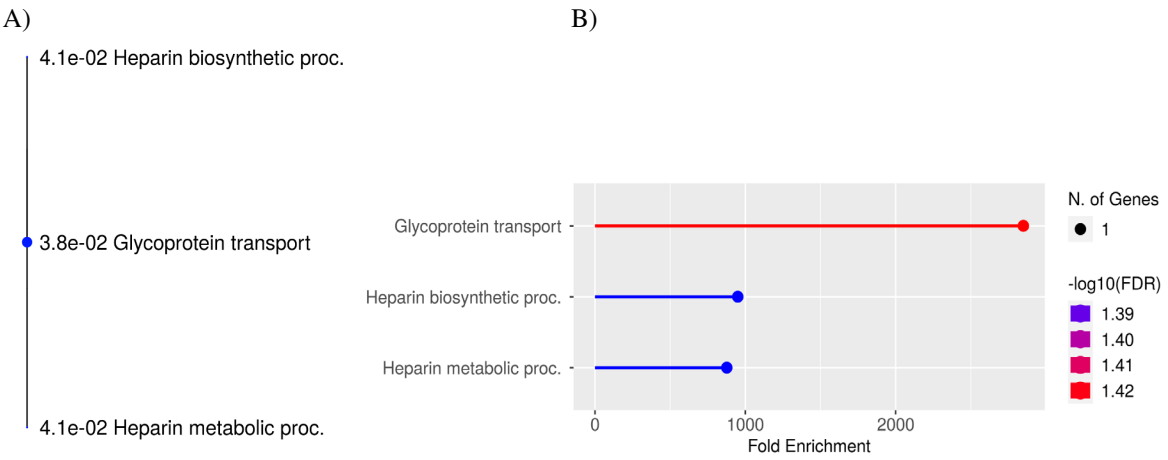


Figure 7. Summary information from gene enrichment analysis for a group of genes related to RNA and mRNA degradation. A) Dendrogram of similarities for GO biological processes. B) Dotplot depicting enriched biological processes.

GTPase Activating Proteins and Receptors

Genes: ARHGAP39, SORCS3, DCC

This group focuses on GTPase activating proteins (ARHGAP39) and receptors (SORCS3, DCC), presenting a diverse array of molecular players with potential implications in neuropsychiatric and neurodevelopmental processes. ARHGAP39 functions as a GTPase activating protein, regulating GTPase activity and influencing signaling cascades critical for neurodevelopment [18]. SORCS3, a receptor, plays a role in cellular processes, potentially contributing to diverse molecular mechanisms associated with neuropsychiatric and neurodevelopmental functions [19]. The convergence of GTPase activating proteins and receptors in this group underscores their collective influence on signaling cascades critical for neurodevelopment.

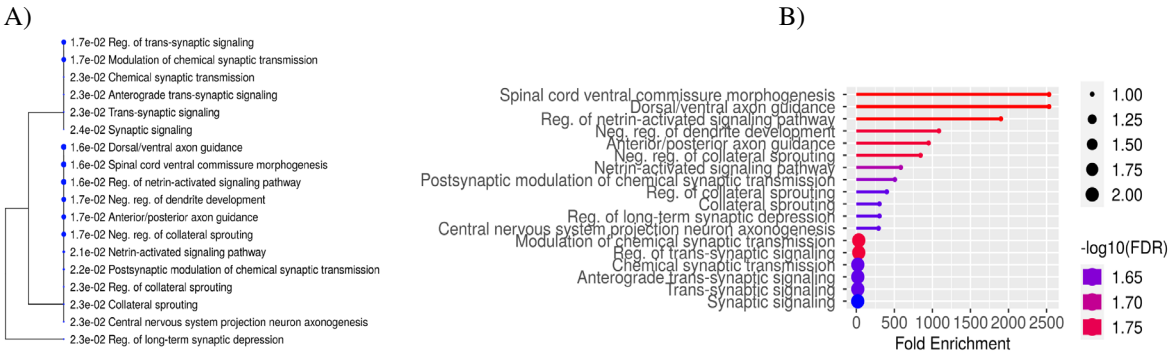


Figure 8. Summary information from gene enrichment analysis for a group of genes with relation to GTPase Activating Proteins and receptors. A) Dendrogram of similarities for GO biological processes. B) Dotplot depicting enriched biological processes.

Miscellaneous Proteins

Genes: METTL15, POC1B

This group encompasses miscellaneous proteins, METTL15 and POC1B, with diverse functions that may hold relevance to neuropsychiatric and neurodevelopmental processes. The diversity within this group highlights the complexity of molecular players with roles yet to be fully understood in the context of neural development and function.

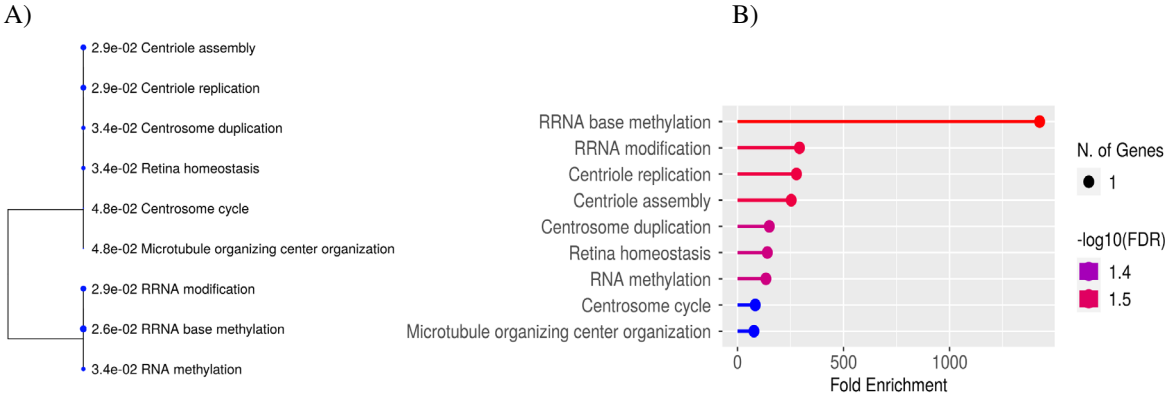


Figure 9. Summary information from gene enrichment analysis for a group of genes with non-specific functions. A) Dendrogram of similarities for GO biological processes. B) Dotplot depicting enriched biological processes.

Cell Adhesion and Extracellular Matrix Proteins

Genes: CDH8, COL19A1

This group focuses on cell adhesion and extracellular matrix proteins, specifically CDH8 and COL19A1, which play integral roles in cellular interactions and structural support. The interplay between cell adhesion and extracellular matrix proteins within this group suggests a collective impact on neural development and function. CDH8, a cell adhesion protein, is involved in cellular interactions and may contribute to neural development through its role in mediating adhesion between cells [20]. COL19A1, an extracellular matrix protein, likely plays a role in structural support, suggesting its involvement in shaping the extracellular environment and potentially influencing neural development and function [21]

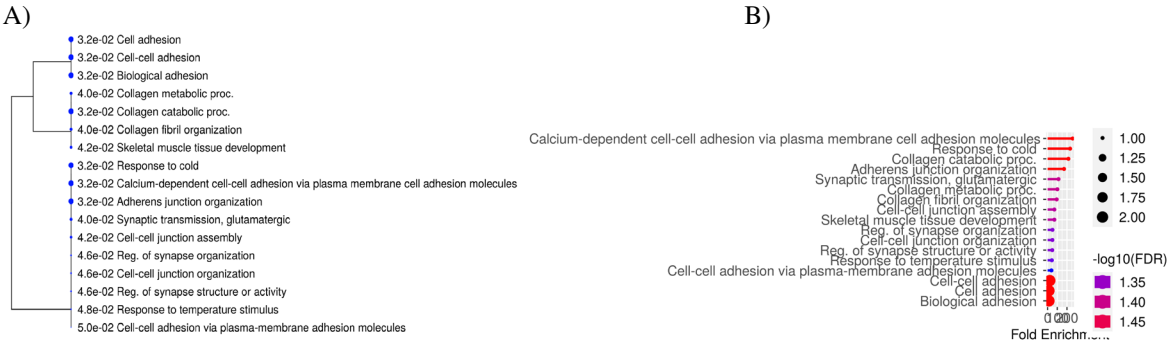


Figure 10. Summary information from gene enrichment analysis for a group of genes with functions relating to cell adhesion and extracellular matrix proteins. A) Dendrogram of similarities for GO biological processes. B) Dotplot depicting enriched biological processes.

Spatial Colocalization of Selected ADHD Risk Loci

In this study, we have analyzed the genomic locations of several genes to gain insights into their distribution across the human genome. The genomic coordinates of these genes were retrieved from the GRCh38/hg38 reference genome. The following genes and their respective genomic locations were examined (above) along with their spatial colocalization utilizing Hi-C datasets.

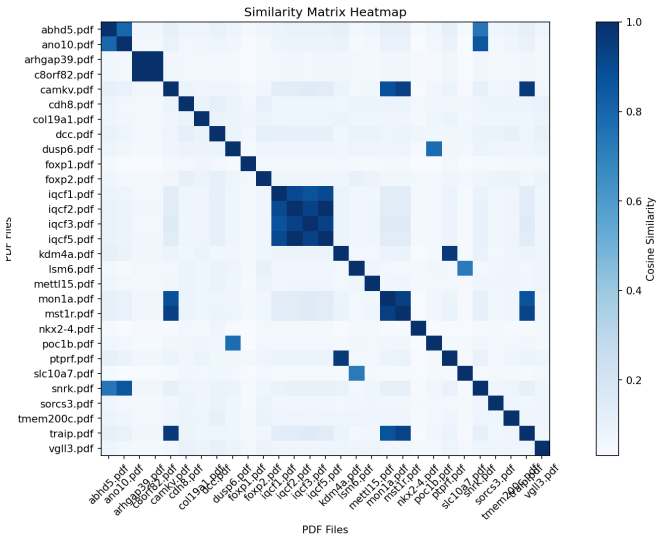


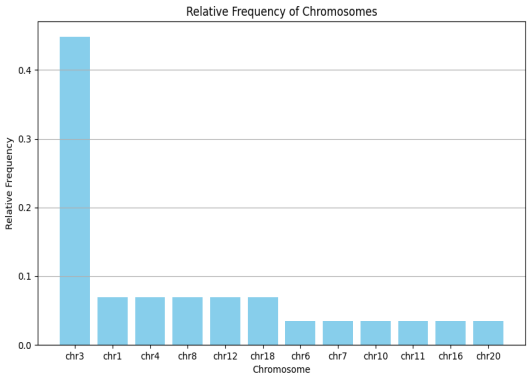
Figure 11. Text similarity comparison across Hi-C datasets.

The heatmap produced as a result of inputting a folder with pdf's of Hi-C datasets for previously examined genes associated with genomic risk loci that cause ADHD.

The provided code successfully analyzed Hi-C datasets represented in PDFs containing gene information. After calculating cosine similarities between the genes' descriptions, the code identified pairs of genes that were highly similar in terms of their functional context. Noteworthy findings include the similarity between ABHD5 and SNRK, ANO10 and SNRK, as well as the interconnectedness of CAMKV, TRAIP, MST1R, and MON1A, revealing potential functional relationships in these gene clusters. The script's heatmap visualization showcased the highlighted gene pairs with the highest cosine similarity scores, facilitating a quick grasp of the most closely related genes in the dataset.

The analysis of gene loci data reveals the distribution of genes across different chromosomes. The results, summarized in the table below, provide insights into the relative frequency of genes associated with each 18, 6, 7, 10, 11, 16, and 20 each have a lower relative frequency, with each contributing approximately 3.45% of the genes in the dataset.chromosome within the dataset.

A)



B)

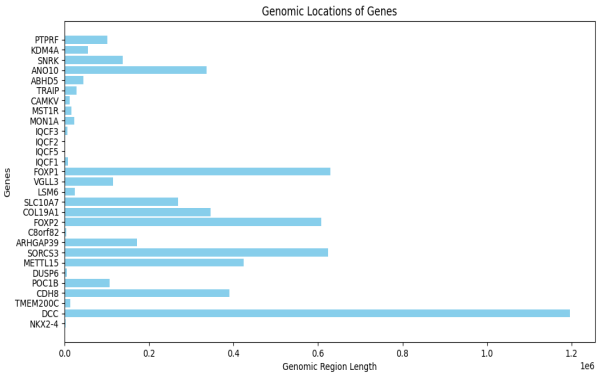


Figure 12. Chromosomal propositions of explored genetic loci. A) Relative frequency of explored genetic loci across human genome. B) Length of genomic region across which are selected genes spanning.

The results indicate that chromosome 3 (chr3) has the highest relative frequency, accounting for approximately 44.83% of the genes in the dataset. Chromosomes 1, 4, 8, 12, 18, 6, 7, 10, 11, 16, and 20 each have a lower relative frequency, with each contributing approximately 3.45% of the genes in the dataset.

Conclusion

This study provides a comprehensive spatio-functional annotation of 27 genetic loci associated with an increased risk of ADHD, shedding light on the intricate genetic underpinnings of this neurodevelopmental disorder. Through gene enrichment analysis and classification into similarity groups, we have gained valuable insights into the diverse functional roles of genes linked to ADHD, spanning neuronal functions, transcriptional regulation, receptor signaling, immune responses, DNA binding, and more.

Furthermore, our exploration of the spatial context of these genes using Hi-C datasets and 3D genome models has offered a glimpse into their potential regulatory interactions and chromatin-level contributions to ADHD etiology. This research bridges the gap between genetic discoveries and clinical understanding, providing a deeper comprehension of ADHD's genetic basis and paving the way for targeted therapeutic strategies.

The findings presented here not only enhance our knowledge of ADHD but also hold promise for future interventions aimed at benefiting individuals affected by this disorder. By unraveling the intricate interplay between genetics, brain function, and ADHD, this study opens avenues for precise and effective treatments. Ultimately, this research advances our understanding of the complexity of ADHD and points towards promising directions for future research in the field of neurodevelopmental disorders.

Acknowledgments

I would like to thank my advisor for the valuable insight provided to me on this topic.

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