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Article

Mendelian randomization reveals shared genetic landscape in autism spectrum disorder and Alzheimer's disease

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SUMMARY

Autism Spectrum Disorder (ASD) and Alzheimer's Disease (AD) represent the most common neurodevelopmental and neurodegenerative disorders, respectively. ASD and AD are considered disparate diseases given the differences in age at manifestation and disease phenotypes. However, AD may be related to ASD, as recent studies showed that adults with ASD are 2.5 times more likely to develop AD than age-matched controls without ASD. While some studies have implicated environmental factors in ASD-AD comorbidity, it is unknown whether genetics play a role in the increased risk of AD in ASD. Here, we hypothesized that the shared genetic factors are responsible for an increased risk of AD in ASD. To determine whether ASD and AD are genetically linked, we preformed genome-wide association studies (GWAS), revealing genomic loci across the human genome that are associated with ASD or AD. Subsequently, we performed Mendelian randomization (MR) analysis to evaluate the causal effect of ASD (exposure) on AD (outcome). Interestingly, MR analysis showed significant horizontal pleiotropy, suggesting the existence of shared genetic components between ASD and AD. In support, variant-to-gene mapping and gene ontology analysis showed that pathways involved in synaptic regulation were significantly enriched in both ASD- and AD-associated SNPs. Together, these data imply that shared genetic factors related to synaptic regulation may contribute to an increased risk of AD in individuals with ASD, providing insights into underlying disease mechanisms.

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder affecting over 75 million individuals in the world today (0.76% global prevalence). ASD features a wide spectrum of symptoms, including delayed learning skills, repetitive behaviors, and unusual emotional patterns (1). While palliative treatments to alleviate symptoms of ASD like behavioral therapy exist, there are currently no effective strategies to treat ASD directly (2). Family studies have revealed that ASD has a high heritability (40-80%), suggesting a substantial genetic contribution to ASD (3-5). In support, genome-wide association studies (GWAS) have identified many genetic loci associated with ASD, with some studies discovering shared genetic risk variants in ASD (6).

Although such discoveries have significantly widened our knowledge of ASD, they still do not fully explain certain aspects of ASD, such as comorbidity patterns. For example, individuals affected by ASD are more likely to develop symptomatically and temporally related medical conditions such as epilepsy and attention deficit hyperactivity disorder (ADHD) compared to non-ASD individuals (7). Studies suggest that comorbidity in ASD is attributable to common environmental exposures and genetic factors (8-10). Notably, patients with ADHD and ASD have been found to share risk genes at several genetic loci, suggesting the possibility of shared underlying genetics in diagnostically similar disorders (11).

Interestingly, a recent study has also discovered an increased occurrence of outwardly unrelated disease in ASD; for example, adults with ASD are 2.5 times more likely to develop Alzheimer's disease (AD) compared to age-matched controls (12). Some studies have attributed the comorbidity between ASD and AD to the interactive role of genetic and environmental factors (13). However, it is unclear whether shared environmental factors (i.e. airborne pollutants, lifestyle choices, etc.) explain most of the increased risk of AD in ASD considering that both ASD and AD are multifactorial and display similar clinical phenotypes (i.e. dementia, cognitive impairment, and speech impairments), yet commonly manifest at two opposing ends of the lifespan (i.e. childhood and post-adulthood, respectively) and are diagnosed at different times with different diagnostic criteria and treatments strategies (13-16). As such, determining whether environmental or genetic factors play a larger role in the ASD-AD comorbidity requires further investigation. Interestingly, recent genome wide association studies (GWAS) with a focus on ASD or AD revealed genetic factors (i.e. Single Nucleotide Polymorphisms (SNPs), genetic loci) that suggest a shared genetic landscape in ASD and AD (17; 18). However, these studies do not directly investigate the genetic etiology of the comorbidity between ASD and AD, which therefore remains to be investigated.

To formally investigate the ASD-AD comorbidity, we hypothesized that shared genetic factors may contribute to an increased risk of AD in ASD. Since understanding the underlying reason for ASD's comorbidity patterns may shed light on the mechanisms of ASD and therefore inform potential therapeutics, we set out to identify shared genetic factors that contribute to increased AD in ASD through genetics approaches such as a genome-wide association study (GWAS), Mende-

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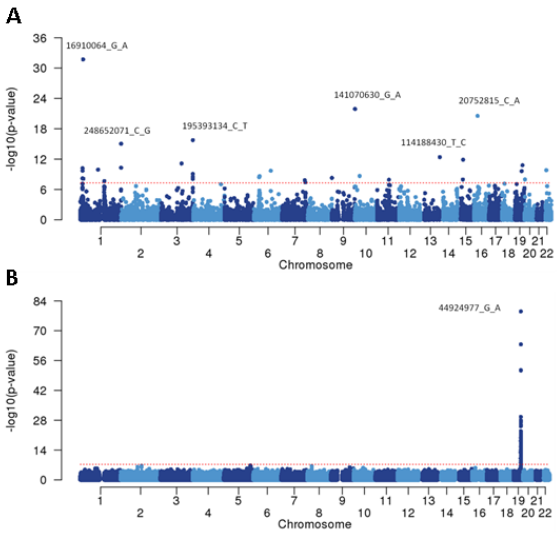

Figure 1: Discovery of ASD-associated and AD-associated SNPs by GWAS. GWAS Manhattan plots show significance (i.e., -log10(p-value); Y-axis) vs. locus (i.e., SNP location; X-axis) for ASD (A) and AD (B) in the logistic regression analysis to discover ASD-associated and AD-associated SNPs. Blue circles above the dotted red line denote SNPs significantly associated with their respective disease outcome. The most significantly associated SNPs for both ASD and AD are specifically identified.

lian Randomization (MR), and pathway analysis. Through this pipeline, we discovered the presence of pleiotropic genetic factors (i.e. shared outlier SNPs) commonly enriched in synaptic dysregulation between ASD and AD. These findings suggest a shared genetic landscape in the ASD-AD comorbidity, which may provide unique opportunities for additional genetic investigation into the underlying mechanisms of ASD.

RESULTS

Identification of SNPs associated with ASD or AD

Firstly, we performed a genome-wide association study (GWAS) to discover genetic loci associated with ASD or AD, and then compared their genetic underpinnings. Following initial imputation and quality control analysis of ASD whole exome data and AD whole genome SNP data, GWAS logistic regression analysis results did not show significant statistical inflation as evidenced by quantile-quantile plots and genomic inflation factors (ASD genomic inflation factor, 0.858; AD genomic inflation factor, 1,031). Subsequent Manhattan plotting revealed several significantly associated ($p<0.01$) SNPs for ASD (n=463) or AD (n=80,463) (**Figure 1**). For example, SNPs on chromosomes 1, 3, 10, 14, and 16 yielded genome-wide significant association signals in ASD GWAS, meaning those genetic loci are significantly associated with ASD (i.e. loci that have high probability to contain causal ASD genetic variations) (**Figure 1A**). Notably, the APOE

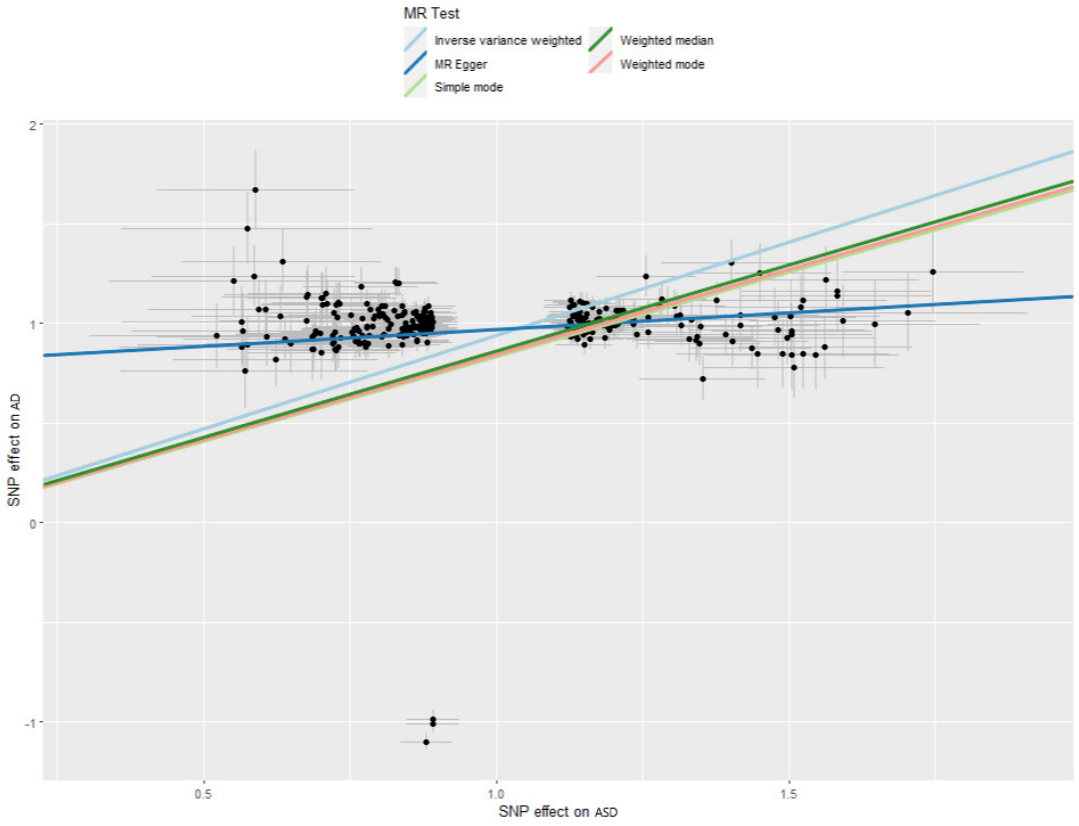

Figure 2: MR analysis to determine the causal effect of ASD on AD. ASD-associated SNPs with association level p-value < 0.01 (463 SNPs) were selected for MR analysis and are indicated by the black dots. ASD was selected as exposure and AD was selected as outcome. The slope of each colored line represents estimated causal effect, beta. MR tests all illustrate significant causal relationship between ASD and AD. For example, MR Egger (indicated by the dark blue line) demonstrated a p-value of 0.028. Other MR tests including Inverse variance weighted, Simple mode, Weighted median, and Weighted mode demonstrated p-values of 0, 2.08e-244, 0, and 4.86e-275 respectively.

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(Apolipoprotein E) locus on chromosome 19 produced very strong association signals (p-value ~1E-80) in AD GWAS as expected (**Figure 1B**) (19).

MR analysis and subsequent tests of pleiotropy

As GWAS did not reveal direct similarity between ASD and AD, we performed Mendelian randomization (MR) analysis using the GWAS data to determine whether ASD plays a causal role in the development of AD (20). MR uses genetic variations as instrumental variables, and therefore are less likely to be influenced by confounding factors including age, intelligence quotient (IQ), or educational attainment (21). Briefly, we set ASD as an exposure and AD as an outcome in the two sample MR method (22). The MR revealed a significant causal relationship between ASD and AD (p-value=0.028) **(Figure 2)**. We also performed MR analysis using AD as an exposure and ASD as an outcome to test the possibility of horizontal pleiotropy, where the same genetic factors result in different disease outcomes. Interestingly, this analysis also revealed a significant relationship (p-value=7.1E-6), supporting the presence of pleiotropy **(Figure 3)**. Since pleiotropy suggests shared genetic components between ASD and AD, we formally tested the significance of pleiotropy, revealing an Egger intercept (a measure of the average pleiotropic effect of a genetic variant in the MR) of 0.938. This deviated significantly from 0, indicating significant horizontal pleiotropy between ASD and AD. In the context of exposure and outcome, significant levels of horizontal pleiotropy indicated the presence of shared independent genetic factors (i.e. SNPs) directly or indirectly (through other traits) driving MR analysis in place of a causal relationship of ASD on AD.

SNP to gene mapping to identify shared genetic factors

Our MR analysis did not establish a causal link between ASD and AD because MR analysis revealed significance when using either ASD as an exposure and AD as an outcome or MR analysis using AD as an exposure and ASD as an exposure. Rather, our data indicated significant pleiotropy, which implied shared genetic components. Associated SNPs with a significance level of p-value < 0.001 for ASD (n=112) and p-value < 0.0001 for AD (n=948) were then selected for variant-to-gene mapping, which resulted in 25 candidate ASD-associated and 24 AD-associated genes. Furthermore, based on the odds ratio, the candidate genes were sorted based on risk effect (odds ratio > 1) or protective effect (odds ratio < 1) on ASD or AD. This resulted in 15 ASD-associated risk genes, 10 ASD-associated protective genes, 16 AD-associated risk genes, and 8 AD-associated protective genes **(Table 1)**. Of these candidate genes, notable ASD-associated genes include CHD8 and KANSL1, which have been well documented as ASD-associated risk genes (23). In addition, APOE2 and APOE4 are candidates which have also been

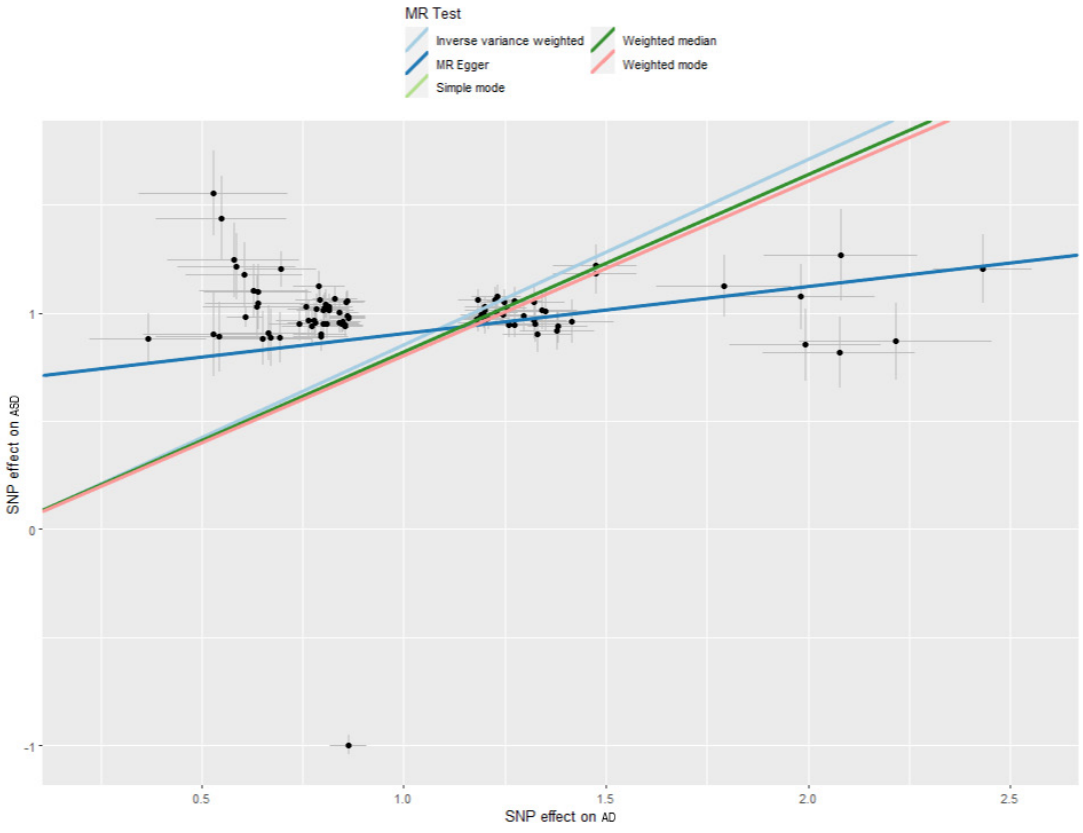

Figure 3: MR analysis to determine the causal effect of AD on ASD. To validate the directionality of the causal relationship of ASD onto AD, a subsequent MR with AD as exposure and ASD was performed. The slope of each colored line represents estimated causal effect, beta. MR tests all illustrate a significant causal relationship between AD and ASD. For example, MR Egger (indicated by the dark blue line) demonstrated a p-value of 7.1E-6. Other MR tests including Inverse variance weighted, Simple mode, Weighted median, and Weighted mode all demonstrated p-values of 0.

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ASD Candidate genes		AD candidate genes	
ASD risk genes	ASD protective genes	AD risk genes	AD protective genes
CUX1	PRAMEF4	CDH23	GRIP1
TRMT11	ARMC4	CLPTM1	BCL3
MAPT	OR2T33	TOMM40	ABCA4
PLEKH	OTOA	CD177	SLC9A4
CCSER1	PCDHB11	BCAM	ADAMTS17
BCO1	LIFR	ADAMTS	1QCK
CRHR1	PDE4DIP	NECTIN2	APOC1
HLA-A	CYP2A6	PPP1R37	APOE2
CES3	OR5H1	PVR	
SYCP1	RFPL4L1	KIRREL2	
SPPL2C		CLASRP	
MLH3		APOE4	
KANSL1		RELB	
NINL		APOC4	
CD8B		FGD4	
		OR51L1	

Table 1: Variant to gene mapping of ASD-associated and AD-associated genes. Significantly associated SNPs from ASD and AD GWAS were mapped to their respective genes for 25 ASD-associated and 24 AD-associated candidate genes. Risk and protective genes were determined using odds ratio (i.e. odds ratio > 1 is risk; odds ratio < 1 is protective). There are no shared candidate genes between ASD and AD.

well-documented in scientific literature (24).

Pathway analysis of ASD-associated and AD-associated genes

Significant pleiotropy in our MR analysis supported shared genetic factors in ASD and AD. However, genes mapped from associated SNPs did not reveal shared genes between ASD and AD. Thus, to gain insights into the biological pathways of ASD and AD and to determine whether ASD and AD shared polygenic pathways despite possessing non-overlapping risk genes, gene ontology (GO) pathway analysis was performed. The 25 ASD genes showed significant fold enrichment and statistical significance (false discovery rate < 0.05) for biological pathways related to synaptonemal complex assembly and synaptonemal complex organization **(Figure 4)**. The 24 AD genes showed significant fold enrichment and statistical significance (false discovery rate < 0.05) for biological pathways related to cell migration in brain, cell axon guidance, and synapse organization **(Figure 5)**. As pathways related to synaptic regulation were significantly enriched in both ASD- and AD-associated genes, our data suggested an important role for synaptic regulation in ASD-AD comorbidity.

DISCUSSION

Understanding the mechanisms that are responsible for comorbidities in individuals affected by ASD will shed light on the fundamental biology of ASD and thus may inform therapeutic strategies for this widespread medical condition. Although the increased prevalence of related neurologic disorders (e.g. ADHD, epilepsy, and obsessive-compulsive disorder) have been well documented in the literature, the underlying etiologies behind such comorbidity still remain unexplained (7). For example, individuals diagnosed with ASD were found to be at 2-fold higher risk of developing obsessive-compulsive disorder (OCD) later in life. However, the etiological mechanisms behind this comorbidity have yet to be explained (25). Likewise, up to 70% of children with disruptive mood dysregulation disorders like ADHD also satisfy criteria for ASD. Although similar diagnostic criteria for ASD and ADHD may explain this phenomenon, the underlying pathophysiological features that explain this high prevalence have yet to be fully studied Interestingly, shared pleiotropic genomic loci were recently discovered between ASD and ADHD, with ADHD conferring a causal effect on ASD (11). Such a discovery suggests the presence of shared genetic factors in ASD and diagnostically similar neurologic disorders. However, the extent of the effect that these genetic factors have on comorbidity between ASD and ADHD remains to be investigated. Importantly, as diagnoses for ASD and ADHD become more specific with improved diagnostic criteria and awareness, the extent of the genetic role in the ASD-ADHD comorbidity can become more discernable.

In contrast to the above examples, which show comorbidity of similar medical conditions with ASD, an increased prevalence of AD with ASD cannot be explained by such diagnostic similarities, as ASD and AD have disparate diagnostic criteria and share different treatment strategies. Also, our MR analysis showed that ASD does not exert causal effects on AD as the MR Egger intercept showed significant horizontal pleiotropy. Instead, our data indicated the existence of shared genetic factors between ASD and AD and suggested that dysregulation of a similar biological pathway may lead to ASD and AD. For instance, our Gene Ontology (GO) analysis revealed the enrichment of pathways related to the regulation of synapses in the ASD and AD GWAS data. Since current literature suggests that ASD features increased synaptic connection due to decreased synaptic pruning and AD shows decreased synaptic connections due to neuronal loss, GO implies that pathways related to synaptic regulation explains at least some part of the comorbidity patterns (26-30). However, it should be noted that due to the correlative nature of GWAS, the candidate genes discovered through GWAS which are suggested to be enriched in pathways relating to synapses through GO are not direct causal pathways of ASD and AD. As such, further investigations into specific gene pathways are warranted.

Interestingly, although they yielded similar pathways, ASD and AD did not share any candidate risk or protective genes. However, among the candidate genes exists genes that have direct correlation with synaptic regulation. For example, for

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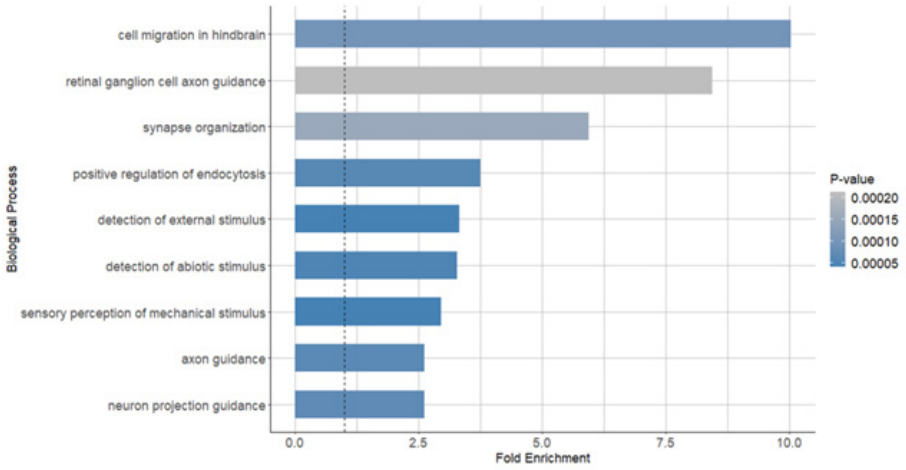

Figure 5: Significantly enriched biological pathways in AD-associated genes. ASD and AD-associated candidate genes were searched with GO to identify significantly enriched biological processes. The horizontal axis represents fold enrichment. The color or bars reflect the levels of significance, and the dotted line is y-intercept equals 1, providing a general reference to the scaling of fold enrichment.

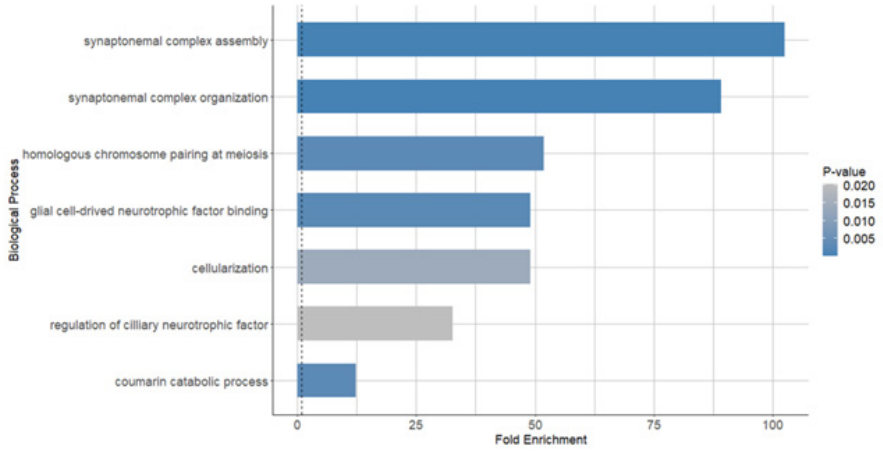

Figure 4: Significantly enriched biological pathways in ASD-associated genes. ASD and AD-associated candidate genes were searched with GO to identify significantly enriched biological processes. The horizontal axis represents fold enrichment. The color of each bar reflect the levels of significance, and the dotted line indicates a fold enrichment of 1, providing a general reference to the scaling of fold enrichment.

AD, we chiefly detected APOE, a notable AD risk gene that has been suggested to initiate synaptic dysfunction and neurodegeneration in AD (19; 31). Interestingly, for ASD, we detected MAPT as a candidate risk gene. Importantly, MAPT, which encodes the microtubule-associated protein tau, has been shown to be linked to AD, and recently, ASD (32-34). Interestingly, we did not detect MAPT as a significant gene in AD GWAS, which is validated by other scientific literature which performed GWAS using ADGC data (35). The discovery of such candidate genes and biologic pathways related to synaptic regulation in ASD and AD are significant as they suggest a role of synaptic regulation in neurologic conditions like ASD and AD.

Similar examples of synaptic regulation in neurologic conditions are also found in the literature. Approximately 2-3% of all patients with ASD develop Fragile X Syndrome (FXS), which can be explained by abnormal patterns of neural "wiring" or connectivity (36). Such abnormal connects are suggested to arise from mutations in *FMR1*, which is a critical factor in the development of synapses (37-39). Interestingly, FMRP Knockout mice have also shown autistic-like behaviors, with impaired synaptic plasticity alterations in dendritic morphology and neurocognitive deficits (40-42). These observations suggest that quite distinct disease outcomes might occur due to a shared genetic underpinning in synaptic function (10). Similarly, a mechanism that potentially explains increased AD in ASD is the hyper-connectivity of neurons or lack of synaptic pruning, (i.e. the natural process by which excess neuronal connections are removed) in ASD, versus the synaptic loss caused by neurodegeneration in AD (28; 29). Here, it is suggested that synaptic dysfunction (i.e. synapse hyperconnectivity or synapse loss) is the shared pathway between ASD and AD, and may a precursor to other neurodevelopmental or age-related disorders (43). Intriguingly, although ASD was reported to increase risk of AD, the disparate synapse mechanisms of ASD and AD suggest a

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protective effect of ASD on AD. It is currently unknown whether synaptic dysfunction is responsible for such a phenomenon, but further investigations into the effect of synaptic dysfunction in ASD and AD are warranted. Therefore, it will be important to key synaptic regulation genes whose functions promote synaptic pruning and protect synaptic loss. Furthermore, due to the disparate manifestation of ASD versus AD, it may be informative to investigate changes in gene expression of ASD and AD risk and protective genes in the human lifespan. Additionally, investigating gene products (i.e. transcription factor or synaptic proteins) of specific candidate genes can help understand the genetic underpinnings of the comorbidity between ASD and AD.

In summary, investigating various ASD comorbidities presents a unique opportunity to reveal underlying mechanisms in ASD. While comorbidities with similar psychiatric disorders have been well documented (i.e. ADHD and epilepsy), an increased risk of ASD in ASD is an intriguing phenomenon that features comorbidity of apparently different diseases. Our investigation highlighting the presence of shared genetic factors between ASD and AD, therefore, may provide insights into how to modify disease without effective treatments.

MATERIALS AND METHODS

Genotype data

The Autism Sequencing Consortium (ASC) has a collective goal of compiling Autism Spectrum Disorder (ASD) samples and genetic data for sequencing approaches to resolve a substantial fraction of genetic factors involved in ASD (44). Recent whole-exome case-control, parent offspring trio data generated by ASC provides sequencing data for 3,247,511 SNPs across 9,778 de-identified patients (3,783 female and 5936 male, from age 1 to 37) for association analysis. The Alzheimer's Disease Genetics Consortium (ADGC) aims at identify genetic variants associated with risk for Alzheimer's Disease (AD) [43]. Recent whole-genome case-control data generated by ADGC provides sequencing data for 7,986,401 SNPs across 6,065 de-identified patients for association analysis (2,595 female and 3,470 male, from age 38 to 89).

Quality control and genotype imputation

Original genotype data for ASD (12,772 de-identified patients) and AD (6,065 patients) were subject to quality control (QC) analysis to generate the data that were compatible with genotype imputation. During AC, we included SNPs with SNP minor allele frequency (MAF) greater than 1% to exclude rare variations, SNP missing call rate less than 5%, and Hardy Weinberg Equilibrium p-value greater than 1e-6 (45). After QC, genotype imputation was performed using the TOPMed Imputation Server (46). The TOPMed data of 133,597 human genomes containing 445,600,184 genetic variants were used as the reference panel.

Identification of ASD- or AD-associated SNPs through GWAS

To identify ASD- or AD-associated variants, imputed genotypes for ASD and AD data were analyzed. Briefly, we used the PLINK program to perform logistic regression analysis to determine the levels of significance of each SNP (47). During logistic regression, genetic ancestry inferred from the genotype data was used as one of the covariates in PLINK Principal Component Analysis (PCA).

Mendelian Randomization of ASD-associated SNPs and AD-associated SNPs

Utilizing the TwoSample MR package in R, Mendelian randomization (MR) analysis was performed using our GWAS summary statistic data (48). To test the causal effect of ASD on AD, instrument SNPs from ASD and AD GWAS data were first extracted from both ASD (exposure) and AD (outcome) summary data. Subsequently, the exposure and outcome data was harmonized to ensure the effect of the SNP on the exposure and outcome correspond to the same allele. Lastly, MR was performed with MR scatterplot of results being plotted. Subsequently, a separate MR test was performed to validate the directionality of the causal relationship between ASD and AD, with AD being set as the exposure and ASD as the outcome. Among various MR algorithms, we used the 'MR Egger' approach, which can robustly detect pleiotropic effects at the expense of a weaker InSIDE assumption (49). In both tests, Egger method was used to determine a p-value adjusted to overall directional pleiotropy. Subsequently, given exceedingly significant p-values in both directions, horizontal pleiotropy test was performed using the "mr_plieotropy_test" function to assess whether shared variants between ASD and AD led to significant results.

Gene ontology pathway analysis

Gene ontology analysis was performed to identify biological pathways that are highlighted in the ASD-associated and AD-associated genes. Briefly, 24 ASD-associated and 24 AD-associated candidate genes were input into the gene ontology resource, which is powered by PANTHER (50; 51). Specifically, we selected the 'biological processes' and 'Homo sapiens' to identify pathways that were enriched in the candidate ASD-associated and AD-associated genes. We considered pathways that generated a false discovery rate less than 0.05 as significant.

Multiple test correction

Since GWAS performed several sequential tests for each SNP, the identification of candidate ASD-associated and AD-associated genes were corrected via Bonferroni method to get adjusted p-values. Mendelian randomization utilized previously generated summary statistic data from ASD and AD GWAS and thus did not require an adjusted p-value. The significance of Gene Ontology analysis was corrected via Bonferroni method for multiple testing. We used R version 4.1.0 for all statistical analyses.

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