PERSPECTIVE

Major psychiatric and neurodegenerative illnesses share common pathways

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ABSTRACT

The focus of our research is on whether common psychiatric and neurodegenerative disorders share pathogenesis while having similar epidemiological risks. We discover eight significant genetic associations between psychiatric and neurodegenerative disorders using 25 GWAS results and LD score regression. To identify cis- and trans-transcripts and proteins that are compatible with a pleiotropic or causal function in each disease, we combine the GWAS data with human brain transcriptomes (n=888) and proteomes (n=722); these proteins are referred to as causal proteins for brevity. We discover a wide variety of unique and common causative proteins within each illness group. Surprisingly, psychiatric illnesses and neurodegenerative diseases share 30% of the causative proteins. Furthermore, compared to what would be expected by chance, we discover 2.6 times more protein-protein interactions among the psychiatric and neurodegenerative causative proteins. Our findings collectively imply that many psychiatric and neurodegenerative disorders share genetic and molecular pathogenesis, which has significant implications for early diagnosis and the development of therapeutics.

INTRODUCTION

Multiple lines of evidence connect late-life neurodegenerative illnesses with psychiatric disorders that normally present in ea--rly or middle adulthood. The neurodegenerative diseases include alzheimer's disease, lewy body dementia, parkinson's disease, amyotrophic lateral sclerosis, and frontotemporal dementia. The psychiatric disorders include major depressive disorder, bipolar disorder, schizophrenia, anxiety disorders, post-traumatic stress disorder, and problematic alcohol use. First, those who have one of these psychological disorders are up to four times more likely to go on to acquire dementia or another neurodegenerative disease in later life. Second, debilitating psychiatric symptoms are experienced by roughly 65% of those who have a neurodegenerative disease over the course of the illness. Third, current research reveals that schizophrenia and parkinson's disease are both inherited risks. Given these associations, we proposed that these psychiatric and neurodegenerative illnesses share a genetic and molecular foundation.

New, potent treatments for both the psychiatric and neurodegenerative diseases as well as for the psychiatric symptoms that occur as a result of the neurodegenerative diseases may be developed as a result of insights into pathways shared by these psychiatric and neurodegenerative diseases. Dementia and neurodegeneration risk may be reduced by treatments for early- or mid-adulthood psychiatric illnesses that target the common processes because many neurodegenerative diseases have an incubation period of ten years or more prior to symptoms. For the development of new drugs to treat various brain diseases, brain proteins are interesting targets. The majority of current drug targets are proteins since they are frequently the ultimate executors of cellular processes or biological functions and are typically stable. Additionally, neurodegenerative illnesses frequently exhibit aberrant protein accumulation, conformations, and interactions. The difficulty that brain mRNA levels are typically not strongly connected with brain protein abundance can be avoided by studying brain proteins directly rather than transcripts. This is likely because of multiple tiers of post-transcriptional, post-translational, and post-translational control. Here we use two methods to investigate the idea that some psychiatric and neurodegenerative disorders have a common genetic and molecular foundation. First, using LD score regression and the most recent data from Genome-Wide Association Studies (GWAS), we conducted a thorough pairwise genetic link between the aforementi-

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-oned psychiatric and neurodegenerative disorders. As certain brain structural alterations in specific regions may either predispose to illness or result from the illness (for example, hippocampus and Alzheimer's disease), we also included this variation to help assess these relationships. This amount of genetic connection spans the entire genome. Second, we integrated each GWAS result with the largest set of thoroughly profiled human brain proteomes (n=722) using multiple complementary approaches, including Proteome-wide Association Study (PWAS), Mendelian randomization, and genetic colocalization analysis. Our goal was to identify specific genes that specifically confer disease risk through their effects on brain protein abundance. The discovery of proteins that are consistent with pleiotropy or a causative function in each disease was made possible by the three analytical methodologies used in a sequential fashion (and will be referred to as consistent with a causal role or causal proteins for simplicity henceforth). We identified shared and unique causal proteins for the proteins involved in the pathogenesis of the studied psychiatric and neurodegenerative conditions, and we looked for evidence of enrichment of physical protein-protein interactions, which would be expected for proteins involved in the same molecular or biological pathways. To add additional layer of support, we later used the same analytical pipeline on 888 human brain transcriptomes. Our findings opened the door for precision medicine and the creation of new treatments by implicating several unique and shared causative brain proteins and illuminating probable shared pathways among various psychiatric and neurodegenerative illnesses.

RESULTS

Study designs

We used the most recent GWAS results for five neurodegenerative diseases (Alzheimer's Disease (AD), Lewy Body Dementia (LBD), Frontotemporal Dementia (FTD), Amyotrophic Lateral Sclerosis (ALS), Parkinson's Disease (PD), and eight psychiatric traits, Major Depressive Disorder (MDD), Bipolar Disorder (BD), schizophrenia, anxiety, anxiety, Post-traumatic Stress Disorder (PTSD), alcoholism, neuroticism, and insomnia Because the two GWAS for AD had different study designs, we included them both. The other used a sizable part of people from the UK Biobank using family history of dementia as proxy-cases or controls. One study concentrated only on clinically diagnosed AD. We initially determined whether there is a shared genetic foundation between these psychiatric and neurodegenerative illnesses by looking at pairwise genetic correlations between these brain features using LD score regression based on these GWAS results. Then, using a combination of PWAS, Summary data-based Mendelian Randomization (SMR), and colocalization analysis, we integrated 722 deep human brain proteomes with results from each GWAS to identify cis- and trans-regulated brain proteins that are compatible with a causal role in each trait. We looked at brain expression by area and cell type and checked for evidence of protein-protein interactions for brain proteins with evidence supporting a causal involvement within and among the groupings of features (PPI). Lastly, to discover shared mechanisms between the examined psychiatric and neurodegenerative disorders, we gathered biological processes from these shared causative proteins and PPI networks.

Brain structural, neurodegenerative, and psychiatric groups' genetic relationships with one another

We used LD score regression to evaluate genetic associations between variables within and within the groups of psychiatric, neurodegenerative, and brain structural phenotypes. Participants of European heritage provided the GWAS summary statistics that we used. By design, the LD score regression method is resistant to sample overlap in GWAS and reduces the possibility of bias due to variations in LD structure. We discovered a considerable number of favourable genetic associations between the brain structures and psychiatric diseases, which is in line with previous research.

Cis-regulated proteins that are compatible with a causal involvement

We looked for specific genes that impart disease risk through their effects on brain protein abundance in order to add to the evidence that psychiatric and neurodegenerative diseases share a genetic foundation. In order to achieve this, we used 722 reference human brain proteomes in a PWAS of each brain trait to discover the cis-regulated proteins connected to each feature. With the aid of tandem mass tag mass spectrometry, the brain proteomes were mostly profiled from the frontal cortex. Prior to integration, we performed quality control, normalisation, effects of clinical and technical factors removal, and Z-scale standardisation of protein abundance in each of the proteomic datasets independently.

Trans-regulated proteins consistent with a causal role

We searched for trans-regulated proteins, which are consistent with a causal function in each of these brain features, in addition to cis-regulated proteins. Using the 722 reference human brain proteomes and matching genome-wide genotypes, we first conducted a trans-pQTL analysis among the genome-wide significant SNPs discovered by the 25 GWAS. Trans-pQTLs, which are located outside of the 500 kb window of the protein-coding gene, were declared for SNPs related with protein abundance.

DISCUSSION

The strong genetic relationships between psychiatric and neurodegenerative disorders and the 13 shared causative proteins serve as evidence for the common genetic predisposition. A roughly three-fold increase in physical PPIs between a causal neurodegenerative protein and a causal psychiatric protein provides more proof of a shared molecular basis and points to specific gene networks and molecular mechanisms that are involved in both groups of disorders. Furthermore, we identified the brain proteins involved in these biological processes for further mechanistic analysis, and we found that the SNARE complex, vesicular transport, synaptic transmission, immunological function, and mitochondrial functions are implicated in the shared pathways. The management and advancement of therapeutics for these prevalent brain diseases are greatly impacted by these shared genetic and molecular pathways. For comparison, these neurodegenerative diseases affect about 44 million people worldwide, mostly in later life, and there are no effective treatments to slow or stop the underlying neurodegeneration, whereas these psychiatric disorders affect about 30% of the population annually in early or midlife (age 65). Additionally, neuropsychiatric symptoms, also known as psychiatric symptoms or neuropsychiatric symptoms, are experienced by about 65% of people with neurodegenerative diseases and are linked to earlier institutionalization, higher caregiver burden, and faster cognitive decline. However, there is no safe and effective treatment for these neuropsychiatric symptoms. The most common causes of impairment worldwide are both these psychiatric and neurodegenerative disease categories, and there is an urgent need for potent treatments for these brain disorders. Given the shared molecular basis, therapies that concentrate on the shared pathophysiology may be able to treat early- and midlife psychiatric disorders as well as the typical neuropsychiatric symptoms of late-life neurodegenerative disorders, thereby reducing the risk of late-life neurodegeneration and dementia. Synaptic transmission and the SNARE complex play a more established function in the pathophysiology of neurodegenerative illnesses, even though evidence of their role in the pathophysiology of certain psychiatric disorders is still developing. Here, we add to the body of research by highlighting the significance of synaptic transmission, specifically as it pertains to the SNARE complex and SNAP receptor, in the shared pathways between psychiatric and neurodegenerative illnesses. Additionally, mitochondria in the neurons control presynaptic calcium levels, which in turn control the release of neurotransmitters.

These mitochondria produce ATP to power the neurotransmission process. As a result, mitochondria are essential for maintaining synaptic activity and transmission. Notably, we discovered that mitochondrial mechanisms are related to the pathophysiology of both neurodegenerative and mental disorders. Although this is a novel finding, it is in line with the observation that mitochondrial dysfunction starts early in the progression to neurodegeneration and persists into the late stages of the diseases because the shared mechanisms are more likely to act early since psychiatric disorders first appear in early adulthood or midlife while neurodegenerative diseases manifest in late life. We predicted that our results would likely reflect the weak correlations between mRNA and protein expression levels for the same genes in the brain. According to the existing literature, we discovered that 32% of the causative proteins are also causal mRNAs. The role of microglia in the pathophysiology of AD has recently come to light. For instance, increased microglial expression was observed in about 5% of the 400 genes identified from the AD GWAS. In conclusion, we showed that the major psychiatric and neurodegenerative disorders share genetic susceptibility and pathophysiology, identified 13 shared causal proteins, 118 interacting causal proteins, and highlighted the critical roles of synaptic transmission, immune response, and mitochondrial processes in the shared pathogenesis. There are significant ramifications for disease management and pharmaceutical development in terms of precision medicine, early treatment, and reducing the risk of neurodegeneration and dementia due to the genetic and molecular link between these two groups of prevalent brain illnesses.