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REVIEW ARTICLE

Molecular Genetics Of Major Depressive Disorder

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ABSTRACT: Major depressive disorder (MDD) is a severe psychiatric illness known to be highly complex due to its difficulty in identifying genetic factors and its polygenic nature. While genetic studies and research into epigenetic changes have advanced our understanding of MDD, the precise role of genetics in MDD's manifestation remains elusive. This paper reviews the current state of research on MDD genetics, encompassing findings on MDD's biological blueprint and investigations into epigenetic modifications associated with MDD development. Furthermore, this paper explores the interplay between depression and the immune system and the impact of inflammation on the disorder. Neuroimaging studies have also impacted comprehension of MDD, revealing alterations in brain size and chemistry. These insights shed light on the biological underpinnings of MDD and hold promise for developing more effective treatments and therapies for patients.

KEYWORDS: Genetics, MDD, epigenetics, neuroimaging, immune system.

Introduction

Major depressive disorder (MDD) is a psychiatric illness that casts a shadow on society and healthcare systems due to its ever-expanding prevalence. Depression is associated with sadness, severe illness, psychosis, and suicidality.[1] The World Health Organization (WHO) states that 350 million people worldwide suffer from depression or depressive disorders.[2] MDD is the most common psychiatric illness and the worldwide leading cause of disability.[3] MDD has demonstrated its complexity due to its polygenic nature, vast heterogeneity, and consistent overlap with symptoms and risk factors.[4] Many therapeutic activities and medications are tailored to the treatment of MDD, however they are primarily symptomatic. Considering the vast amounts of those worldwide who showcased their struggle with MDD and the difficulty of composing a diagnosis,[2] it is imperative to investigate the biological aspect of MDD to understand the illness properly. Understanding MDD's biological part can also work to reduce the stigma associated with mental health disorders; by highlighting the genetic factors that come into play, society can learn to recognize that mental illness and MDD are not a sign of weakness but rather a combination of complex interactions involving genetic, environmental, and psychological factors.

From twin studies, it is commonly known that MD has an estimated heritability of 37%, and the risk of inheriting MDD from first-degree relatives is 2.84 times higher than that of the general population.[5] However, due to MDD having a complex polygenic nature, many experts in the field have expressed difficulty in understanding the genetic factors behind MDD. As time has passed, more progress has been made toward understanding the biological mechanisms of depression. A few genes are associated with the risk of MDD development.[2] Epigenetics, the processes affecting gene expression and translation without changing DNA sequences,[6] has been proposed to be involved in depression's pathogenesis due to genetic and environmental factors. The application of GWASs assists with understanding which genes and loci are associated explicitly with MDD. The aspect of brain imaging has been used to study the neurobiological aspects of depression extensively and which genes cause changes within the brain and its components. The immune system has also been discovered to aid with further understanding the genetic basis of depression, considering how MDD is related to alterations in the immune system.[7] Considering this, it is crucial to understand whether or not genetics, including epigenetic mechanisms, neuroimaging, and immune system compromise, are directly involved with the manifestation and pathogenesis of depression. Due to depression's ever-growing detrimental impact on the world, it is evident that many medications and treatments could do a more proficient job of treating and mediating the illness. With better comprehension of MD's biological and genetic mechanisms, more effective therapies can emerge, leading to a better impact on the world's mental health outlook and the mood of society.

This review will discuss the progress made towards understanding the genetic basis of depression, the epigenetics aspect of depression, GWAS (genome-wide association studies) results, neuroimaging and brain-aspect findings based on genetics, and immune system alteration connected back to MDD and genetics. There will be exemplifications of epigenetic mechanisms that mediate abnormalities and genetic factors that lead to these epigenetic changes and how they manifest into depression, epigenetic mechanisms, DNA methylation, and histone modifications, which are associated with the manifestation and progression of MDD. This review will feature the neuroimaging findings that demonstrate changes in the hippocampus and amygdala of the brain, as well as the genes that are connected back to said changes. There will be discussions on the alterations in the immune system and inflammation that are found to be associated with MDD and can also be traced back to specific genes and changes in gene expression. Using past GWAS results, this review will showcase particular genes

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and variants associated with the risk of MDD manifestation and conduct secondary data analysis with said specific genes.

Discussion

Experts and researchers have identified that the nature behind MD goes beyond its psychological dimensions and delves into the realm of biology and genetics. This section explores the underlying biological mechanisms and genetic factors that play a vital role in the pathogenesis of depression. With understanding MDD's complex blueprint due to its heterogeneity and analyzing the results of gene studies, more context can be found on how genetic elements collectively shape the development of MDD. Not only that, but this exploration can also lead to innovative approaches to treatments and MDD's diagnosis.

Heterogeneity and Heritability:

Although there's been stagnancy in understanding MDD's biological and genetic mechanisms, a vast amount of progress has been made these past few decades. With large-scale genetic studies taking place, more comprehension of the genetic risk factors behind MDD, which genes and/or loci are associated explicitly with MDD, and what susceptibility MDD patients can have to other diseases. It is also known that MDD patients have about a 60% increased risk for type 2 diabetes.[8] Although it's crucial to emphasize that estimating any disease or illness heritability can vary from population to population depending on specific circumstances and environmental factors. Depression can also manifest itself differently among populations due to differences in cultural norms and variations in study participation, and since genetic studies of MDD have focused primarily on Europeans, there's a large cap in comprehending MDD's genetic factors worldwide.[9]

MDD's heritability has been showcased and demonstrated through evidence. Still, its polygenic nature makes it difficult to pinpoint one specific genetic change that leads to its development, indicating that an extremely large sample size is required for this investigation. The genetic risk profile of MDD that's been uncovered so far only accounts for less than 10% of its overall architecture.[10] An analysis conducted in 2023, with 30,701 middle-aged white British participants from the UK Biobank, dissected genetic associations and fMRI-based measures of brain function.[4] With this analysis, it was found that MDD and ADHD have eight loci that overlap with one another. Another analysis to evaluate MDD's heterogeneity found no substantial evidence for genetic differences in gender in the context of MDD development.[11] MDD's complexity brings a similar genetic architecture to other psychiatric illnesses and makes it more difficult to pinpoint any genetic specificities it has on its own. It is inferred among experts that multiple genes and loci are involved in a small portion of MDD's development, which leads to differing phenotypes and treatment responses.

Genome-wide association studies:

Using GWAS allows for the evaluation of millions of common genetic variants to find specific loci involved in MDD's pathogenesis. This task has been arduous for experts due to MDD's heterogeneity, but there have been several crucial findings as time has passed. For example, a GWAS conducted in 2018 involving 135,458 cases and 344,901 controls resulted in the identification of 44 risk variants and independent loci that were significant and supported among many SNPs (single nucleotide-polymorphisms; the most common type of genetic variation); these findings mainly emphasized pathways related to MDD, the most significant being RBFOX1, RBFOX2, RBFOX3, CELF4 regulatory networks, genes linked to FMRP-bound mRNAs, synaptic genes, genes involved in neuronal morphogenesis and projection, genes associated with schizophrenia, genes engaged in central nervous system neuron differentiation, genes encoding voltage-gated calcium channels, genes tied to cytokine and immune response, and genes known to bind to the retinoid X receptor.[12] Since these pathways share characteristics and genes associated with schizophrenia, it is implied that MDD and schizophrenia share specific biological mechanisms.

Another GWAS that displayed significant results and kickstarted further progress within this field was done on 807,553 individuals with 246,363 case subjects and 560,190 control subjects and identified 102 independent variants, 269 genes, and 15 gene sets that were found to be associated with MDD.[13] With this study, a clearer picture of MDD's close relationship with other psychiatric disorders, more specifically schizophrenia and ADHD, was painted. VRK2, RSRC1, and MEF2C are all essential genes for controlling brain function, were linked to schizophrenia, and were close to the genetic variants associated with MDD. Another gene is TCF4, which contains brain cell activity and demonstrates two separate links to MDD and has also been linked to schizophrenia. In the context of ADHD and MDD's genetic connection, the CDH13 gene, which makes cell adhesion molecules, was found to be associated with both psychiatric illnesses. Not only that, but the ASTM2 gene, which plays a crucial role in brain development, and genes like DRD2 and ANKK1, which function in dopamine transmission, are also implicated in both MDD and ADHD. Another exciting notion that this study has showcased is the genetic links that MDD shares with menarche and menopause, indicating that the pair shares a possible bidirectional relationship. The LIN28B gene, which shows significant involvement in cell development, was prevalent in this context. However, the underlying biological mechanisms that connect it to MDD are still yet to be understood.

A GWAS conducted on 5,303 Han Chinese women as subject cases and 5,337 control subjects is crucial to discuss in this review because, before this study, no significant progress has been made in identifying loci or genetic mechanisms behind MD.[14] There's been a failure of GWAS studies amounting to 9,000 cases of MDD to find loci that exceed genome-wide significance, which further reinforces the notion that most of the genetic variance occurring in MD is due to the combined effect of multiple loci having minor effects.[5] In this study, two loci had been discovered, and both were located on chromosome 10. One loci was near the Sirtuin 1 gene (SIRTI), and the other was in an intron of the LHPP gene.

Even with the variety of studies and experiments that led to substantial progress in uncovering MDD's genetic architec-

ture, GWAS fails to provide a comprehensive overview of why these genetic links occur in the first place. Not only that, but a vast majority of GWAS are conducted with a small sample size, which doesn't provide enough identification of possible genetic links and heritability of MDD.

Protein Analysis:

In 2021, a study took place to investigate what brain proteins are associated with the development of MD to help the search for effective treatments.[15] The results were the identification of 19 genes that were possibly associated with MDD's pathogenesis by monitoring brain protein levels. Also, 9 of the 19 genes were replicated in an independent study, boosting confidence in these findings.

Figure 1: An overview of the replicated genes with a possible association to MDD. The figure was made with BioRender.

As seen in Figure 1, five of the nine replicated genes were found through TWAS (transcriptome-wide association studies) from the frontal cortex of postmortem brain samples and were found to have had cis-regulated mRNA levels associated with depression. Notably, the other genes were identified only through PWAS (proteome-wide association studies), emphasizing how imperative analyzing proteins is.

This study also showcased the role of synapse-related genes found through the PWAS conducted. For example, B3GALTL is a gene that plays a significant role in stabilizing TSP-1, which is a protein that induces synaptogenesis; their findings suggested that patients with decreased amounts of B3GALTL in the brain had possible disrupted TSP-1 stability, which may contribute to the pathogenesis of depression.[15] Another gene that was identified was CTNND1, which took a significant role in facilitating synaptic signaling.[15] It's indicated that dysregulation of synaptic signaling could have implications for psychiatric disorders like MDD. This study also touched on genes involved in synaptic plasticity, EPHB2, and P2RX7, examining studies showing how altered EPHB2 expressions in mice caused them to exemplify depressive-like behavior and mentioning how P2RX7 has previously been linked to depression.[15]

Mendelian Randomization (MR):

MR is a widely-used analytical approach involving genetic variants linked to a specific risk factor to assess whether or not the observed link between the risk factor and health outcome could indicate a casual relationship.[16] Regarding MR studies being done on MDD, various associations between MDD causation and risk factors were found. For example, genetic liabilities to MDD were associated with an increased likelihood of experiencing a small vessel stroke, elevated risks of coronary artery disease and heart attacks, as well as diminished functional recovery after a stroke.[16] Not only that, but there were cases where MDD was the proposed outcome given specific genetic backgrounds. For example, it was found that those who experience early menarche display higher levels of depression symptoms at 14 or per risk allele, shorter telomere lengths also increase the risk for childhood-onset MDD, and a genetic predisposition to high and hazardous alcohol consumption is associated with an increased risk of death or hospitalization with MDD.[16]

Epigenetics and MDD:

Through many family and twin studies, it is now widely known that the estimated risk for MDD heritability is approximately 40%, which is a distinct contrast to the estimated heritability of ADHD, schizophrenia, and bipolar disorder, which are about 75%-80%.[6] With this, it can be inferred that the heritability of MDD works alongside other possible environmental factors to allow the illness to come to fruition.[17] Environmental triggers such as stress or trauma cause long-lasting alterations within one's genetics, behavior, and brain circuitry, as well as experiencing challenges during development and adulthood. However, many studies are now proposing that these changes are being sustained and supported by epigenetic changes.[18] Epigenetics is a group of processes that affect gene expression and translation without changing DNA sequences.[6] Epigenetic processes such as DNA methylation and histone modifications offer more insight and explain why environmental triggers tremendously impact MDD's progression.

DNA Methylation:

DNA methylation (DNAm) has showcased its prevalence in studying epigenetic mechanisms. DNAm is the addition of methyl groups to the 5' position of cytosines.[6] There's been a plethora of research on DNAm, focusing on peripheral and brain tissue. Regarding peripheral blood and tissue, candidate gene studies have showcased that MDD patients exhibited increased methylation in the regions responsible for encoding brain-derived neurotrophic factor (BDNF) and SLC6A4, the gene for the serotonin transporter. However, these findings are still inconsistent with other studies.[6] A large-scale MWAS (methylome-wide association studies) published in 2018 helped experts identify a portion of the CpG methylome in blood and brain samples.[19] This study found significant overlap with findings in the blood and brain and several genes associated with the brain's function and development: BDNF, LHPP, SORCS3, CELF4, DRD2, and RERE. Another study with this group, containing blood samples from 581 MDD patients, predicted disease after six years based on methylation patterns and found overlap with genes in previous GWAS associated with inflammation and other autoimmune diseases.[20] A 2019 review of DNAm studies found that BDNF and SLC6A4 hypermethylation were consistently linked with MD, while other candidate genes recorded mixed findings.[21] A meta-analysis of EWAS published in 2022 identified 127 differentially methylated regions (DMRs) associated with MD and an implication NRXN-NLGN pathway in suicide, also unveiling involvement with GABBR2 and RUFY which in-

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fluence neurotransmission and neuronal polarity.[22] This study also showcased an overlap of DMRs between brain and blood tissues. Considering this, it can be inferred that DNAm has a significant role in epigenetics by predicting MDD, maintaining it, and leading to its development. With more laboratories and large sample sizes, studies can display the impact of environmental factors on epigenetic changes, leading to more effective treatments and better comprehension of MD's pathogenesis.

Histone Modifications:

Histone modifications haven't been as prevalently researched or studied as DNAm has. However, it's crucial to note that studies have emphasized further evaluating histone acetylation and methylation in the context of MDD. Histone acetylation is a process that makes it easier for chromatin to read and access DNA; it's managed by histone acetyltransferases (HATs), which add acetyl groups, and histone deacetyltransferases (HDACs), which remove acetyl groups.[6] A study with mice published in 2004 found that chronic social defeat stress-induced MDD is possibly associated with histone acetylation and imipramine reduces histone acetylation, therefore curing MDD.[23,24] Not only that, but this study also found that overexpression of BDNF was also accompanied by an increase in H3 acetylation at specific regions of the BDNF promoter. Human studies have also demonstrated similar results. A study published in 2014 found that H3 acetylation at the CaMKIIA promoter region was decreased in patients who were taking antidepressants, in contrast to patients who were not.[25] Overall, decreased histone acetylation has been implicated in MDD, underscoring the importance of its research, considering how targeting histone acetylation could lead to effective treatments for MDD. Histone methylation involves adding or removing small chemical groups on specific parts of the histone proteins to impact how different proteins interact with the chromatin and read the genetic information.[26] Some cases demonstrated that changes in the H3K4me3 at gene promoters like SYN1 have been linked to brain tissues in MDD patients who passed due to suicide.[24,27] It was also found that changes due to histone methylation can lead to depressive-like behaviors. An example is the absence of the protein PRMT1, which influenced said behavior in mice.[24,28] To summarize, an increase in histone methylation studies can manifest into a better understanding of MDD's biological mechanisms and lead to more treatments tailored to target these modifications specifically.

Immune System and Inflammation:

The central nervous system (CNS) and the immune system are now known to share a bidirectional relationship, with signals from the immune system affecting the brain and the brain influencing the immune system; this concept is known to experts as the cytokine theory.[2] Cytokines, which are made from immune cells, can impact mood, behavior as well as having pro or anti-inflammatory effects.[2]

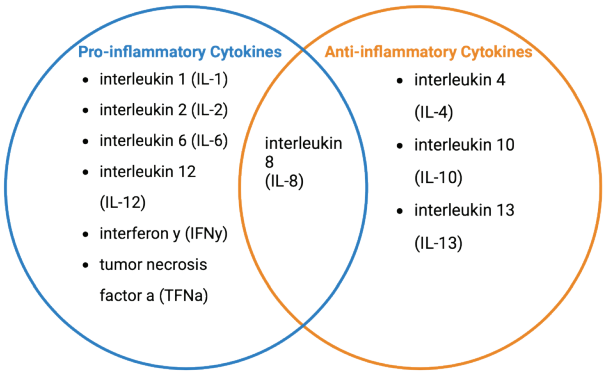

Figure 2: Created with BioRender. A venn-diagram of the cytokines divided into two classes.

As seen in Figure 2, it's notable that interleukin 8 was one of the cytokines that can be considered both due to different concentrations.[2] An MR analysis of an association with MDD and immunological proteins and traits published in 2021 found evidence for a casual relationship between MDD and IL-6.[29] Since IL-6 is a proinflammatory cytokine, this indicates that MDD and inflammatory changes have a relationship. A systematic review published in 2016 showcased the most prevalently replicated genetic variants connected with MDD, such as IL-1B, IL-6, IL-10, MCP1, TNF-a, CRP, and PLA2; however, it's crucial to underscore that there are inconsistencies with the effects of these variants on MDD behavioral changes and immune system mechanisms, as well as inconsistencies reported within studies.[1] A meta-analysis published in 2017 involving over 6,000 participants and 82 studies found that MDD patients showcased increased levels of IL-10, soluble IL-2 receptor (sIL-2), C-C motif ligand (CCL) 2, IL-13, IL-18, IL-12, IL-1 receptor antagonist (IL-1RA), and soluble TNF receptor 2 (sTNFR2).[30,31] Not only that, but gene expression studies exemplified upregulated inflammatory pathways in peripheral blood mononuclear cells (PBMCs) of depressed patients.[30] With this, it was found that Il–1b, Il-6, TNF, mif, and lfng showed increased expression in MDD.[30,32] A systematic review and meta-analysis published in 2020 discusses anti-inflammatory agents' role in treating MDD.[33] The findings indicated that anti-inflammatory medication may have similar effects to that of antidepressant treatments, which further emphasizes evidence of inflammation being a component of MDD. Genetic data has helped identify specific mutations impairing the functioning of proteins like interleukins or C-reactive protein (CRP), which could make patients more susceptible to MDD; CRP is a systemic inflammation marker consistently found in individuals suffering from MDD.[34] A meta-analysis of epigenome-wide association studies of MDD (EWAS) demonstrated noteworthy findings with neuroinflammation implications in MDD, specifically Th17 cells.[22] This study exemplifies that Th17 cells have been shown to increase in preclinical depression animal models, and inhibition of Th17 cell differentiation has shown resistance to this process.[22,34] With this, it's implicated that MDD contains a broad involvement of inflammatory pathways.[22] It can be inferred that with more studies working to decipher

the specific inflammatory pathways involved in MDD, more antidepressants and therapeutics can emerge attacking these inflammatory pathways, which can be a possible effective cure for MDD. A study published in 2015 genotyped five SNPs in genes associated with CRP to investigate depression in senior citizens, notably found two alleles, rs1130864 and rs1417938, that are associated with a lower depression rate in women.[34,35] However, it's crucial to emphasize that the relationship shared between inflammation and MDD is seen in other factors. Stress, which is linked to MDD, can be linked to an inflammatory response; interestingly enough, it was found that healthy volunteers who don't have a mental illness can show higher levels of inflammatory markers due to stress, which can be tied to developing MDD symptoms.[30,36] Since stress can cause inflammatory responses, it's inferred that environmental factors also tie into the connection between inflammation and MDD. Childhood trauma was shown to have long-lasting effects on peripheral inflammation later in life and also increase the risk of developing MDD.[30, 37-40]

Neurogenetics:

Understanding the neurogenetics involved with MDD is paramount since it allows experts to understand MDD on a circuitry level and more context behind the underlying mechanisms for individuals having MDD. Not only that but studying neurogenetics and neuroimaging can provide insights for more novel treatments for patients.

Gene Expression:

As time has passed, gene expression studies on MDD have pinpointed enrichment in human brain tissue, expressing the importance of researching brain-expressed genes.[10,12,41] It was also found that GWAS associations with MDD are highly enriched in genes expressed in neurons.[10,41] Another notable finding was genes linked to ion channels, neurotransmitter receptors, and synaptic proteins implicated in GWAS on MDD.[10,13] A study published in 2022 found significant genomic overlap between genetic variants linked to the rate of change in brain structure and associated with MDD; these findings also aligned with specific gene-level findings, where some genes were related to metabolic processes (APOE, DACH1, GPR139, NECTIN2), cognitive functioning (CDH8), and psychiatric traits (GPR139, SORCS2, CDH8).[42] With confirmation that the genetic architecture in the brain occurs within MDD and other psychiatric illnesses, more intricate and precise studies on neurogenetics can be revolutionary in understanding changes in brain regions, neural circuits, signaling, and other neural pathways when it comes to MDD.

Neurogenetics:

A variety of MRI studies have reported MD patients having a smaller size amygdala, hippocampus, and prefrontal cortex.[43] Due to research conducted on epigenetic mechanisms, GWAS, and inflammation, a lot of insight and basis has been inferred on the genetic background behind MDD. However, discussions of brain volumetric differences in MDD patients compared to that of an average person sparked curiosity about more context behind MDD's neurological blueprint. A review of 17 MRI studies published in 2004 found that a smaller amygdala is apparent in only female MD patients, and a reduced normalized left inferior anterior cingulate volume was apparent in depressed males.[43] This indicates that sex-specific changes in brain structure are associated with MDD and a possible biological mechanism of MDD. Fifteen years later, a genome-wide meta-analysis of MDD found 102 genetic variants associated with MDD and further context on the genetic aspect of the changes in brain regions.[13] With this study, enrichment in the frontal cortex, anterior cingulate cortex, and cortex brain regions were identified, as well as an overlap with genes in dopamine, serotonin, and brain function and development. A study published in 2022 revealed an association of the S100A13 gene, which is involved in CNS development and expression in the hippocampus and temporal cortex; not only that but this gene was also found to be expressed in the orbitofrontal cortex of suicide victims, which further underscores a possible link to MDD.[22]

A review paper published in 2023 helped identify a plethora of genes and variants that are associated with the brain, more specifically serotonin and dopamine:[34]

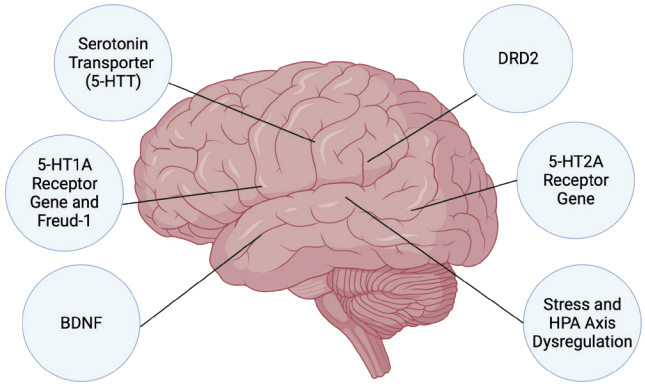

Figure 3: Made with BioRender. A reflection of the critical genes and variants involved in dopamine and serotonin pathways, neuroplasticity, stress, and hypothalamic-pituitary-adrenal (HPA) axis dysregulation.

The genes and variants demonstrated in Figure 3 have all been linked with a relationship to MDD. The Val66Met mutation in brain-derived neurotrophic factor (BDNF) has been associated with increased negative emotions and worse antidepressant responses. Studies with knockout models revealed silencer Freud-1's role on anxiety and serotonin signaling. Polymorphisms like rs6295 in the 5-HT1A gene were associated with altered antidepressant responses. The serotonin-transporter gene contains polymorphisms like 5-HTTLPR associated with increased susceptibility to MDD. The dopamine D2 receptor gene (DRD2) was scrutinized for its susceptibility to MDD and its impact on antidepressant response. 5-HT2A has variants associated with MDD symptoms, but studies have not shown clear associations with genotypes and symptoms. The role of stress and HPA axis dysregulation led to studies of glucocorticoid receptor (GR) gene polymorphisms; Bc11 and Asp3635 mutations in the GR gene were associated with increased MDD risk, and mutations in the FBPP5 gene were linked to altered hormone-receptor interactions and stress responses.

However, it's crucial to note that interpreting results of the brain's structural changes remains uncertain to experts due to

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the lack of correlation with histopathology, explicitly speaking of changes in brain water content, dendritic or axonal atrophy, neuronal degeneration, or other factors.[7] Also, since MDD is almost entirely dependent on the patient's report of their symptoms and their overlap with symptoms and risk factors in other psychiatric illnesses, MDD is extremely difficult to diagnose. Due to this, it's unclear whether or not structural brain changes are due to MD or childhood maltreatment and trauma.

Conclusion

The pursuit of understanding the genetic underpinnings of MDD has witnessed significant advancements through GWAS studies, uncovering specific loci and genes associated with MDD's development. Other approaches like Mendelian randomization and protein analysis have enriched understanding by providing information that GWAS alone couldn't cover. Despite these findings, MDD's heterogeneity and polygenic background continue to be challenging in discovering MDD's genetic architecture. Future efforts should focus more on higher sample sizes and diversity, protein investigation, bias mitigation, and replication studies to confront this. MDD's complexity emerges from the intricate interplay between genetic predisposition and environmental factors.

The intricate interplay between genetic predisposition and environmental triggers helps form the complex landscape of MD, especially considering MDD's differing heritability rates compared to other psychiatric disorders. Exploring epigenetic processes like DNA methylation and histone modifications has offered notable findings on how environmental triggers influence MDD. Candidate gene studies and MWAS highlighted vital genes linked to brain function and development, such as BDNF, LHPP, SORCS3, CELF4, DRD2, and RERE. Histone modifications, specifically acetylation and methylation, have also helped identify specific genes and proteins in MDD's biology. Histone acetylation studies in mice and humans were found to be associated with stress-induced MDD and antidepressant response. In contrast, histone methylation has been linked to the gene SYN1 and the protein PRMT1. Holding further investigation of these epigenetic mechanisms with rigorous methodologies and diverse and broad sample sizes can help researchers uncover valuable insights about the interaction of environmental triggers and genetics. This will inevitably lead to improved insights into MD's complex biological blueprint and the promise of more effective treatments.

Integrating neurogenetic research and neuroimaging techniques provides insights into MD on a circuitry level, helping experts uncover the underlying mechanisms of this illness. It's also notable that studying neurogenetics uses neuroimaging techniques since they provide essential evidence of MDD's neuronal basis. Gene expression studies revealed an enrichment of brain-expressed genes in MDD and an association of GWAS findings with genes expressed in neurons. Genes linked to ion channels, synaptic proteins, and neurotransmitter receptors were implicated in MDD GWAS, and other recent studies demonstrated connections between genetic variants linked with MDD and those related to structural brain changes. However, challenges persist since uncertainty about how brain structure changes and MD's relationship with trauma and childhood maltreatment raises questions about the origin of structural changes. But as research progresses, more is discovered by identifying essential genes and variants associated with neuronal function and stress, providing an understanding of the neuronal basis of MDD.

With more findings discovered even today, society's understanding of MDD's genetic, epigenetic, inflammatory, and neuronal foundation deepens, promising the development of effective treatments and interventions for this mental health disorder.

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