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INTEGRATION OF SYSTEM BIOLOGY TECHNIQUES TO IDENTIFY PRIORITY GENES IN DEPRESSION

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Abstract

Depressive illness is a complicated and multifaceted psychiatric condition that is impacted by a variety of variables, including hereditary, environmental, and neurobiological factors. In spite of the vast study that has been conducted, the molecular processes that are at play are still only partly known, which impedes the development of medicines that are both effective and personalised. Over the last several years, systems biology has emerged as a strong multidisciplinary strategy to uncover the complexity of such illnesses. This is accomplished by merging high-throughput omics data with computer modelling and network-based analysis. The purpose of this research is to discover priority genes that are linked with depression by using methodologies from the field of systems biology. These approaches include gene expression profiling, protein-protein interaction (PPI) networks, gene ontology (GO), pathway enrichment analysis, and network topology evaluations. In order to discover differentially expressed genes (DEGs), transcriptome datasets that were accessible to the public and were taken from patients who suffered from depression and healthy controls were analysed. By mapping these differentially expressed genes (DEGs) onto PPI networks, hub genes and important regulatory modules were identified. Additional insights into the biological processes and signalling pathways that are substantially changed in depression were obtained by the combination of KEGG pathway databases and GO keywords. Prioritisation of candidate genes for additional functional validation was made possible by the use of centrality metrics such as degree, betweenness, and proximity. These measures were utilised to rank genes according to the relevance they have in the network. Through the use of an integrative method, numerous genes with a high degree of confidence were identified as having the potential to be implicated in the pathophysiology of depression. These genes include those associated with synaptic signalling, immunological response, neuroinflammation, and neuroplasticity. Our knowledge of the molecular architecture of depression is improved as a result of these results, which also identify intriguing targets for future diagnostic and treatment approaches. Taking everything into consideration, the research highlights the usefulness of systems biology in terms of prioritising genes in complex psychiatric diseases and prepares the way for precision medicine methods in the field of mental health.

Keywords: *system biology, techniques, depression, priority*

Introduction

Depression is a frequent and severe mental disease that affects more than 280 million individuals all over the globe. It is also known as major depressive disorder (MDD), which is another name for depression. Depression is a condition that is characterised by persistent feelings of melancholy, anhedonia, exhaustion, cognitive deficits, and suicidal thoughts. It places a substantial strain on people, families, and healthcare systems. The particular molecular pathways that underlie depression are still not fully known, despite the

fact that decades of study have been conducted on the subject. This has contributed to the restricted development of effective and targeted medicines. Epigenetic modifications, environmental triggers, genetic predispositions, and neurobiological changes, such as changes in neurotransmitter systems, neuroinflammation, and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, are thought to play a role in the pathogenesis of depression. This complex interaction is believed to be the cause of depression. Despite the fact that a large number of genome-wide association studies (GWAS) and transcriptomic analyses have identified potential candidate genes and pathways associated with depression, the challenge that still needs to be overcome is distinguishing causal genes from background noise and gaining an understanding of how these genes interact within biological networks. Through the integration of multi-omics data (genomics, transcriptomics, and proteomics) with computational and network-based methodologies, systems biology provides a comprehensive framework for addressing the complexities of depression. Systems biology highlights the dynamic interactions among genes, proteins, and metabolites, exposing how changes at one level may spread across biological systems to alter mental health. This is in contrast to classic reductionist techniques, which analyse specific genes or pathways that are isolated from one another. Using this integrative technique, researchers are able to discover not just genes that are expressed differently but also genes that are functionally significant and act as hubs or bottlenecks in biological networks. These genes are referred to as "priority genes." Applying techniques from the field of systems biology, such as gene co-expression networks, protein-protein interaction (PPI) mapping, gene ontology (GO) analysis, and pathway enrichment analysis, makes it possible to identify key molecular players and interactions that are responsible for the development and progression of depression. In addition, the incorporation of network topology measurements makes it possible to prioritise genes that may be essential for the maintenance of network stability or the management of information flow, which in turn provides unique insights into the processes that underlie illness. The objective of this research is to combine a number of different systems biology approaches in order to systematically discover and rank the genes that are implicated in depression. The goal of this study is to identify high-confidence candidate genes that might be used as biomarkers or therapeutic targets. This will be accomplished by conducting an analysis of publically accessible datasets including persons with and without depression, as well as by establishing interaction and functional networks. By doing so, this study makes a contribution to the expanding body of information that is necessary for the development of therapies for depression that are more individualised and successful via the use of precision psychiatry.

Gene Expression and GWAS in Depression Research

Attempts have been made in traditional genomic research to find single nucleotide polymorphisms (SNPs) that are related with depression. According to Howard et al.'s 2019 research, genome-wide association studies (GWAS) have uncovered a number of loci that have only a weak connection to depression. These loci include those located close to SIRT1, LHPP, and OLFM4. These results, on their own, have a limited capacity to explain the phenomenon since the impact sizes are rather tiny and there is no functional validation. On the other hand, transcriptome research that made use of microarray and RNA-seq technologies has uncovered genes that are differentially expressed (DEGs) in the brain and peripheral tissues of people who suffer from depression. As an example, Mostafavi et al. (2014) conducted a meta-analysis in which they discovered dysregulated immunological and neuronal genes in the postmortem brain tissues of persons who had been diagnosed with depression. On the other hand, these studies often have discrepancies

because of tissue specificity, sample variability, and restricted interpretability in the absence of network-level analysis.

Network Biology and Protein-Protein Interactions

Within the field of psychiatric genomics, network-based techniques have become more popular. It is possible to discover the core regulators of illness via the use of protein-protein interaction (PPI) networks. In these networks, nodes represent proteins and edges signify interactions. In their 2004 study, Barabási and Oltvai highlighted the relevance of hub genes, which are genes that have a high degree of interconnectedness, as possible disease drivers. The construction of PPI networks via the use of databases like as STRING, BioGRID, or IntAct has made it easier to identify core modules and hub genes in the field of depression research (Goh et al., 2007). The PPI network analysis was applied to depression-related DEGs in a study that was conducted by Zhao et al. (2020). The researchers found that BDNF, MAPK1, and CREB1 were major hubs, which suggests that these genes have the potential to be therapeutic targets.

Gene Ontology and Pathway Enrichment Analysis

The Gene Ontology (GO) and pathway enrichment tools such as DAVID, Enrichr, and KEGG are used by researchers in order to assess the biological significance of differentially expressed genes (DEGs). These tools classify genes according to the biological processes, molecular roles, or cellular components that they share within the same organism. According to Liu et al. (2018), enrichment studies of genes linked with depression have shown that there are persistent changes in pathways related to synaptic signalling, neuroinflammation, immunological response, and neurotrophic signalling. As an instance, persons who suffer from major depressive disorder have been shown to commonly exhibit dysregulation in the HPA axis and cytokine signalling pathways, which suggests that the condition is associated with a neuroimmune component.

Weighted Gene Co-expression Network Analysis (WGCNA)

The WGCNA methodology is yet another strong method that is used to generate gene co-expression modules and to find correlations between modules and traits. Modules linked with immunological response, mitochondrial function, and neurotransmission have been discovered by the use of WGCNA in research to investigate depression. Using WGCNA on RNA-seq data from human brain tissues, for instance, Li et al. (2019) revealed depression-linked modules that were enriched in genes that are involved in the inflammatory response. Not only can these module-based studies help discover individual genes, but they also assist in identifying groups of functionally linked genes that are contributing to disease processes.

Integration of Multi-Omics and Machine Learning

Through the use of machine learning and systems biology technologies, recent advancements have been made in the integration of multi-omics data, which includes genomes, transcriptomics, epigenomics, and proteomics. The integration of data layers and the extraction of patterns that are biologically significant are accomplished via the use of tools such as iCluster, SNF (Similarity Network Fusion), and Cytoscape plugins (for example, ClueGO and MCODE). A number of new candidate genes, including FKBP5, IL6, and TNF, have been discovered by the integration of several omics, which has shown a connection between stress

response and inflammation and depression (Hoffmann et al., 2016). Furthermore, prediction models that have been trained on integrated omics data have shown enhanced accuracy in identifying biomarkers for the diagnosis of depression and the response to therapy.

Prioritization Techniques in Systems Biology

In order to prioritise disease-associated genes from big datasets, it is necessary to rank genes according to centrality metrics (such as degree, proximity, and betweenness) and functional significance. The procedure may be automated with the use of programs such as ToppGene, GeneMANIA, and Endeavour. For the purpose of identifying actionable targets for drug development, research have used such prioritisation in the context of depression. As an example, pathways that include BDNF-TrkB, NF-κB, and serotonin transporters have been identified several times in prioritised gene lists across a variety of research that have been conducted in the field of systems biology.

Pathophysiology of depression

Major depressive disorder (MDD) is a condition that has a major impact not just on individuals but also on society as a whole. There is a lifetime prevalence rate of up to twenty percent throughout the globe, and it has been predicted that around six percent of men and ten percent of women may suffer a depressive episode in any given twelve-month period. Depression is often episodic, meaning that it disappears after a period of time ranging from several months to years. However, it has a recurrence rate of sixty to seventy-five percent and has the potential to become chronic. As a result of the persistence of a number of symptoms that include numerous behavioural and physiological indications, major depressive disorder (MDD) is diagnostically determined. Changes in cognitive and emotional functioning are the most prominent among them. them changes include difficulties in doing activities that are reliant on the hippocampi, difficulties in focussing, psychomotor slowness, and a reduced affective response. Feelings of worthlessness and guilt, worry or agitation, and intrusive thoughts of death and suicide are some of the other emotional symptoms that may be experienced. Depression may be identified by its physiological manifestations, which include shifts in activity level, exhaustion, changed sleeping and eating habits, and either an increase or decrease in weight. According to the results of the dexamethasone suppression test, the vast majority of patients also exhibit abnormal activity along the hypothalamic-pituitary-adrenal (HPA) axis. In addition, people who have been diagnosed with depression are at an increased risk for developing additional illnesses, such as anxiety disorders, alcoholism or drug addiction, cardiovascular disease, and other similar conditions. In conclusion, depression may be fatal, since up to fifteen percent of sufferers go on to take their own lives.

The symptoms are not a typical reaction to the loss of a loved one (bereavement), and there is no evidence to suggest that they are caused by an organic cause. One of the most well-established risk factors for the development of depression is being exposed to stressful situations consistently throughout one's whole life. Depression is characterised by a number of physical symptoms, including elevated levels of stress hormones and abnormal activity along the HPA axis. It is possible to normalise hypercortisolemia, which is found in around fifty percent of patients who are depressed, by the effective treatment of depression with antidepressants. In mice that were selectively selected for a depressed phenotype, baseline corticosterone levels were found to be increased in the "helpless" mice in comparison to the controls. This finding suggests that high corticosterone levels may be a role in the tendency to depression. There is a clear correlation between the high levels of stress hormones, namely cortisol in humans and corticotrophin in rats, and the

health of the neurones. The CA3 pyramidal neurones of the hippocampus have been shown to be particularly sensitive to the effects of stress: acute stress or glucocorticoid treatment makes the neurones more susceptible to insults such as excitotoxicity, while chronic glucocorticoid treatment or stress induces neuronal atrophy, and, in severe cases, neuronal death. When CA3 neurones are injured by excessive levels of glucocorticoids, they are unable to appropriately control the release of corticotrophin releasing factor from the hypothalamus. This results in hypercortisolemia and progressive atrophy of the hippocampi. There is a lack of agreement on the location of depression in the brain, which seems to indicate that numerous circuits are implicated (Figure 1). Imaging investigations, both static and functional, have generally focused on the neocortex and the hippocampus, since these regions are expected to be responsible for mediating cognitive elements of the neurodegenerative illness. An intriguing finding is that a number of human imaging investigations have found a reduction in the volume of the hippocampi in individuals who suffer from depression. The magnitude of this reduction is correlated with the entire lifetime length of major depressive disorder. Chronic stress or depression, as well as a reduction in hippocampal volume and/or neuronal proliferation in the hippocampus, has been shown to be associated with poor performance on hippocampal-dependent memory tasks in studies conducted on both rodents and humans. This suggests that the changes in hippocampal volume that have been observed have functional consequences.

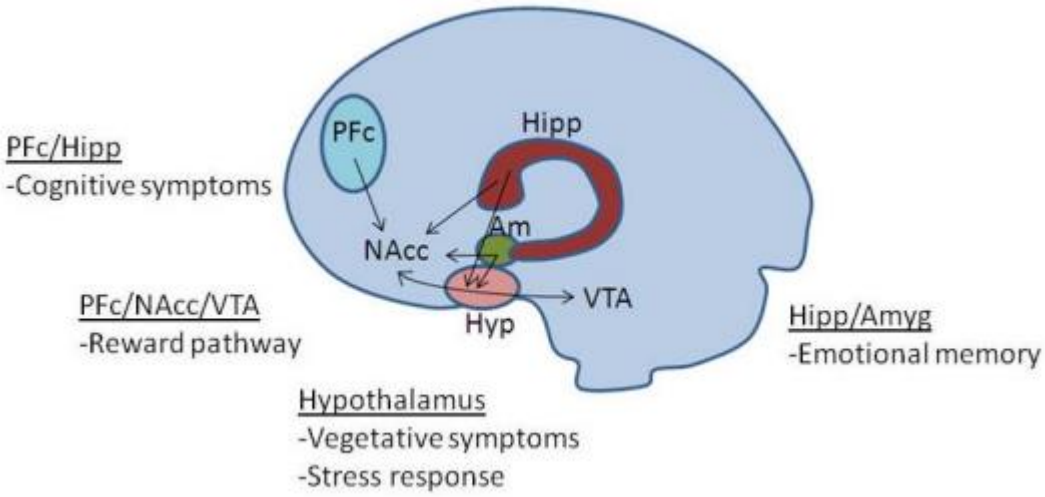

Figure 1. This article provides an outline of the neuroanatomical areas that are involved with the symptoms of depression.

It is believed that the prefrontal cortex (PFc) is responsible for mediating cognitive symptoms such as feelings of worthlessness and guilt. Additionally, the PFc is a component of the neural circuitry that is responsible for motivation and reward. This circuitry includes the nucleus accumbens (NAcc), the amygdala (Am), and the ventral tegmentum (VTA). It is the location of ongoing neurogenesis in adulthood, the hippocampus (Hipp), which is linked with learning, memory, and emotion. Additionally, the hippocampus controls the stress hormone axis by limiting the production of corticotrophin releasing factor from the hypothalamus (Hyp).

In recent years, it has been proposed that the striatum and the amygdala may potentially play a part in the development of depression. These areas are often connected with emotional response and memory, and they may be responsible for the symptoms of anhedonia, anxiety, and diminished motivation that are noticed in individuals who are depressed. The evidence that these structures play a role is mostly gained from their

participation in the reward pathways that are involved with drug addiction, which is a possible model for anhedonia, as well as from the data that stress increases dopaminergic transmission in the mesolimbic circuitry. As an additional point of interest, the control of neurotransmitter signalling in the amygdala of rats has the potential to influence behaviour in testing paradigms linked with depression. A reduction in the amount of grey matter in the cingulate cortex and amygdala, as well as an alteration in the activity of these circuits, are both connected with genetic variants that are linked to an increased risk of depression in humans. Lastly, the hypothalamus, which is responsible for mediating many of the vegetative symptoms of depression, is a region that is likely to be implicated in the condition of depression. Different nuclei of the hypothalamus are responsible for regulating both the consumption of food and circadian rhythms, both of which are disturbed in those who suffer from depression. In recent times, it has been shown that a mouse that has a mutation in a fundamental circadian rhythm gene exhibits symptoms that are consistent with affective disorders. Furthermore, it has been demonstrated that disruptions in sleep patterns may either induce or temporarily ameliorate depression symptoms in people. Furthermore, the hippocampus, which is responsible for regulating the stress response and the production of corticosteroids, provides direct input to the hypothalamus, as was discussed before. Last but not least, the hypothalamus is influenced by the striatum and the amygdala, which may be responsible for regulating the sensation of fullness in relation to food and sleep.

Sources of heterogeneity

Scientists have come to understand that depression may manifest in a variety of ways. To begin, there is symptom heterogeneity, as mentioned earlier. At least 256 distinct symptom combinations may be used to diagnose MDD, and some of these criteria are also diverse. For instance, people with MDD may have hyposomnia or hypersomnia, hypoweight or overweight, and psychomotor agitation or retardation, which are contrasting symptoms that point to different causes.

Second, depression often develops with other medical issues, as is the case with the majority of mental diseases. The majority of major depressive disorder (MDD) patients (approximately 75%) also suffer from a co-occurring neuropsychiatric disorder; these can include anything from substance use disorders to phobias to PTSD to generalised anxiety disorder to personality disorders. The biology behind the diverse symptom presentations in depression and other associated diseases may be influenced by transdiagnostic pathways, as shown by the high rates of co-morbidity. In a recent study that followed 1037 individuals from birth to age 45, it was found that 85% of those with a psychiatric diagnosis also had multiple comorbidities. Additionally, there was a significant amount of flux not only between closely related psychiatric conditions, like major depressive disorder and generalised anxiety disorder, but also between apparently disparate families of disorders, like internalising and externalising disorders. This highlights the important fact that mental health diagnoses, including depression, can be unstable over time. Surprisingly, out of 1037 patients, 692 had distinct lifetime trajectories for mental disorders; of them, 605 (87.4%) belonged to a single individual. The importance of recruiting samples with a variety of linked diseases and conducting longitudinal investigations is highlighted by these results in human neuroimaging studies. Below, we'll go into more depth about how important it is to carefully consider subject recruitment tactics and accurately measure present mood state. This is because the processes that cause and sustain certain symptoms and behaviours might vary depending on one's mood.

Thirdly, there is a great deal of variation among patients in terms of the longitudinal course of their illness. This includes differences in the age of onset (adolescence vs. young adulthood vs. late-life), the frequency of episodes, and the temporal dynamics of episodic changes in depression and euthymia (dysthymia, ultradian cycling, episode duration, durability of remission, "kindling" and cycle acceleration, etc.). Each of these factors may have a neurological basis. For instance, several biological processes may be connected with the age of onset, which in turn affects the severity and recurrence rate of depression. As a fourth point, the exact ways by which sex, a major depressive disorder risk factor, adds to diagnostic variability remain unclear. A history of hardship, trauma, or abuse, for example, may have a different impact on the systems behind "spontaneous" depressive episodes than a particular antecedent psychosocial stressor. The way the brain reacts to psychosocial stress is a reflection of both the short-term physiological costs of stress reactions and the long-term psychological and physiological impacts of those responses. This means that different people's neurobiological responses to the same stressor might vary greatly depending on their unique life circumstances, including whether or not they have experienced known risk factors like poverty, prejudice, financial hardship, or abuse in their formative years. You can see the relative dangers of the most significant risk variables in Table 1.

Table 1. Risk factors for major depressive disorder (MDD).

Risk Factor for MDD	Reference	Timeline	Relative Risk (RR)
Female	Male	10-year follow-up	2.13, $p < 0.001$
Age of onset 55–64	45–54	10-year follow-up	0.65, $p = 0.040$
Age of onset 65+	45–54	10-year follow-up	0.43, $p = 0.005$
Underweight	Normal weight	10-year follow-up	3.34, $p = 0.007$
Family stress (yes)	Family stress (no)	10-year follow-up	1.48, $p = 0.049$
Traumatic life events (yes)	Traumatic life events (no)	10-year follow-up	1.46, $p = 0.001$
Chronic disease (with)	Chronic disease (without)	10-year follow-up	2.47, $p = 0.001$
Higher income inequality	Lower income inequality	Pooled across 12 studies (6 in U.S.)	1.19, all studies $p < 0.05$
Family history of mental health problems (yes)	Family history of mental health problems (no)	4-year follow-up	1.92, $p < 0.001$
Daily smoking	Non-smokers	10-year follow-up	1.72, p = 0.007
Occasional drinker	Abstainer	4-year follow-up	1.56, $p < 0.001$
Work-related exposure to violence or threats (yes)	Work-related exposure to violence or threats (no)	Pooled across 4 studies	1.42, $I^2 = 0\%$

The relative risk (RR) for recognised depression risk factors is the cumulative incidence with regard to the reference group that was given. Within the timeline column, the amount of time that passed between the first study and the follow-up study that was used in the calculation of the relative risk is shown. In the two meta-analyses, the chronology column denotes the total number of studies that were combined in order to get the average relative risk (RR) across all of the investigations. P-values, also known as I2 values, are labelled next to each RR. A measure of the consistency of findings across studies that are utilised in meta-analyses is referred to as I2.

3. Genetics of depression and treatment efficacy

Multiple twin studies have shown a 40-50% heritability of depression, with a relative risk that is two to three times higher for first degree relatives. If the proband's major depressive disorder (MDD) is marked by an early age of start or numerous depressive episodes, the relative risk and heritability are greatly increased. Bipolar illness, schizoaffective disorder, and schizophrenia are all more common among relatives of depressed probands. Genetic analysis of depression has mostly failed to further our knowledge of the disorder's origins, even if heredity plays a demonstrable role in the disorder's incidence. Depression and bipolar illness have been linked to areas on almost every human chromosome so far. It is probable that variations in research design (phenotype, sampling methods), heterogeneity, and population structure and size are just as to blame as false positive findings for the bulk of these studies' failure to repeat. Nevertheless, several investigations have shown the presence of some areas, such as loci on 6q, 12q, 13q, and 15q. Sadly, the cloning of additional genes linked to depression has not proceeded due to the enormous size of these loci, which may reach 70 Mb. While genome-wide scans have shown some success, candidate gene approaches have shown somewhat better results. The tandem repeat, insertion/deletion polymorphism in the promoter region of the serotonin transporter (SLC6A4, the molecular target of SSRIs) has been the most extensively researched as a potential depression locus. This variant may be expressed as either a long (l) or short (s) form. Anxiety, depression, and the risk of depression and suicide after stressful life events are all worsened when the s allele is present, and decreased levels of SLC6A4 mRNA and protein are linked to a s/s genotype. There are over a hundred publications that discuss how this tandem repeat and other SLC6A4 polymorphisms are linked to suicidality, drinking, depression, and antidepressant responsiveness. The rate-limiting enzyme in serotonin production in the brain, Tryptophan Hydroxylase 2 (TPH2), is another gene with a well-established function in depression. Statistically, depressive people are more likely to have a single nucleotide polymorphism (SNP) that alters the gene's coding than non-depressed controls, and this variation is linked to an inadequate response to pharmaceutical antidepressants. We still don't know much more about the molecular physiology of depression beyond what is known from existing pharmaceutical therapies since these beneficial correlations have mostly only included the major regulators of the serotonin neurotransmitter system. In addition to trying to understand and anticipate the diverse treatment responses found in patients, genetic techniques have also been used to obtain more insight into the underlying illness and the medications' modes of action. Even while many people with depressive episodes do get some relief from existing treatments, the effectiveness of the meds that are presently on the market is low and unpredictable. Several weeks of antidepressant medication are required before any noticeable improvement in symptoms occurs, and initial treatment only works for 30–40% of patients regardless of the drug combination. After a few weeks or months of gradually increasing the dosage, if the patient still doesn't feel better, the doctor may prescribe a new medication or suggest an alternative course of treatment. There is presently no method to forecast which medication would work best for a given patient, and while 60-70% of patients will eventually discover a therapy that offers relief, the process might take months or even years. If one member of a family has a good reaction to a class of drugs, it's usually a good indicator that other members of the family will have the same reaction. Several studies, however, have shown that this capacity to respond favourably to a specific treatment is genetically determined. When it comes to treating bipolar illness with lithium and unipolar depression with antidepressants, this insight is equally valid. The genetic study of this effectiveness characteristic has also been limited by its emphasis on a restricted number of well-established candidate genes. We do not yet know which genes are associated with SSRI effectiveness since no genome-wide association studies have been performed. Once again, genetic investigations have

mostly concentrated on establishing a connection between treatment success and polymorphisms in genes directly related to the regulation of the serotonergic signalling system, often yielding contradictory findings. Results from studies examining the serotonin transporter's short promoter variation have shown either a more favourable reaction to SSRI medication, a less favourable response, or no connection at all. Concerning the role of coding SNPs in 5-HT2A, a serotonin receptor, and SSRI effectiveness, similar contradictory findings have been found for TPH2, the primary enzyme regulating serotonin production. Some progress has been made, nevertheless, in establishing a causal relationship between antidepressant effectiveness and genes involved in metabolism. About 5% of people have CYP2D6 polymorphisms, which cause fluoxetine to be cleared from the body very quickly and has a negative impact on the drug's effectiveness.

Conclusion

A very complex and varied psychiatric condition, depression is governed by complicated interactions among genetic, molecular, and environmental variables. Depression includes a wide range of symptoms and manifestations. There have been times when traditional reductionist techniques have been successful in gaining significant insights; nonetheless, they have often failed to capture the entire breadth of the biological complexity involved in the beginning and course of depression. When seen in this light, systems biology provides a promising and all-encompassing paradigm for investigating the multifaceted nature of mental health diseases. The purpose of this study was to demonstrate the potential of systems biology in identifying and prioritising candidate genes involved in depression. This was accomplished by integrating data on gene expression with network-based analysis techniques such as protein-protein interaction (PPI) mapping, gene ontology (GO) classification, pathway enrichment analysis, and co-expression networks. The use of topological metrics such as degree centrality, betweenness, and clustering coefficients is an additional method that assists in the identification of major hub genes that have the potential to act as biomarkers or therapeutic targets. The results of this research reveal a number of genes and biological pathways that are considerably dysregulated in depression. These genes and pathways are notably connected to synapse function, immunological signalling, and neuroplasticity. Not only do these prioritised genes improve our knowledge of the illness at the molecular level, but they also offer up new opportunities for the development of targeted drugs and personalised therapy options. In spite of the fact that the incorporation of systems biology methodologies has shown to be an effective instrument in elucidating the molecular landscape of depression, there are still problems that need to be addressed in potential future study. These challenges include the heterogeneity of the data, the constraints of the sample size, and the complexity of brain tissue-specific expression. This will further improve gene prioritisation methodologies and boost the translational value of research results. Additionally, the inclusion of multi-omics datasets (including epigenomics and proteomics), longitudinal patient data, and prediction models based on machine learning will be used.

At the end of the day, systems biology acts as an essential link between raw high-throughput data and therapeutically useful findings in the field of depression research. In the end, it contributes to the creation of more effective diagnostic, preventative, and therapeutic methods by paving the way towards a more precise and data-driven understanding of mental health diseases. This is accomplished via its integrated and holistic approach.

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