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The Influence of Genetic Markers on the Development of Mental Disorders: A Systematic Review of Studies

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Abstract **Introduction:** The etiology of mental disorders is largely influenced by genetic elements. Several studies have shown that genetic elements influence major mental disorders (MDs). However, the quantity and type of the genetic input remain unknown and require further research. **Objective:** In this review, we aim to investigate the impact of genetic markers on the development of mental disorders. Methodology: In our study, we included English studies from online databases such as Web of Science, Scopus, Google Scholar, PubMed, and the Cochrane Library using the following keywords “genetic factors”, “genetic markers”, “mental disorders”, “anxiety”, “depression”, and “schizophrenia” till March 2024. **Results:** The result of the search utilizing the strategy of our search was 2107 studies. We selected the articles that were relevant to our topic by screening these articles. After eliminating the remaining papers based on title and abstract screening, we conducted a full-text screening of 318 publications. In the end, we consulted 68 articles to learn more about our subject and compose this evaluation. **Scientific Novelty:** Most of the previous studies discovered that genetic elements contribute to major MDs. However, the nature and extent of the genetic contribution have not been determined. In our review, we discussed the genetic contribution to the occurrence of MDs. **Practical Significance of the Results Obtained:** The influence of genetic research on individuals with MDs and their families was one of our review’s main concerns. Understanding the extent of genetic elements’ contribution to MDs may have implications for society, research, patient outcomes, and quality of life. **Conclusion:** This comprehensive study demonstrates that the development and onset of MDs are affected by several elements, which can be genetic polymorphisms and genetic mutations. The potentiality of genetics studies to detect the occurrence of MDs may help in the early recognition of these conditions. It could assist in identifying people who are more susceptible to developing specific disorders according to their genetic profile.

Key Words genetic factor, mds, psychiatry, biomarkers, neuropsychiatric disorders

1. Introduction

No mental or psychiatric disorder has a completely heritable or genetic base, and a variety of environmental elements can have a significant impact on an individual’s probability of having a particular disorder, regardless of whether genetic elements are present or not [1]. Therefore, a large number of these disorders have many causes, some of which are genetic and some of which are environmental [2]. Searching for MD genes is driven by technological advancements in genetics. Several significant findings have been established, despite the fact that the research outcomes have occasionally been difficult to understand [3]. Researchers have identified and located genetic markers linked to Alzheimer’s disease. There is strong evidence from a large and reliable collection of research supporting the involvement of genetic elements in major mood disorders and schizophrenia. Other, fewer sets of data support the concept that genetic elements predispose to obsessive-compulsive disorders and panic disorders [4].

A significant portion of MDs are heritable, which means that if another family member has the disorder, the probability of developing it increases significantly [5]. In addition, there may be certain genetic abnormalities or polymorphisms that predispose people to a greater possibility of MDs even if they have no family history of it. Genetic mutations, poly-

morphisms, or epigenetic modifications can influence brain development, changing the brain's typical wiring [6]. As a result, MDs can develop at any age, including from birth such as Autism spectrum disorder or later in life when paired with environmental elements such as bipolar disorder. Compared to "neurotypical" people, these predispositions may reduce the threshold needed for mental problems to start in adults [7].

Without question, molecular genetics is revolutionizing medicine. Genetic advancements have influenced studies on MDs [8]. Early success in identifying genes associated with mental diseases such as schizophrenia and bipolar disorder (manic-depression) was widely documented [9]. Traditional research methodologies, such as family, twin, and adoption studies, remain the mainstay of MDs genetics, despite the rise of molecular genetics and gene discovery. Characterizing the prevalence and pattern of features across related individuals can shed light on their genetic origin and answer issues such as: Are these characteristics inherited? What is the role of genetic versus nongenetic elements? [10]

A. Research problem

MDs, including schizophrenia, bipolar disorder, autism spectrum disorders, and others have substantial genetic bases involving polymorphisms, mutations, and epigenetic alterations. These disorders can arise spontaneously during development or be inherited directly from an affected parent. However, the degree and form of genetic input remain unknown and are the subject of several studies.

B. Research focus

What researchers discover regarding the genetics of MDs, and what they might know or learn, has an impact on society at large, clinical practice, and research. Our systematic review focused on these implications to determine the relation between the genetic markers and the occurrence of MDs.

C. Research questions

1) Is there evidence that serious MDs have a hereditary component?
2) What are the issues about sharing information regarding genetic risk for MDs?
3) Are there any plans to release genetic diagnostics for major MDs soon?
4) How useful is genetic counseling for MDs based on current knowledge?
5) What more education would be required to ensure that medical professionals are up to date on the genetic components of MDs?

D. Research aim

In this review, we aim to investigate the impact of genetic markers on the development of MDs.

2. Literature Review

A. Mental disorders

A broad category of disorders known as MDs mainly affects behavior, emotion, and cognition. They usually start early in life and are highly prevalent overall in all nations where epidemiology has been studied [11]. MDs are a significant contributor to the global disease burden due to their early onset, high prevalence, clinical course that can be either remitting or chronic and relapsing, and disturbance of essential brain functions. The majority of the burden is caused by years lived with disability (YLDs), especially for those between the ages of 15 and 49, which is a crucial life stage for finishing school, beginning a family, and improving productivity at work [11].

Many cultures and civilizations have social stigmas attached to mental health issues. The slow development of scientific explanations for the causes of MDs and the incorrect belief that these conditions are caused by immoral behaviors or a lack of willpower encourage discrimination and negative attitudes [12]. Psychotic patients can appear threatening, yet those with mental diseases are significantly more likely to be victims of crime than perpetrators, and to commit suicide rather than homicide. Fear and shame are significant obstacles to getting help, getting diagnosed, and receiving treatment. For minor offenses that are directly related to their mental conditions, people with mental problems are frequently locked up without access to proper care [13].

B. Types of mental disorders

There are prevalent MDs such as post-traumatic stress disorder (PTSD), depression, panic disorder, obsessive-compulsive disorder (OCD), phobias, generalized anxiety disorder (GAD), and social anxiety disorder [13].

- **Depression** Depression is a kind of mood disorder characterized by a persistently depressing and sluggish state of mind. The Diagnostic Statistical Manual of MDs, Fifth Edition (DSM-5) of the American Psychiatric Association classifies depressive disorders into the following categories: disruptive mood dysregulation disorder, major depressive disorder, premenstrual dysphoric disorder, persistent depressive disorder (dysthymia), and depressive disorder-related to another medical condition [14]. Major depressive disorder (MDD) was listed by the World Health Organisation (WHO) in 2008 as the third most common cause of illness worldwide. The organization believes MDD will be at the top of the list by 2030. A person may exhibit symptoms such as anhedonia, or a decreased interest in pleasurable activities, feelings of guilt or worthlessness, difficulty concentrating, lethargy, disturbances in appetite, psychomotor retardation or agitation, difficulty sleeping, or suicidal thoughts.

  Major depressive disorder has a complex etiology, involving both environmental elements and genetics [15]. While depression can affect individuals without a family history of the illness, first-degree relatives of depressed individuals have an almost threefold increased risk of

developing depression compared to the general population [16]. There are known biological risk elements that could contribute to depression in older people [17]. A higher risk of neurodegenerative diseases (especially Parkinson's and Alzheimer's), multiple sclerosis, stroke, cancer, macular degeneration, seizure disorders, and persistent pain has been associated with rates of depression. Life events and challenges act as factors for the onset of depression. Traumatic events like the death of a loved person, a decline in or absence of social support, the responsibility of taking care of another person, financial difficulties, interpersonal problems, and disagreements are among the stressors that can lead to depression [18].

- **Alzheimer's disease** At least two-thirds of dementia cases in people 65 years of age and older are caused by Alzheimer's disease (AD). The most common kind of dementia is AD. Alzheimer's disease is a neurological disease that gradually deteriorates behavioral and cognitive functions like judgment, language, comprehension, reasoning, attention, and memory [19]. It begins slowly and progresses over time [20]. It ranks as the sixth most common cause of death in the US. Aging, genetics, brain trauma, infections, vascular diseases, and environmental variables (trace metals, heavy metals, and others) have all been linked to AD, which is thought to be a complex disease.
  Currently, the cause of the pathogenic changes (Aβ, NFTs, and synaptic loss) linked to AD is unknown [21]. While other ideas have been put out to explain AD, two are generally acknowledged as the main causes: one maintains that modifications in the production and processing of amyloid β-protein exist as the main trigger, while others claim that cholinergic dysfunction is a significant risk factor for AD [22]. Over time, it was determined that genetic elements were a major contributing element to the development of AD. Genetic elements accounted for 70% of the cases of AD; mutations in dominant genes such as Presenilin-1 (PSEN-1), Amyloid precursor protein (APP), apolipoprotein E (ApoE), and Presenilin-2 (PSEN-2) are linked to AD. The majority of cases of early-onset AD (EOAD) are inherited in an autosomal dominant pattern [23].
- **Obsessive-Compulsive Disorder (OCD)** OCD, or obsessive-compulsive disorder, is often a debilitating illness marked by distressing, intrusive thoughts. To lessen the agony and anxiety these thoughts cause, the patient may engage in rituals or obsessive behaviours. These rituals could cause a significant decline in function because they are intended to compensate for the ego-dystonic feelings of the obsessional beliefs [24]. They may involve other people or remain private and personal. While the exact cause of OCD is yet unknown, it is most likely complex. There is a genetic tendency for OCD since 45–65% of its variation can be related to hereditary reasons [25]. It's been demonstrated that mutant NMDA stimulates OCD-like behaviour in experiments on humans and animals. For instance, mutations in the NMDA subunit "NR2" have been linked to compulsive cleaning and contamination fears [26] Twin research has provided insight into the environmental and genetic variables that contribute to OCD.
  Based on a meta-analysis of twin analysis, non-shared environments were estimated for roughly 51% of the variance in OCD symptoms, while additive genetic elements explained about 40% of the variance. Furthermore, there is preliminary evidence to support the etiology of gene-environment interactions in OCD and the shaping of OCD symptoms by extremely general aetiological elements (e.g., those impacting negative emotionality). Certain subtypes of OCD, such as early-onset OCD with tics, maybe more heritable than others [27].
- **Generalized Anxiety Disorder (GAD)** Anxiety and worry over several things that the patient generally perceives as excessive or inappropriate are symptoms of GAD. It has proven challenging to characterize "generalized worry" in a way that can be broadly applied. The diagnostic threshold is being adjusted and raised in response to these criteria, which are clearly changing [28]. Genetics (first-degree relatives with GAD account for 25% of the etiology), stress, medical disorders like diabetes or other comorbidities like depression, and environmental variables like child maltreatment may all play a role. The precise mechanism is not fully understood. In children, anxiety can be frequently observed [29].
  Anxiety about strangers starts between months seven and nine. It seems that the noradrenergic, serotonergic, and other neurotransmitter systems impact how the body responds to exposure to stressful events. The serotonin system and noradrenergic system are often linked to anxiety. Many suggest that the low activity of the serotonin system and the strong activity of the noradrenergic system contributed to its formation. Serotonin-norepinephrine reuptake inhibitors (SNRI) and selective serotonin reuptake inhibitors (SSRI) are therefore the first-line treatments for it [30].
- **Schizophrenia** A complex, long-term mental illness, schizophrenia is typified by a wide range of symptoms, including disorganized speech or behaviour, delusions, hallucinations, and cognitive decline. For several individuals and their families, the condition is devastating because of its early start and chronic nature [31]. Negative symptoms (deficits or loss) and cognitive symptoms (difficulties with attention, executive function, or working memory) often coexist to cause disability. Additionally, positive symptoms including suspicion, delusions, and hallucinations might lead to relapse [32]. Positivity in the family history is the biggest risk factor for schizophrenia, which is a multifactorial condition.
  The overall lifetime risk is less than 1%, but for first-

degree relatives of patients it is 6.5%, and for monozygotic twins of affected individuals it is over 40%. The risk is related to the genetic proximity between the proband and the relative, according to research on twins, adoption, and extended families [33].

3. Methodology

A. General Background

In most cases, MDs in children are not identified for months or even years after the onset of symptoms; this is particularly true after the child reaches school age. Environmental, genetic, or a combination of the two may be associated with an increased risk of mental health issues. According to accumulating evidence from research on humans and animals, epigenetic modifications to DNA expression brought on by stressful life events at different times can increase the likelihood of MDs. Technological advances in genomics are driving the search for genes that cause MDs. Several major conclusions have been established, despite the fact that the research results were sometimes difficult to understand.

B. Inclusion Criteria:

- Research methodology includes RCTs, observational studies, meta-analyses, cohort studies, and case-control studies.
- Selected recent articles (i.e. 2010), with a cut-off date, to refresh the knowledge.
- Studies that highlighted the role of genetic markers in the development of MDs.

C. Exclusion criteria

- Non-peer review articles such as study proposals, opinions, and letters to the editor.
- Articles not related to our topic.

SubsectionInformation Sources:

1) Data Collection

We searched multiple online databases including: Web of Science, Scopus, Google Scholar, PubMed, and Cochrane Library. We used the following keywords in the search, “genetic factors”, “genetic markers”, “mental disorder”, “anxiety”, “depression”, and “schizophrenia” throughout the process. It helped us to encompass possibly every academic article that is related to the research topic for analysis.

2) Data Analysis

The involved studies were reviewed following three stages. The first step started with using EndNote Software to import the results of the search strategy from electronic databases into a sheet of Microsoft Excel. During the second phase, the titles and abstracts of the articles put into the sheet of Excel were screened. The next stage was assessing the involved citations from Stage 2’s full text. In addition, we cross-checked the studies’ references for any missed ones.

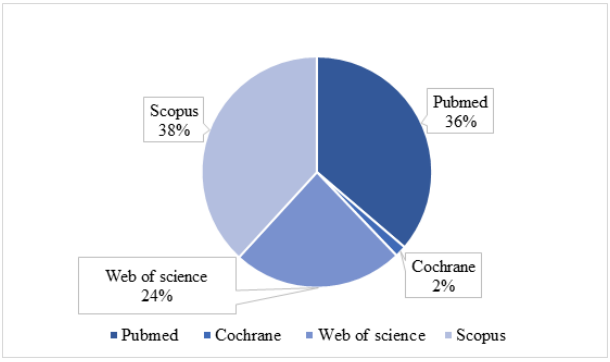

Figure 1: Distribution of selected articles across major databases for systematic review

3) Statistical analysis

We conducted a qualitative study of the previously published studies. We could not do a quantitative analysis because our study is a systematic review. The outcomes that will be measured in the quantitative analysis must be specified, and more than two studies reporting data on these outcomes must be located and compared to conclude. We attempted a quantitative analysis in our research, but we could not identify specific results relevant to our subject or papers that presented similar data. To get strong evidence and current results and conclusions, we conducted a qualitative analysis of papers relevant to our topic, presented their findings, and compared them.

4. Results

Our search approach produced 2107 articles as the outcome of the search. These articles were reviewed, and we selected the ones that were relevant to our topic. After removing papers based on title and abstract screening, we conducted a full-text screening of 318 articles. In order to compile the data for this analysis and write about our subject, we ultimately employed 68 publications (Figure 1).

In a study that used DCTclock as a susceptibility marker for Alzheimer’s disease (AD) and investigated polygenic risk score (PRS) and Apolipoprotein E (APOE) associations with DCTclock composite scores as dependent measurments. They found that in comparison to those without an APOE gene, those with at least one APOEgene had a 2.59-unit lower DCTclock Total Score (p = 0.023). Individuals with a minimum of one APOE gene also showed reduced COP Information Processing scores.

There was a significant correlation between the PRS and the DCTclockTM Total Score (beta = -28.9, p = 0.040). A significant reduction of 28.9 units in DCTclock Total Score was linked with one unit gain in PRS [34]. Several studies proved that the presence of the APOE gene or BIN1 gene was associated with a high risk of AD (OR= 4.24, 95% CI =3.52-5.10, P=1.5 x 10-52) and (OR =1.53 95% CI = 1.35-1.75, P=1.4 x 10-10), respectively [35], [36].

In a study that tried to determine the relationship be-

tween family genetic risk scores (FGRS) and different MDs (schizophrenia, depression, and bipolar disorders). Their analysis revealed that the risk for the development of these conditions was strongly accompanied by high FGRS. The FGRS was highest with major depression disorder then schizophrenia then bipolar disorder [37]. Additionally, there was genetic evidence for the association of NOTCH4 variant rs2071287 with schizophrenia susceptibility. The results of this association analysis indicated that there was a substantial correlation between schizophrenia and rs2071287. Additionally, it was found that rs2071287's GG genotype was linked to a greater risk of schizophrenia (P-value = 6.45×10^{-5}) [38].

The results showed correlations between genetic susceptibility to depression and six single nucleotide polymorphisms (SNPs) (rs1360780, rs3800373, rs4713916, rs9470080, rs9394309, rs9296158) [39]–[41]. Furthermore, compared to healthy controls, depressive patients showed increased levels of FKBP5 mRNA expression. However, the genotypes and alleles associated with a hereditary predisposition to depression showed variation throughout research projects. Research from Poland, Germany, Italy, the United States, and certain European countries showed that FKBP5 gene polymorphisms were linked to depression susceptibility [39]–[43]. In contrast, some research from China, Denmark, and Germany, and studies with Black participants did not show a link between FKBP5 gene polymorphisms and depression susceptibility [44], [45].

A family genetic study of obsessive-compulsive disorder (OCD) and frequent comorbid diseases revealed that The participants had significantly higher rates of anxiety, depression, disruptive behavior, and tic disorders, although the rates in the siblings were higher at a point where the individuals and controls were not. Of first-degree relatives, 26% had clinical OCD, 9% had Tourette's syndrome or persistent tics, and 21% fulfilled the requirements for attention-deficit/hyperactivity disorder (ADHD) [46].

Genome-wide single nucleotide polymorphism (SNP) data for eight neuropsychiatric disorders utilizing a combined sample of 494,162 controls and 232,964 cases were analyzed. Schizophrenia and bipolar disorder had the strongest genetic correlation (rg = 0.70 ±0.02), while OCD and AN had the second-highest correlation (rg = 0.50 ±0.12). It's interesting to note that MD was positively connected with two childhood-onset diseases, ADHD (rg=0.44 ±0.03) and autism spectrum disorder (ASD) (rg=0.45 ±0.04), according to genome-wide genetic correlations. For the majority of disorder pairs, substantial genetic associations were seen, despite differences in amplitude; this suggests that psychopathology is supported by a complex, higher-order genetic structure [47].

Schork et al. conducted a cross-disorder genome-wide association research and verified earlier results of people and cross-disorder SNP-heritability for major psychiatric diseases. They found four new major loci across the genome that are likely to control genes expressed in interneurons and radial glia in the midgestation-developing neocortex. Partitioning cross-disorder SNP-heritability, which is enhanced at regulatory chromatin active during neurodevelopment of the fetus, supports this period. These results imply that gene dysregulation directing neurodevelopment due to frequent genetic variations may lead to a general susceptibility to several psychiatric consequences later in life [48].

Our findings revealed that several MDs such as depression, schizophrenia, Alzheimer's disease, OCD, and bipolar disease are affected by genetic elements. Most of them may cause by gene dysregulation or uncontrolled expression of genes. Most of them are hereditary diseases that pass through families.

5. Discussion

This is a systematic review that aims to find a correlation between genetic elements or markers and the development of MDs such as depression, schizophrenia, Alzheimer's disease, OCD, and bipolar disease. We conducted a qualitative analysis of previously published articles and found a strong relationship between the development of MDs and genetic overexpression or gene dysfunction.

Genetic research has gained substantial interest as it may recognize persons at high risk for acquiring MDs according to their genetic vulnerability before the appearance of the clinical symptoms [49]. A greater understanding of the genetic components behind MDs and their effects on brain structure and cognitive function from a young age has been made possible by recent developments in neuroimaging and genomics. Genetic investigations can help identify people who are more susceptible to disease according to their genetic profile, which has the ability to completely change our knowledge of these complicated polygenic forms of MDs [50].

In the past few decades, numerous genes have been successfully investigated, offering important new information about the molecular epidemiology of this condition [51]. More than 100 loci linked to schizophrenia have been identified by several studies on genetic polymorphism, which also showed that the condition is multiple genetic (polygenic), characterized by different genetic variations but small impact sizes [52], [53]. Research on the correlation between candidate genes and this mental illness has identified several genes, including brain-derived neurotrophic factor (BDNF), neuregulin 1 (NRG1), protein kinase 1 (AKT1), and catechol-O-methyltransferase (COMT), that may be presumed to play a role in both functional and positional aspects. The BDNF gene's rs6265 SNP, which has been investigated the most, may be related to this condition [54].

The results of relatively few articles that investigated variations in other domains of cognition, such as the speed of processing, have been inconsistent. Previous studies that investigated variations in cognitive performance based on APOE status in healthy individuals have demonstrated that APOE carriers are susceptible to minor variations in memory performance relative to non-carriers [55], [56]. In preclinical

AD and cognitively unimpaired samples, research has more recently looked at relationships between cognitive trajectories and PRS. The findings indicate that while PRS predicts impairment of cognition impairment, these impacts are frequently predominantly driven by the APOE genotype [57], [58].

A more accurate assessment of AD risk may result from combining PRS and APOE haplotypes with additional risk variables. The impact of AD genetic burden on early-life cognitive health in individuals without dementia, however, remains largely unresolved [59]. While some studies indicate that the relationship between cognitive decline and APOE may have early life roots, care must be taken when interpreting causal relationships because a number of variables, including gender, age, ethnicity, and the kind of cognitive evaluation used, can influence the results. Furthermore, variations in cognitive assessments may introduce bias into the PRS estimation, producing inconsistent results across studies. Determining the validity of AD-PRS when removing the APOE $\epsilon 4$ allele risk in different healthy populations at variant ages is an important factor to take into account [59].

Relatives' higher rates of disease occurrences [60]–[63] than predicted by genetic correlations raise the possibility that the latter, which are based only on common variants, may be overestimated. As a matter of fact, pleiotropy has been consistently observed for rare variations with respect to neurodevelopmental and behavioral disorders [64], while genetic connections are now limited to common variants. It is unknown if uncommon variations exhibit greater degrees of genetic association and/or pleiotropy than common variants [65].

There is a strong correlation between mutations in the D2S2944 124 bp allele and MDD. The linkage of D2S2944 with MDD has been shown to be special and seems to be sex-related by differentiating MDD relapses, nonpsychotic individuals, and early-onset persons [66]. This may be because of a chain difference in susceptibility genes near the marker locus. Cuzzoni et al. found that by altering the glucocorticoid receptor's function, the NR3C1 rs41423247 (C/G) polymorphism might impact the development of MDD [67]. A homozygote mutation in NR3C1 rs41423247 was shown to be accompanied by depressive symptoms in the general population (P=0.01) and in Caucasians (P=0.02), according to a meta-analysis [67].

After examining gender variations in the structure of the genes of depression, five genetic markers accompanied by a higher risk of depressive symptoms in females were found using qualitative analysis. These markers included rs79442975, and rs62640397 in FDX1L, rs201432982 in PDE4A, and the other two rs820148 and rs820182 in MYO15B [68]. A decrease in neuronal activity and a dysregulation of negative feedback via the hypothalamic-pituitary-adrenal axis can result in depression problems in individuals with PDE4A variants [44].

6. Limitation

The major drawback of our study is that it includes several types of MDs, not a specific one. This lack of specificity may affect the strength of our evidence. The data from the summarized trials is apportioned into paragraphs and compared to each other without being pooled together. The topic of our review is very wide as each MD may influenced by genetic elements in different ways so each disorder should be discussed in a separate article to reach conclusions with strong evidence.

7. Conclusion

This comprehensive study demonstrates that the development and onset of MDs are affected by several elements, which can be genetic polymorphisms and genetic mutations. The potentiality of genetics studies to detect the occurrence of MDs may help in the early recognition of these conditions. It could assist in identifying people who are more susceptible to developing specific disorders according to their genetic profile.

8. Suggestions for Future Research

Future research should focus on developing effective therapeutic and preventive strategies for MDs, taking into account the complex interactions of environmental, lifestyle, and genetic elements. Investing in healthy cohort research and solving important issues can cause considerable advances in diagnosing multiple MDs, which could enhance the lives of people at high risk of acquiring MDs and their families.

Conflict of interest

The authors declare no conflict of interests. All authors read and approved final version of the paper.

Authors Contribution

All authors contributed equally in this paper.

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