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Insignificance of Variant Analysis in Neuropsychiatric Disorders

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Abstract

Neuropsychiatric disorders encompass a wide range of complex disorders where not only the brain of an affected individual but also their behaviour is poorly affected. These disorders include attention deficit hyperactivity disorder (ADHD), eating disorders, Bipolar disorder, Schizophrenia and Autism, arising from the complex interplay of different factors like environment, genetics and epigenetics. Among all genetics plays quite a significant role in the progression of these disorders. Genetic variants like SNPs, CNVs and genetic mutations are important in influencing the progression of these disorders. Several technologies such as Genome-wide association studies can be used to identify the key gene loci and pathways for the progression of neuropsychiatric disorders. This article aims to have an overview of all genetic variants of various neuropsychiatric conditions with an understanding of their pathways. Moreover, it also highlights different techniques that are used in finding these key gene variants. Also, the complexities that create challenges to genetic variant analysis for medical relevance and how upcoming technologies be used to overcome this problem.

Keywords: Neuropsychiatric disorders, Bipolar disorder, Schizophrenia, Anxiety, CRISPR-Cas9, omics, gene loci, SNPs, CNVs and Genome-wide association studies (GWAS).

INTRODUCTION

Neuropsychiatric disorders are a wide range of complex disorders where not only the brain of an affected individual but also their behaviour is poorly affected. This often makes it hard for them to fit into society leading to behavioral, cognitive and social challenges. It majorly encompasses a wide range of conditions ranging from psychiatry and neurology (1). These disorders include attention deficit hyperactivity disorder (ADHD), eating disorders, Bipolar disorder, Schizophrenia and Autism. Several factors lead to the development of these disorders (2). These symptoms include trauma caused to the brain, environmental factors, microbiota of the gut, nutritional deficiency and many more but one of the most important factors among all is genetic variations in the genome that are directly or indirectly associated with the development of neuropsychiatric disorders. It has become a strong and quite significant area of research (3). Genetics plays an important role in several neuropsychiatric disorders such as in the cases of Schizophrenia and bipolar disorder. The twin studies and family

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studies have shown that the conditions of these disorders become more common among close bloodline relatives. It suggests the heredity link of these disorders (4). Moreover, mutations in the specific gene can significantly increase the chances of these conditions. The best example is variations in the genes related to neurotransmission and neurodevelopmental processes which increases the risk of neuropsychic disorder in an individual. In addition, these disorders can be directly linked with genetic syndromes (5). Such as in the case of Fragile X syndrome the person has intellectual disabilities which result in Autism-like behaviour (6). 22q11.2 Deletion syndrome where a small piece of chromosome 22 is deleted, is highly related to the development of Schizophrenia (7). Furthermore, as discussed above genetics is not solely responsible for the development of these disorders rather several factors sum up to produce these conditions in the individual. Environmental factors such as stress, trauma, infections and epigenetics can interact with genetic factors to instigate the onset of neuropsychiatric disorders. These interactions are also known as gene-environment interactions (8).

Several genetic loci associated with neuropsychiatric disorders have been identified by using advanced genetic research such as genome-wide association studies (GWAS) and Next-generation sequencing. These understandings help to develop new therapeutic strategies like gene therapy and pharmacogenomics approaches to alter and rectify genetic mutations (9). The analysis of variants is an important method to identify and assess genetic variations within an individual's genome resulting from these disorders. Diving deep into understanding and analysing variants to find the molecular mechanisms of neuropsychiatric disorders can be used to enhance the therapies for these disorders (10).

Genetic Variants and their contributions to different neuropsychiatric disorders.

The differences in DNA sequence that occur among people are known as genetic variants. These differences or alterations play quite a significant role in the development of neuropsychiatric disorders as they affect gene expression and the overall health of an individual (11) (12). There are different types of genetic variants including Single nucleotide polymorphism also known as SNPs where their alteration of the single nucleotide (A, C, T or G) in the sequence of DNA to another nucleotide (13). Certain SNPs that happen in the coding sequence can increase the risks of neuropsychiatric disorder in a person (14). Genetic variations where there is a change in copy number such as deletion or duplication can affect gene expression which eventually leads to neuropsychiatric disorders (15). Indels refers to the insertion or deletion of a small segment of nucleotide within the genome. These indels can cause frameshifts in protein-coding sequences. This leads to the synthesis of some non-functional proteins. There are some quite uncommon structural variants where there is a large-scale change in the genome (16). These consist of inversion, large deletion, large duplication in genomic segments and translocation. These alterations can lead to disrupting protein formation that affects the cognitive part of the brain and leads to neuropsychiatric disorders like Autism. Individualistic study of these variants in a specific disorder is required to understand their role in the etiology of various neuropsychiatric disorders (17).

Genetic variants in Schizophrenia.

Schizophrenia is a chronic mental condition where the person's behaviour and thoughts are adversely affected (18). A person with schizophrenia experiences delusions, and hallucinations and hard to differentiate between the real world and imagination. There are a wide range of causes for the development of schizophrenia in an individual which involve epigenetic factors, and environmental and genetic factors(19). Genetic components play the highest role among all the factors. Several Polygenic variants contribute to it which can be identified by GWAS (genome-wide association studies). The variants in the C4 genes can cause abnormal synaptic pruning leading to the development of Schizophrenia (20). Dysregulation in the Dopamine receptor caused due to DRD2 alteration is one of the main causes of the pathophysiology of Schizophrenia (21). Neuronal signaling and plasticity are adversely affected because of the variants in CANA1C which is associated with calcium channel regulation of neurons (22). Some rare genetic variants that lead to schizophrenia are 22q11.2 deletion syndrome, where there is deletion or duplication in 15q11.2 and 1q21.1 genes (23) (24). Several single nucleotide variants such as SETD1A affect the transcriptional regulation and lead to the expression of abnormal proteins responsible for schizophrenia (25). There are several epigenetic modifications like histone modifications and DNA methylations which also contribute to gene expression without causing any change to DNA sequence. Variants of these genes cause neurotransmitter dysfunction like DRD2 is related to alterations in dopamine receptors and GAD1 genes with GABA synthesis (26). This leads

to synaptic pruning and neurodevelopmental abnormalities. However, it becomes quite challenging to determine genetic variants as they vary across populations. Also, there are several genes associated with it that overlap with other neuropsychic disorders like Autism (27). Several techniques like CRISPR can be used to explore gene function. Moreover, Genome-wide association studies can be done to identify common variants.

Genetic variants in Bipolar Disorder

Bipolar disorder is a complex mental condition where the affected person experiences extreme shifts in energy and mood. People can have manic episodes when they feel energized and depression episodes when they feel sad (28). These mood shifts are abnormal and quite severe than normal ups and downs. This condition is linked with several significant components. The heritability estimate is approximately 60 to 85 % as demonstrated by several family studies (29). There are several genetic loci linked with Bipolar disorder which are identified by using GWAS (Genome-wide associated studies). The key genes such as CACNA1C encode for the subunit of voltage-gated channels, which plays a significant role in neuronal signalling. Genes like ODZ4 and NCAN play an essential role in neurodevelopment (30). GRIN2A is linked with glutamatergic signalling and ADCY2 is involved in cAMP signalling pathways, these genes influence the regulation of mood in humans (31). The variants of these genes can contribute to the development of Bipolar Disorder in the person. The copy number variants of DCLK1 and NRXN1 are linked with Bipolar Disorder. The combined effect of all variants can increase the chances of Bipolar Disorder in a person. These variants generally affect the neurotransmitter systems which adversely affect ion channels leading to problems in neuronal excitability and eventual mood stabilization (32). Moreover, variants of CLOCK can also affect circadian rhythms that are frequently disturbed in Bipolar Disorder. There are several epigenetic factors also involved like altered methylation patterns and dysregulation of histone modification involved in it (33). Interaction of BDNF genes with the environment can sometimes be responsible for early life trauma (34). A deep understanding of these variants can help in the development of Precision medicines that involve targeted mood stabilizers. Moreover, 'omics' involvement like genomics, proteomics and transcriptomics can be useful in better understanding of genetic variants of Bipolar disorder and also in evaluating the progression of the disorder(35).

Genetic Variants in Anxiety

Anxiety is a neuropsychic condition where there is an abnormal behavioural disturbance with excessive worry and fear. Though environmental factors like stress and trauma play a significant part in the course of development in a person, genetic variants also play a crucial role in it. The family studies and twin studies have demonstrated that there are approximately 30 to 50 % chances that Anxiety is heritable (36). The GWAS findings show alteration and polymorphism of 5-HTTLPR in the promoter region of SLC6A4 can affect serotonin reuptake responsible for increasing anxiety sensitivity in a person (37). The Val158Met variant of COMT i.e. Catechol-O- Methyltransferase which regulates the metabolism of Dopamine can influence cognitive controls in Anxiety. The hippocampal functions are dysregulated due to the Val66Met variants of BDNF which can eventually increase susceptibility towards Anxiety in a person (38) (39). Variants of CRHR1 genes (Corticotropin-releasing hormone receptor 1) are linked with increasing stress and Anxiety levels (40). Variants of GABRA2 which encodes the GABA receptor's subunit can alter the inhibition of neural signals, eventually increasing risks of Anxiety (41). The combined effect of some copy number variants like 1q21.1 with other neuropsychiatric conditions plays quite a crucial role in the progression of Anxiety Disorders (42). The variants of gene CACNA1C also contribute to the course of development of Anxiety disorder (43). FKBP5 is responsible for the regulation of glucocorticoid receptors. The variants of this gene are often linked with the Anxiety induced by stress (44). The risk for Anxiety is also increased because of the polymorphism in the MAOA (Monoamine Oxidase A) gene which is responsible for the breakdown of dopamine and serotonin (45). Epigenetic factors like excessive methylation of SLC6A4 regions are often responsible for decreasing serotonin transportation which eventually increases sensitivity towards anxiety. The HPA axis is often disrupted by the variants of FKBP5 that up-level the cortisol and lead to Anxiety. Variants like BDNF often interact with environmental factors like stress to modulate anxiety risks (47). A better understanding of these genetic factors and variants can contribute significantly to developing personalized medications for Anxiety Disorders (46). Genetic markers can be developed as a potential biomarker for the diagnosis of Anxiety Disorders (49). Moreover, integrating CRISPR-Cas9 technologies can boost the study of the functions of genetic variants (48).

CONCLUSION

Genetic variants play a significant role in the progression of several neuropsychiatric disorders. Genetic factors like copy number variants (CNVs), SNPs, Indels, and epigenetics play quite a crucial role in Bipolars, Schizophrenia and Anxiety. However, these factors are not solely responsible for the progression of neuropsychic disorders, environmental factors also play a significant role in the occurrence of these disorders. Though several genetic factors are studied independently, the combined effect of them still needs to be studied at different levels. Moreover, 'omics' involvement like genomics, proteomics and transcriptomics can be useful in better understanding genetic variants of neuropsychiatric disorders and also in evaluating the progression of the disorder. Advancing technologies like next-generation sequencing and CRISPR-Cas9 technologies are promising for a better understanding of these disorders that can be used in diagnostics and personalized treatments for neuropsychiatric disorders in future.

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