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Genetics of Bipolar Disorder

Salma Abdeljalil*

Centre of Biotechnology of Sfax- University of Sfax, Tunisia

***Corresponding Author:** Salma Abdeljalil, Centre of Biotechnology of Sfax- University of Sfax, Tunisia, Tel:+21699731917, Email :Salma.abdeljalil@gmail.com

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Abstract

The heritability of schizophrenia and bipolar disorder (BD), which exceeds 80% in twin studies, is complex and multimodal. Since genome-wide association studies (GWASs) have shown that the risk of schizophrenia and BD is conferred by a large number of alleles with small effect sizes, all of which together explain only a portion of susceptibility, the idea that schizophrenia and BD are monogenic disorders has, however, long since been abandoned. Additionally, some conclusions from research using a candidate gene strategy have not been supported by GWASs.

It has been discovered that the polygenic risk score, which was created based on GWASs, mediates about 20% of familial liability for schizophrenia, indicating a significant role for non-genetic factors. Additionally, it has been suggested that some cases of schizophrenia may be caused by uncommon structural aberrations, including as copy number variations, deletions, duplications, and translocations, which have mild to significant impacts. It has been established that schizophrenia and BD may have similar genetic roots, which further complicates matters.

Keywords: Bipolar Disorder; Risk Factors; Genomic Variants; Structural Variants; Mendelian Disorders; Genetic Testing

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Introduction

Bipolar Disorder

Bipolar disorder is a mental health condition that causes extreme shifts in mood,energy, and behavior. This disorder most often appears in late adolescence or earlyadulthood, although symptoms can begin at any time of life.

People with bipolar disorder experience both dramatic "highs," called manic episodes,and "lows," called depressive episodes. These episodes can last from hours toweeks, and many people have no symptoms between episodes. Manic episodes arecharacterized by increased energy and activity, irritability, restlessness, an inabilityto sleep, and reckless behavior. Depressive episodes are marked by low energy andactivity, a feeling of hopelessness, and an inability to perform everyday tasks. Peoplewith bipolar disorder often have repeated thoughts of death and suicide, and they havea much greater risk of dying by suicide than the general population.

Manic and depressive episodes can include psychotic symptoms, such as falseperceptions (hallucinations) or strongly held false beliefs (delusions). Mixed episodes,which have features of manic and depressive episodes at the same time, also occur insome affected individuals

Bipolar disorder often occurs with other mental health conditions, including anxietydisorders (such as panic attacks), behavioral disorders (such as attention-deficithyperactivity disorder), and substance abuse.

Frequency

Bipolar disorder is a common form of mental illness. At some point during their lifetime, 2.4 percent of people worldwide and 4.4 percent of people in the United States arediagnosed with this condition [1].

Causes

Very little is known for certain about the genetics of bipolar disorder. Studies suggestthat variations in many genes, each with a small effect, may combine to increase therisk of developing the condition. However, most of these genetic variations have beenidentified in single studies, and subsequent research has not verified them. It is unclearwhat contribution each of these changes makes to disease risk. Some of the geneticchanges associated with bipolar disorder have also been found in people with othercommon mental health disorders, such as schizophrenia. Understanding the genetics of bipolar disorder and other forms of mental illness is an active area of research.

Studies suggest that nongenetic (environmental) factors also contribute to a person'srisk of developing bipolar disorder. Stressful events in a person's life, such as a death inthe family, can trigger disease symptoms. Substance abuse and traumatic head injuries

have also been associated with bipolar disorder. It seems likely that environmental conditions interact with genetic factors to determine the overall risk of developing this disease [2].

Inheritance Pattern

The inheritance pattern of bipolar disorder is unclear. Overall, the risk of developing this condition is greater for first-degree relatives of affected individuals (such as siblings or children) as compared to the general public. For unknown reasons, the risk of inheriting the disorder appears to be higher in some families than in others. However, most people who have a close relative with bipolar disorder will not develop the condition themselves.

Many individuals with bipolar disorder have relatives with other mood, anxiety, and psychotic disorders (such as depression or schizophrenia). These disorders may run in families in part because they share some genetic risk factors with bipolar disorder. However, these conditions are relatively common in the general population, and so it would not be surprising to see more than one case in a family just by chance [3].

Altered potassium levels in neurons may cause mood swings in bipolar disorder

CA3 neurons were hyperactive due to increased potassium currents. When potassium channel blockers were administered, the hyperactivity subsided. But when given lithium, the medication not only lowered potassium currents while also reversing hyperactivity. The results support

the theory that potassium currents contribute to bipolar illness.

By taking a closer look at the CA3 neurons of lithium responders, the team discovered that these cells had a higher-than-usual number of potassium channels, as well as stronger potassium currents across these he channels. Tincreased potassium currents, the scientists showed, were responsible for the hyperactivity of the CA3 neurons: when they exposed the cells to a potassium channel inhibitor, the hyperactivity disappeared. Curiously, when they exposed the cells to lithium, the drug not only reversed the hyperactivity, but also reduced potassium currents.

Researchers at Salk have recently discovered previously unknown information that explains why particular neurons in bipolar patients alternately become overexcited and underexcited.

Moreover, they used experimental and computational methods to describe how variations in potassium and sodium currents in the brain cells of people with bipolar disorder may help to further explain why some patients respond to lithium and others do not in two papers that were published in the journal Biological Psychiatry in February 2020 and October 2019 [4].

The team plans further studies on what happens to large neural networks when they alternate between hyperexcitable and hypoexcitable phases to understand whether these changes may be behind the manic and depressive moods seen in bipolar disorder.

Diagnosis and Management

Interactions between Variation in Candidate Genes and Environmental Factors in the Etiology of Schizophrenia and Bipolar Disorder: a Systematic Review

Bipolar disorder (BD) and schizophrenia are complex, multifaceted illnesses with significant heritability rates. The role of many risk variants with tiny effect sizes, which may only account for a small portion of susceptibility, is becoming acknowledged as playing a role in the etiology of various disorders. Numerous environmental elements have been discovered to play a significant impact in their causation at the other site. In order to bridge the gap between genetic foundations and environmental damages, a number of research have recently focused on gene-environment interactions. We conducted a systematic evaluation of papers examining the connections between genes and environments in BD and schizophrenia spectrum traits for this study.

The interaction between variations in the genes encoding catechol-O-methyltransferase (COMT), brain-derived neurotrophic factor (BDNF), and FK506-binding protein 5 (FKBP5) has been investigated in the bulk of studies in this subject. Numerous outcomes of schizophrenia spectrum disorders and BD were found to be affected by polymorphisms in the COMT, BDNF, and FKBP5 genes, which may combine with early life stress and cannabis addiction or dependency. Additional replication of several relationships in larger clinical and non-clinical samples is still necessary. Future research should also focus on the direction of causation and probable mechanisms of the connection between gene and environment interactions and many categories of outcomes in BD and schizophrenia [1].

Genetic variations in FOXO3A are associated with Bipolar Disorder without confering vulnerability for suicidal behavior

The genetic component of Bipolar Disorder (BD) and suicide propensity is significant. However, particularly among BD patients, little is understood regarding the genetic contribution to the risk of suicide. Since FOXO3A participates in various behavioral processes that are relevant to mood, it may be a new gene candidate for BD. Therefore, it was investigated to see if FOXO3A polymorphisms are related to bipolar disorder and suicidal conduct in bipolar patients [5].

Several studies suggest that genetic variants play a role in suicide risk, indicating that heritable factors have a significant impact on vulnerability to suicidal behavior. However, little is known about the hereditary pathways that may contribute to the risk of suicide in people with bipolar disorder. Although the causes of BD are unknown, gene expression analysis of postmortem brains, neuroimaging, and genetic association studies provide compelling evidence that disruptions in dopaminergic (DA) and serotonergic (5-HT) neurotransmission may play a role in BD susceptibility

and suicidal behavior.

From a genetic standpoint, FOXO3A is an intriguing gene candidate connected with the DA and 5-HT systems that may help us comprehend the hereditary link between BD and suicidal conduct. This gene is a member of the Forkhead (Fox) transcriptional factor superfamily, which is distinguished by a conserved DNA-binding domain that regulates genes involved in cell proliferation, apoptosis, metabolism, and neurodevelopment.

FoxO3a affects various behavioral processes associated with anxiety and depression. A recent study employing a knockout (KO) mouse model suggested that FoxO3a could be a transcriptional target for the treatment of anxiety and mood disorders.

Furthermore, brain-derived neurotrophic factor (BDNF) and lithium, a well-known mood disorder treatment (Fountoulakis et al., 2008), lower FoxO3a transcriptional activity. Thus, we hypothesize that genetic variations in the FOXO3A gene may have a role in BD and suicidal behavior.

Researchers wanted to determine whether FOXO3A genetic variants are linked with BD and suicide vulnerability in BD patients for the first time using a case-control association research in a Brazilian population.

The study included 273 BD patients of type I or II (30.6% males: 41.4 12.9 years; females: 40.5 12.3 years). FOXO3A SNPs were detected using TaqMan genotyping in 273 BD patients and 264 control persons. Three SNPs (rs1536057, rs2802292, and rs1935952) were linked to BD, but none were linked to suicide conduct.

Furthermore, there is no single bipolar gene that affects whether an individual will be diagnosed with bipolar during their lifetime, but the condition has a hereditary component. According to one analysis published in Neuroscience, bipolar illness is one of the most heritable medical conditions.

However, genetics is merely one component of most mental health illnesses. Mental health is influenced by genetics, experiences, lifestyle choices, and your current and prior surroundings.

Testing for chromosomal diseases and monogenic Mendelian disorders is well established; however, testing for common variations is still debatable. Before novel genetic tests can be presented, the basic idea of genetic testing involves at least three major requirements that must be met: analytical validity, clinical validity, and clinical utility. These criteria are currently not met for common genetic variations associated with psychiatric illnesses. There is certainly more work to be done before genetic testing for common variations in psychiatric diseases can be developed.

Because bipolar illness is a prevalent complicated disorder with a wide range of clinical manifestations, it has also been conceived as a set of linked mood disorders known as bipolar spectrum disorders. Furthermore, anxiety disorders, substance addiction, alcoholism, and attention deficit/hyperactivity disorder frequently co-occur with bipolar disorder. This occurrence is not fully understood. Although some specialists believe these illnesses share hereditary risk factors with bipolar disorder, others are skeptical. Bipolar disorder manifests itself between youth and early adulthood, however diagnosis is frequently delayed by several years.

The complex clinical picture at disease beginning, with often very modest symptoms, is a factor. This is particularly unfortunate, given around half of the individuals with bipolar disorder attempt suicide at least once in their lifetime, and many complete the attempt. Despite severe symptoms, treatment can be effective if the accurate diagnosis is made and treatment is started as soon as possible. As a result, significant attempts have been made to uncover genetic risk factors or biomarkers that would identify persons at risk and potentially aid in early diagnosis and treatment [6].

Salivary glutathione in bipolar disorder: A pilot study

Some studies of bipolar patients show lower levels of glutathione (GSH), a crucial cellular antioxidant. Although saliva offers a straightforward and practical way to measure GSH, it has not yet been used in the investigation of bipolar disorder. Comparing salivary levels of GSH and oxidized glutathione (GSSG) in bipolar patients and healthy controls was the aim of the study [7].

Sleep-wake cycle and melatonin rhythms in adoles-

cents and young adults with mood disorders: Comparison of unipolar and bipolar phenotypes, The potential of circadian measurements as early markers of different kinds of mood disorders has been examined by Robillard et al.

In comparison to those with unipolar depression, patients with bipolar illnesses showed significantly lower levels and a later onset of melatonin secretion. Additionally, aberrant phase angles between temperature, melatonin, and sleep have been seen in a few of cases [6].

Treatment for Bipolar Disorder

Many people with bipolar disorder are unaware of the significant fluctuations in their moods and the impact those changes have on their life and the lives of their loved ones. As a result, far too many people with the ailment go untreated, despite the fact that it could improve their quality of life.

Although hospitalization may be necessary in some cases of bipolar illness, the condition may usually be successfully treated outside of the hospital setting, ideally by consulting a psychiatrist.

If the patient is diagnosed with bipolar disorder, the first line of treatment will be medication to stabilize the moods. Once the mood swings and other symptoms have been stabilized, the doctor will devise a long-term treatment strategy to control the disease. To treat bipolar disorder, the doctor may prescribe one or more of the following medications: mood stabilizers, antipsychotics, antidepressants, and antianxiety medications.

Many persons with bipolar disorder will require mood stabilizing medication to deal with manic or hypomanic episodes as well as depressed ones. The doctor may prescribe one of the following medications: divalproex sodium (Depakote), lamotrigine (Lamictal), lithium (Lithobid), or carbamazepine (Tegretol, Equetro). An antipsychotic medicine may also be prescribed by the doctor to treat periods of depression or mania that persist despite therapy with other medications.

Antipsychotics can be used alone or in combination with a mood stabilizer to treat bipolar illness, especially in more severe situations if an individual is suffering delusions or hallucinations. Aripiprazole (Abilify), lumateperone (Caplyta), ziprasidone (Geodon), lurasidone (Latuda), olanzapine and samidorphan (Lybalvi), risperidone (Risperdal), quetiapine (Seroquel), cariprazine (Vraylar), and olanzapine (Zyprexa).

Concerning the Side Effects of Bipolar Disorder Medication, one of the challenges of bipolar disorder medication is the possibility of a wide range of side effects, some of which may be dangerous.

Acne, blurry vision, dizziness, dry mouth, fatigue or drowsiness, feeling thirstier than usual, frequent urination, nausea, skin rash, twitching of the face, hands, or other muscles, and weight gain are some of the most common side effects of bipolar medications, according to Mental Health America.

Aside from potential adverse effects, several medicines used to treat bipolar disorder can interfere with birth control pills or have health consequences during pregnancy, such as depakote. If the patient is taking birth control, pregnant, or wanting to become pregnant, she should consult her doctor before beginning any medication for bipolar disorder. According to the Depression and Bipolar Support Alliance (DBSA), certain bipolar illness drugs may increase the chance of birth abnormalities.

Furthermore, Psychotherapy for Bipolar Disorder may aid in the treatment of bipolar disorder. In fact, in addition to medication, the doctor will most likely offer psychotherapy (also known as talk therapy) or some other sort of counseling. If you have addiction in addition to bipolar disorder, this may include therapy for drug or alcohol use.

There are numerous sorts of psychotherapy. Cognitive behavioral therapy (CBT) is a popular type. A mental health professional (a psychiatrist, psychologist, or social worker) will work with the patient to identify bipolar episode triggers and build healthy and effective stress management and bipolar symptoms solutions. Interpersonal and social rhythm therapy (IPSRT) is another popular and successful treatment option for those suffering from bipolar illness.

IPSRT teaches people how to regulate their daily

rhythms, such as mealtimes, sleeping, and waking. Creating a daily regimen for food, exercise, and sleep might help maintain a steady mood. The doctor may also advise the patient and family on educational and support programs. These programs may aid in better understanding of the condition and its symptoms, as well as how to manage it.

Teachers, school administrators, and other support personnel are frequently involved in treatment when a kid is diagnosed with bipolar disorder to ensure the child is doing well and has access to the supports they require. (https://www.everydayhealth.com/bipolar-disorder/guide/treatment/).

Perspectives

Although bipolar illness is a frequent and complex genetic disorder, the method of transmission is yet unknown. Many scientists believe that common chromosomal variations increase the likelihood of the disease appearing. The first genome-wide substantial links between frequent single nucleotide polymorphisms (SNPs) and bipolar disorder have been welcomed by the scientific community. These discoveries are currently being attempted to be used to clinical practice, genetic counseling, and predictive testing.

Some experts are still being wary, though. After all, common variants only account for a relatively minor portion of genetic risk, and the functional implications of the identified SNPs are yet unclear. The linked SNPs are also not disease-specific, and most people who have a "risk" allele are healthy. On the other hand, rare structural variants and mutations in genes that were previously known to produce hereditary syndromes and monogenic Mendelian illnesses have been rediscovered in population-based genome-wide investigations in psychiatric disorders.

Psychiatric symptoms are common in many Mendelian disorders. These conditions frequently display nonspecific psychiatric symptoms that cut across diagnostic lines, such as intellectual disability, behavioral abnormalities, mood disorders, anxiety disorders, attention deficit, impulse control deficit, and psychosis, even though they do not fit the traditional definition of any particular psychiatric disorder. Testing for common variations is still debatable despite being well established for chromosomal diseases and monogenic Mendelian disorders. Before new genetic tests should be made available, at least three general requirements from the conventional concept of genetic testing must be met: analytical validity, clinical validity, and clinical utility. Currently, prevalent genetic variations in psychiatric illnesses do not meet these requirements. Prior to genetic testing for common variations in psychiatric diseases, further research is unquestionably required.

Moreover, eating healthy is also very important. In fact, healthy food and psychological profile are linked together. Sport is also recommended to equilibrate the secretion of brain hormones and other ones related to bipolar disorder. In fact, sports help also a lot to have a happy life and to live with a stable mood status especially for those who are suffering from bipolar disorder indeed.

Conflict of Interest statement

The author declare that there is no conflict of Interest.

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