The Role of Genetical Factors in Bipolar Disorder and the Underlying Mechanisms

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Abstract. Bipolar disorder (BD) is a type of mental disorder and nowadays it is more and more prevalent. It has some overlapped symptoms with some other mental disorders, including major depressive disorder (MDD) and schizophrenia (SCZ). Its familial and social factors have been largely investigated, whereas its genetic factors and relevant mechanisms still remained unclear. Several genetical loci of BD have been tested in the latest genome-wide association studies of BD. Also, familial and genetic risk factors have been found in studies of twins and families. It indicates that people who have relevant genetic variants in the family at risk may not have BD, which is astonishing. This shows the unclear relationship between the genetic and the environmental factors since the occurrence of BD is likely be a result of interactions between them. Future studies can employ longitudinal designs to explore the developmental trajectory of children with a familial risk of BD and examine the gene-environmental interactions related to BD.

Keywords: bipolar disorder, genes, familial factor.

1. Introduction

Bipolar disorder (BD) is a type of mental disorder characterized by episodes of depression and mania. It is a serious type of mental disorder which impacts the social and emotional functioning of the patients. They behave differently during the manic and the depressed period. During the manic period, exaggerated excitement and self-confidence, increased verbal activities, aggressive action would occur. However, patients are down during the depression period. Their actions are also slowed down. However, its factors, especially genetic factors, still remained unclear for scientists and psychologists to explore even though the related research has testified that factors including familial, seasonal, social, etc., exist. For example, during seasons of higher temperature, BD patients tend to act manically and exaggeratedly whereas they tend to act negatively and depressively during seasons of low temperature. There is a higher risk for BD to develop under societies with rigid stereotypes or great social norms which put great psychological pressure on patience.

BD is one of the most severe mental disorders in the world. There are about two hundred million people struggling with BD (2% of the world's population), and for each type, the possibility of patients struggling with BD throughout their whole life is approximately 1% (BD I, 0.1%-1.7%, BD II, 0.1%-3.0%). Both BD I and BD II feature episodes of mania and depression, whereas the mania period is different [1]. Mania episode in BD I lasts for at least for a week. Hypomania episode in BDI and BD II which lasts for four days. It is struggling to transfer mutually between the manic and depressive episodes with no sign. This transference for the patient may occur anywhere and anytime, which leaves a massive psychological burden and pressure on the BD patient. This significantly contributes to the suicide risk. Cognitive deficit (CD) has been found in BD. The relation between cognition and emotionality has also been indicated in the research [1]. CDs are categorized differently according to the timeline of BD. Before the occurrence of BD, which is before onset, with a significant focus of intelligence quotient (IQ), comparatively worse executive functions and poorer visuospatial ability before onset of BD patients were suggested in the experiment. Relatives of who are diagnosed with BD are also tested with CD. Their executive functions are impaired, including verbal and visual learning. Indicator of BD, which is response inhibition has been found. This needs further study and should gain more attention. Thus, CD is more significant to be the sign of BD than just to be a general symptom of BD.

Fortunately, specific treatments of BD have been researched. Treatment of mania in BD is certificated by the experiment conducted with tests of efficiency of a large number of different medications [2]. Antipsychotic medication is testified to be more adequate in the short term of treatment of BD, whereas anticonvulsants and lithium is proved to be more effective in continuous and long-term treatment. The treatment of depressive period in BD is always affected by the rigid controversy on the usage of anti-depression, whereas recent studies have shown no difference in effects of both anti-depression and placebo. Now antidepressants and antipsychotics are both used in the treatment of depressive episode in BD, but further research and experiments are still waiting to be conducted. Additionally, Lithium is always used in the long-term treatment of BD whereas alternative medications such as placebo and lamotrigine are used at the same time since the limitation, for example the risk of congenital malformations during lithium-intake period. Other therapies generally are also being applied to the BD patients, including psychosocial treatment, adjunctive psychotherapy in acute treatment, adjunctive psychotherapy in long-term maintenances, family-focused therapy, cognitive-behavioral therapy and interpersonal and social rhythm therapy. This review aims to explore genetic factors contributing to BD.

2. Genome-Wide Examination in BD

Researchers conducted genome-wide association studies (GWAS) from more than forty thousand BD cases of more than three hundred controls [3]. The study identified the existence of 64 genomic loci associated with BD. Risk alleles in the passage of the synaptic expressing and the expression of the brain are testified to be enriched with BD risk alleles which means these genes significantly contribute to the BD occurrence, especially. The characteristic of neural centers which are positioned in the frontal parts of the brain and the hippocampus. Researchers also found a large number of signals which interact with psychiatric medication. Fifteen genes which encode targets additionally are successfully proved their massive link to BD. Furthermore, a GWAS with the size about 1.5 times larger than PGC2 is conducted subsequently. New loci overlapped with BDD, SCZ and BD are found successfully [3]. This result at the same time identifies the negative relation between inadequate daily routines, including overwhelming alcoholic beverage as well as cigarette abuse, and the risk of occurrence in BD.

In another scientific research, researchers conducted GWAS from more than twenty thousand BD cases of more than thirty thousand controls. Subsequently, 822 variants are found in a follow-up analysis from additional nearly 95 hundred BD cases and nearly 138 hundred controls [4]. Eight of nineteen variants were suggested to be GWS. This finding concludes the genetic heterogeneity even though the power is limited due to its small size. Thirty GWS loci were included in the combined analysis, including 20 new loci [4]. The genes contributing to ion channel encoding, transporting of neurotransmitter and synaptic components were included. The pathway research significantly indicated nine enriched gene-sets, regulation of insulin secretion and endocannabinoid signaling included [4]. It is a wide consent that BD I and BD II are respectively related to SCZ and MDD. However, it is essential to know that there is a close relationship between SCZ and the hypomania episode.

Subsequently, 8 of these 30 loci were testified to associate with SCZ, whereas the conditional analyses directly show the independence character between BD and SCZ from the 3/8 shared loci. Thus, it is essential to acknowledge the clinical difficulties in distinguishing these disorders even though they are so closely related. What is more, humanity factors are interestingly found related to the etiology of BD. For instance, significant positive genetic correlations with educational attainments have been observed but it is not related to either adult or childhood intelligence quotient (IQ). Therefore, educational attainment of BD genetics independently researched from general intelligence. Furthermore, a new GWAS conducted to confirm BD loci from more than 18 hundred cases and more than 46 hundred controlled cases among Chinese individuals is finished, following the independent replication [5]. At the same time, replication research is done to compare the results. The research

interestingly found a new genetic BD locus in Han Chinese individuals, near the gene of encoding transmembrane protein 108, which contributes to the development of dendritic spine development and the glutamatergic transmission dentate gyrus [5]. Some related genes are related at the same time with the finding of the research. For example, according to the results of the experiment, T alleles frequency of rs9863544 (R) is 0.057 for Chinese Han individual, whereas it is much larger in European individuals which is 0.439. Also, SNVs of this gene (R) behave stronger KD in Chinese individuals than it is for European. This indicates the differentiation of BD heteogeneity of loci between Han Chinese and European.

Heterogeneity shows the variety of development in the formation period of a specific disease. For its significant illustration of the formative development BD, researchers have made efforts working out the evidence for genetic heterogeneity between BD I and BD II [6]. This research successfully found eight GWS associated regions and on chromosome 10 a new associated region is found. Additionally, BD cases in the experiment were working with other related mental disorders, SCZ and MDD included. Also, schizoaffective disorder was testified to be with more significant load of schizophrenia risk alleles than both BD I and BD II [6].

Coding genes' new loci are found. One of them is the adducin 3 (ADD3) who contributes to cap the end of the growth of actin filaments and accelerating the collaborating of spectrin to actin in brain [7]. Another is a kind of X-prolyl N-terminal amino acid, XPNPEP1 in peptides with proline. Additionally, the SCZ possibility found in both BD I and BD II are different but the result from experiment of BD I and BD II are all expected. [7].

3. The Impact of Specific Genes and Familial Risk of BD

Whole-exome sequencing (WES) studies of individuals from families being affected by BD were tested resulting in finding 378 new functional variants of BD over 368 genes, including brain expressed RGS12, considered to be the most important candidate genes of BD, which are being carried by three affected members from at least one family [8]. Additionally, detached development of BD in at least two individual families are testified by 8/368 genes and the significant genetic overlap between BD, autism and SCZ, at the variance of unusual sequence degree are checked to be true by the result of later autism and SCZ research. This result suggests the overlap between BD and these several diseases, are working with the following analyses, makes true the high suspicion for the occurrence RGS12 to be a significant factor of BD. This result essentially contributes to the theory set up of NCKAP5 to be a key factor in developing and maintaining mental disorders, BD included [8].

To measure the untypical differentiated development of BD, another WES was conducted in additional 15 BD families, with 117 individuals and 72 of them were affected with BD [9]. The research is successfully performed resulting with a number of genes which are with genetic single-nucleotide variants. These variants are potential for contributing to the etiology of BD. As a structure of importance for BD, the variants were richly expressed in postsynaptic density (PSD), shared in three or more affected relatives in the researching results [9]. Genes like SHANK3 and NRXN1 are the scaffolding proteins which is comprised in the PSD genes that is completely sequence conserved. These newly researched genes are all testified to be contributing to the formative transference period of both SCZ and BD. What's more, PSD genes are proved to be the significant factor in SCZ and BD from the pathological research of the common variants from GWAS data. Additionally, with more younger patients found with more destroyed genes in comparison of some of the older patients, researchers interesting found that the burden of the brain expressing genes may be affected by the number of age [9]. Conclusively speaking, the untypical variants, with the P value merely of 0.2%, are over-emphasized in PSD. Genome-wide burden of the brain-expressed genes were found no different in affected and non-affected experiment samples, whereas this is related to the factor of age. Also, no difference in offspring versus between affected and non-affected samples was found by the de novo variants.

Biologically, another experiment has been done among families with twins [9]. The individual samples included at least one member of BD in all nearly 30 twins and working memory tasks have been conducted, resulting in finding the accelerated activation of brain components including anterior cingulate and medial prefrontal is related to BD. These abnormally attacked brain regions dominate the BD status. For example, during the period of memory engagement for orbitofrontal, irregularly increased activation is suggested to contribute to the genetic possibility of BD. Mutually, parts of the genes are also contributing to the same symptom, which is the acceleration of the activation during memory engagement. Additionally, the orbitofrontal cortex is proved to be extremely contributive in the formation and regulation period of emotions as well as the period of working memory tasks, affecting the memory context by emotions. All these results suggest the positive correlation between the BD status and the brain activation, which indicates the activation is being used to maintain the risk factors of BD [9].

BD has a close relationship with family history since it is largely genetic. More than a hundred samples with their family were tested in the experiment and it resulted in the suggestion of the relationship between the kinship of the family which is affected by BD and the heritability of BD [10]. The inheritance of BD from mother's and father's side is equivalent, whereas the occurrence (number of cases) of BD in males is more typical than it is in females, about 1.3-1.4 times higher. They found the positive correlation between kinship of the family and the heritability of BD [10].

4. Conclusion

Scientists specifically focused on the research and experiment of genetic contributions to bipolar disorder in the latest scientific reports. First, the symptom of cognitive deficit is indicated to be a factor of the early prediction of BD. Treatment of BD is categorized according to the different development periods of BD. As for the mania period of BD, lithium is always used to maintain the manic moods but sometimes it is also replaced or added with other medication since the occurrence of its disadvantages. Anti-depression is used to maintain the survival of BD patients during a depressive episode. However, since the rigid controversy on the usage of BD, anti-depression always works with other antipsychotics. At the same time, extended treatments are conducted, including long-term maintenances therapy, family-focused therapy, etc. As for the genetic factors of BD, which is the key point, GWAS was conducted in several studies. From these latest experiments and research in BD, more than 50 new genetic loci have been found which contribute to the occurrence of BD. These loci had been found to overlap with MDD and SCZ. These results show how the newly found factors matter, including inadequate daily routines and habits, family inheritance, and educational environment. Plus, it shows the equal effects from both mother's and father's side. Future research should explore the developmental dynamics of BD symptoms in children with a familial risk of BD, by conducting longitudinal studies.

References

[1] Lima I. M., Peckham A. D., Johnson S. L. Cognitive deficits in bipolar disorders: Implications for emotion. Clinical psychology review, 2018, 59: 126-136.

[2] Geddes J. R., Miklowitz D. J. Treatment of bipolar disorder. The lancet, 2013, 381(9878): 1672-1682.

[3] Mullins N., Forstner A. J., O'Connell K. S., Coombes B., Coleman J. R., Qiao Z., ... Potash J. B. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. Nature genetics, 2021, 53(6): 817-829.

[4] Stahl E. A., Breen G., Forstner A. J., McQuillin A., Ripke S., Trubetskoy V., ... Reif A. Genome-wide association study identifies 30 loci associated with bipolar disorder. Nature genetics, 2019, 51(5): 793-803.

[5] Li H. J., Zhang C., Hui L., Zhou D. S., Li Y., Zhang C. Y., ... GeseDNA Research Team. Novel risk loci associated with genetic risk for bipolar disorder among Han Chinese individuals: a genome-wide association study and meta-analysis. JAMA psychiatry, 2021, 78(3): 320-330.

[6] Charney A. W., Ruderfer D. M., Stahl E. A., Moran J. L., Chambert K., Belliveau R. A., ... Sklar P. Evidence for genetic heterogeneity between clinical subtypes of bipolar disorder. Translational psychiatry, 2017, 7(1): e993-e993.

[7] Forstner A. J., Fischer S. B., Schenk L. M., Strohmaier J., Maaser-Hecker A., Reinbold C. S., ... Cichon S. Whole-exome sequencing of 81 individuals from 27 multiply affected bipolar disorder families. Translational psychiatry, 2020, 10(1): 57.

[8] Toma C., Shaw A. D., Allcock R. J., Heath A., Pierce K. D., Mitchell P. B., ... Fullerton J. M. An examination of multiple classes of rare variants in extended families with bipolar disorder. Translational psychiatry, 2018, 8(1): 65.

[9] Sugihara G., Kane F., Picchioni M. M., Chaddock C. A., Kravariti E., Kalidindi S., ... McGuire P. Effects of risk for bipolar disorder on brain function: A twin and family study. European Neuropsychopharmacology, 2017, 27(5): 494-503.

[10] Özdemir O., Coşkun S., Mutlu E. A., Özdemir P. G., Abdullah A. T. L. I., Yilmaz E., Keskin S. Family history in patients with bipolar disorder. Archives of Neuropsychiatry, 2016, 53(3): 276.