Comorbidity of Common Personality Disorders and It's Use in Treatment

Weijie He[1, a, *, †], Chong Xu[2, b, *, †]

[1]Shanghai Qibao Dwight High School Shanghai, China

[2]Barstow School Ningbo Campus Ningbo China

[*]Corresponding author: [a]Wjhe_jack@qibaodwight.org, [b]charliexuchong@outlook.com

[†]These authors contributed equally

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Abstract: Personality disorders are some of the most common disorders that affect the social life of the patients seriously. For a decade, psychologists studied each of them. The correlation between each disorder and gene has already been studied and analyzed by many researchers as the heritability and environment are calculated. This research provides us with a basic view of the possible cause of these disorders. However, in real life, many patients having one personality disorder is also likely to have another one at the same time, which is also known as the comorbidity of disorder. However, unlike the study of a single disorder, only a few research discussed the comorbidity. In this research, the comorbidity of borderline personality disorder, bipolar disorder, major depression disorder and schizophrenia are studied by several gene and gene set analyses, a genome wide study and LD-score regression and polygenic risk scores. The assessment shows that there is a significant correlation between these four disorders. This study might provide us with a better understanding of personality disorders and give more clues about curing these disorders.

1. Introduction

The systematic study of personality disorders started in the 19th century by a succession of European psychologists [1]. Modern psychologists generally group all the personality disorders founded into 10 groups based on the symptoms of patients. Researches have been done on each group of personality disorders to evaluate their property and pathological mechanism. Among them, twin studies and family studies are two main methods to measure the heritability and environment of personality disorders.

Heritability, based on common knowledge, is the proportion of differences in that trait is due to genetic differences. It can be calculated for both physical and psychological characteristics [2]. On the other hand, environment refers to the proportion of differences in that trait is due to environmental differences. Throughout studies done on different personality disorders, people now have a general image of the pattern of the phenotype of most personality disorders.

However, that is not the end of the study of personality disorders. The comorbidity of personality disorders is the next topic that needs intense investigation. Previous studies have calculated the heritability and environment of most personality disorders individually, but that's not always the case in real-life situations. Unfortunately, when a person is having one personality disorder, they become highly susceptible to multiple personality disorders. The situation when a person has more than one personality disorder is known as the comorbidity of disorders. Therefore, in this paper, the potential comorbidity of the four common personality disorders-borderline personality disorder, major depression disorder, bipolar disorder, and schizophrenia- will be discussed based on current studies done on those four personality disorders. Several representative twin studies and family studies will be introduced to clarify the genetic influence of each personality disorder. Comparison of symptoms will also be done to examine the potential correlation between the four personality disorders. Last, the possible correlation of genes and pathological mechanisms will be discussed based on several genome-wide association studies results.

2. Introduction of Personality Disorders and Correspond Twin Study

Personality disorders, based on mayo clinic refer to mental disorders that can cause stubborn and unhealthy patterns of thinking, functioning and behaving and negatively affect patients' ability to relate and understand the situation and another individual, which cause serious problems and limitations in patients 'social life [3]. Such a disorder is also hard to be discovered by the patient who naturally acts abnormally and multiple symptoms from different personality disorders can also show at the same time, which make it hard to diagnose and separate different personality disorder.

In some cases, patients can have more than one personality disorder at the same time. The term for this phenomenon is called "Comorbidity". This research will focus on the comorbidity of Borderline personality disorder (BOR) with major depression disorder (MDD), Bipolar disorder (BIR) and schizophrenia (SCZ) will be investigated.

2.1 Borderline Personality Disorder Major Symptoms and Heritability Analysis

Borderline personality disorder or BOR is a personality disorder that impacts the way patients feel and think about themselves and others [4]. The main symptoms include intensive fear of abandonment, the pattern of unstable intense relationships, rapid changes in self-identity and self-image, periods of stress-related paranoia and low contact with reality, impulsive and risky behavior, wide mood swings and suicidal threats or behavior or self-injury. This disorder usually happens in early adulthood and may gradually get better with age.

Based on a family study conducted in 2011 by a different group of researchers also proved that with a sample of 368 probands (132 with BPD, 134 without BPD, and 102 with major depressive disorder) and 885 siblings and parents of the proband, the Tetrachoric Correlation Coefficient between first-degree relatives is about 0.37, which shows a familial factor on the phenotype of BOR, showing a possible high genetic influence on this disorder [5]. Another twin study was conducted by Svenn Torgersen with 92 monozygotic twins and 129 dizygotic twins in 2000 [6]. All the samples were interviewed based on the Structured Clinical Interview for DSM-III-R Personality Disorders. As the result, the frequency among cotwins of probands of monozygotic twins with BOR and dizygotic twins with BOR was found to be 35.3% and 6.7% respectively. Using the Structural Equation Modeling, the estimated heritability of BOR is 0.69, providing further evidence for the possible high correlation between BOR and genetic factors.

2.2 Major Depression Disorder Major Symptoms and Heritability Analysis

Major depression disorder or clinical depression or MDD is a mental disorder that mainly affects patients' mood and thought [7]. The main symptom will include: the feeling of sadness, tearfulness, emptiness or hopelessness, angry outburst over small matters, tiredness and lack of energy, reduce appetite, anxiety, slowed thinking, feelings of worthless or guilty, trouble thinking, concentrating, frequent recurrent thought of death and unexplained physical problems. This disorder has cases in both children, teenagers and adults.

The heritability of major depression disorder based on different sexes and zygosities is given by a study done in 2006 by Kenneth S. Kendler and other researchers on a total of 42,161 twins, consisting of 15,493 complete pairs and 11,175 twins whose co-twin was not assessed, were examined, and the female-female monozygotic twins have a Tetrachoric Correlation of 0.44, while the male-male monozygotic twins have a Tetrachoric Correlation of 0.31 [8]. This difference in correlation due to sex indicates a significant genetic influence on the phenotype of major depression disorder.

2.3 Bipolar Disorder Major Symptoms and Heritability Analysis

Bipolar Disorder or manic depression or BIP is a mental disorder whose patient frequently experience extreme mood swing from emotional high (hypomania) and lows (depression) [9]. The common symptom includes three-episode: in manic and hypomania episodes patients will feel abnormally energetic and confident. In depression episodes, patients will feel tired and depressed. This disorder can be found in children, teenagers and adults.

From an old twin study [10] in 1977 which interviewed 126 probands of same-sexed twin pairs, and the concordance of bipolar disorder in monozygotic twins can go up to 0.67, suggesting a high genetic influence to bipolar personality disorder. In more recent research, an experiment is carried out with 804 monozygotic and dizygotic same and different sex twins with BIP and unaffected twins with some 91604 [11]. With the help of structural equational modeling and inversed probability weighting to estimate the heritability. The result shows that the heritability of the BIP is 60.4%.

2.4 Schizophrenia Major Symptoms and Heritability Analysis

Schizophrenia is a serious mental disorder whose patients will interpret reality abnormally, the main symptom includes delusion, hallucination, disorganized thinking, extremely disorganized or abnormal motor behavior and negative symptom [12]. These symptoms will cause serious disadvantages to the patient daily life. Adult and teenagers can both have this disorder. Schizophrenia is a serious mental disorder whose patients will interpret reality abnormally, [12]. the main symptom include delusion, hallucination, disorganized thinking, extremely disorganized or abnormal motor behavior and negative symptom. These symptoms will cause serious disadvantages to the patient daily life. Adult and teenagers can both have this disorder.

A twin study was done in 2017 also proved that for all twin pairs born in Denmark from 1951-2000, the estimated heritability of schizophrenia is 0.79, which shows a high genetic influence on the disorder [13]. Another family study using the Taiwan Health insurance Database [14] having all proband having schizophrenia from all the beneficiaries (n=23422955) showed that the genetic influence on schizophrenia is 47.3%.

3. Personality Disorders' Potential Comorbidity Analysis

To sum up, by comparing the symptoms of these four personality disorders, several common symptoms such as depressive mood, mood swings, and irritability can be identified. BOR, BIP, and MDD share symptoms of irritability, while MDD shares the symptom of constant sadness with SCZ. The exact overlap of symptoms can be seen in figure 1. All these overlaps of symptoms suggest the possibility that these four personality disorders share some genetic factors.

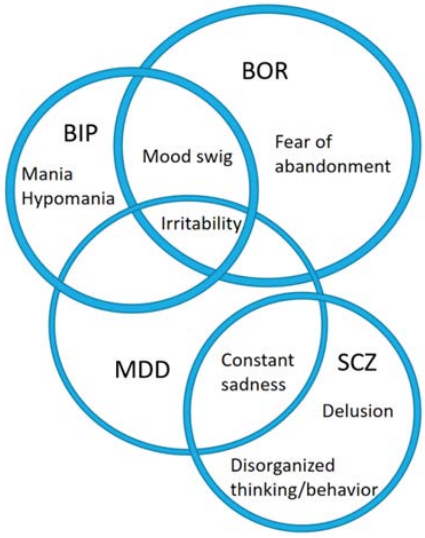

Figure 1. Overlap of common symptoms of four personality disorders.

Besides the overlap of symptoms, the heritability of the four personality disorders further indicates the possible presence of genetic correlation. According to the respective twin studies and family study mentioned above, the heritability is 0.69 for BOR, 0.44 for MDD, 0.79 for SCZ, and the concordance for BIP of 0.67. From these data, a relatively significant genetic effect can be found for each disorder. Therefore, considering the overlap of symptoms of disorders, it's reasonable to infer that there might be some correlation of genetic factors between BOR, MDD, BIP, and SCZ. However, to determine

and verify the exact correlation between personality disorders, further studies using different methods will be needed. In the following section, a recent study on the genetic correlation of the four personality disorders will be analyzed.

4. Genome-wide Association Study of the Four Personality Disorders

Genome-wide association study is a new method for researchers to identify the potential association between certain genes and traits by scanning genetic markers through a complete set of DNA. It is done by scanning the allele frequency differences between individuals who are ancestrally similar but differ phenotypically [15]. Generally, a larger sample of DNA generates a more valid result. After sample collection and genotyping the information, association testing is done using a different model for each genetic variant. From this testing, researchers are able to get summarized statistical data for the genetic correlation to the trait. Further post-genome-wide association study analyses can also be done, such as LD-score regression and polygenic risk score, which can give an exact correlation coefficient between the gene and the trait studied.

4.1 Gene Related to Borderline Personality Disorder

A study done in 2017 with 17755 participants reveals two genes that are significantly related to borderline personality disorder: Plakophilin-4 and DPYD [16]. Plakophilin-4 is a gene located on chromosome 2. It plays a role in regulating Rho activity during cytokinesis. It also contributes to the process of cadherin binding. However, the exact effect of Plakophilin-4 on borderline personality disorder is still unknown. It is possible that since Plakophilin-4 is affecting cell adhesion, it might affect the physiological development of neurons, which thus leads to soaring psychological demand for belonging and safety, and increase the possibility of developing a borderline personality disorder. The effect of a second gene, DPYD, which codes for dihydropyrimidine dehydrogenase is well-studied than Plakophilin-4 gene. A recent study shows that dihydropyrimidine dehydrogenase contributes to the breakdown of thymine, nucleotide, and uracil [17]. If one is having dihydropyrimidine dehydrogenase deficiency, an autosomal recessive disorder, there is the possibility that they may develop neurological disorders such as delayed motor skills and autistic behavior. From this, it is reasonable to infer that dihydropyrimidine dehydrogenase deficiency may also have an effect on a particular body system that leads to the development of borderline personality disorder.

4.2 Some Common Mistakes Gene Related to Major Depression Disorder

Numeral genome-wide association studies have been done in searching for genes related to major depression disorder. Out of all possibly related gene, two genes show a significant correlation with depression disorder: PCLO and HOMER1. In 2008, a study with 1738 major depression cases was conducted, and PCLO was identified as the marker for the disorder [18]. This gene, located on chromosome 7, encodes a protein that is part of the presynaptic cytoskeletal matrix, which contributes to the function of active synaptic zones and the transportation of synaptic vesicles between neurons. Therefore, it can be inferred that the mutation of the PCLO gene may lead to a decrease or stop of the transmission of certain neurotransmitters across the synapse, causing the constant depressive mood and low reaction to stimuli. Another study done in 2010 with 604 patients and 1364 controls revealed another gene, HOMER1, which is strongly related to the phenotype of major depression disorder [19]. HOMER1 protein belongs to the HOMER scaffold protein family. The function of this protein family is to bind the protein and receptors at postsynaptic sites. Thus, if this gene is mutated, a similar problem will occur as the mutation of the PCLO gene. The disturbance to neuron signaling pass away might be the main physiological reason that leads to the phenotype of major depressive disorder.

4.3 Gene Related to Bipolar Disorder

The studies of bipolar disorder are enormous. Out of all those studies, over 15 genes are identified that are correlated with bipolar disorder [20]. Among them, the gene that has the highest correlation coefficient is ADCY2 [21]. ADCY2 gene is found on chromosome 5. It is a gene that code for one

certain protein that regulates the downstream signaling cascades by catalyzing the formation of cAMP signaling molecule in the brain. cAMP signaling has an important role in cell signaling, for which it can regulate transcription of certain genes through protein kinase A. Once mutated, the downstream signaling cascades will be stopped or go out of control. This may lead to the symptoms of the bipolar disorder like mood swings.

4.4 Gene Related to Schizophrenia

It has already been established from the twin study mentioned above that there is a strong genetic influence on the phenotype of schizophrenia. Similar situation as bipolar disorder, 75 genes are identified through 18 genome-wide association studies that are correlated with schizophrenia [22]. Among these 75 genes, the TBX1 gene has the strongest association with schizophrenia [23]. TBX1 gene codes for a protein that plays a vital role during human embryonic development [24]. The TBX1 protein will bind to specific parts of DNA to activate transcription and translation of the gene, regulate the formation of tissue and organ. Therefore, once the TBX1 gene is mutated, patients are more likely to develop schizophrenia because of the brain structure that may increase the susceptibility of having schizophrenia phenotypes, such as delusion and disordered thinking.

4.5 Gene-set Analysis Assessment

Gene-set analysis is an experimental method that summarizes high-dimensional gene expression data based on biologically related sets. With i-Gsea4GwasV2 method, gene-set analysis shows one significant gene set: exocytosis (GO: 0006887; PFDR=0.019) [16]. There is a total of 25 genes in this gene set. Among them, 15 genes show a nominally significant association, while 22 genes are mapped with variants.

Admittedly, the exact influence of the exocytosis gene set on personality disorders is unclear yet. A possible explanation is that this exocytosis gene set may affect the secretion of particular intercellular signals that lead to possible disruption of body systems, which makes people more susceptible to developing personality disorders. The possible causation of major depression disorder and bipolar disorder also suggests that the disturbance of exocytosis and intercellular signaling cascades may be the key to the comorbidity of personality disorders.

4.6 LD-score Regression and Polygenic Risk Score Evaluation

Not many LD-score regression and polygenic risk score calculations had been done for personality disorders correlation. One of the most representative results shows that, after calculation and correction, for borderline personality disorder-major depression disorder, borderline personality disorder-bipolar disorder, and borderline personality disorder-schizophrenia, the correlation coefficient is 0.57, 0.28, and 0.34, respectively. To further solidify the result from LD-score regression, the polygenic risk score is calculated. It reveals that borderline personality disorder has a significant association with the polygenic risk score of bipolar disorder, major depression disorder and schizophrenia. Furthermore, bipolar disorder and major depression disorder are more significantly related than others [16]. The result shows that there is indeed a significant correlation between borderline personality disorder and the other three types of personality disorder.

5. Application of the Comorbidity of PDs in Treatment

Through the genome-wide association study mentioned above, the comorbidity of borderline personality disorder with other personality disorders is clear. This information can provide several benefits for both patient and doctor in the treatment of personality disorders.

First, with the potential comorbidity in mind, doctors can provide a more well-considered medication that minimizes the side effect. For example, if it is known that there is a high correlation between major depression disorder and bipolar disorder, doctors would be more careful when assigning medication such as selective serotonin reuptake inhibitors. This is an effective antidepressant, but it comes with side effects. For doctors, they are usually willing to assign a high

dosage of SSRI to their patients because of its effectiveness and mild side effect. However, that's not always right when considering the comorbidity of major depression disorder with bipolar disorder. Patients with major depression disorder who receive SSRI become highly stimulated in the brain, thus making them more susceptible to comorbid bipolar disorder during the treatment.

Moreover, knowing comorbidity allows doctors to provide more timely treatment and prevention. Some mental disorders, such as schizophrenia, have a relatively long latent period, so people may not displace the symptoms until the late stage of the disorder. Therefore, known comorbidity of disorders can be a reference when doctors assign patients with treatment. For example, with known comorbidity of personality disorders, doctors can provide prevention of schizophrenia when treating a patient with a borderline personality disorder. In this way, the patient can avoid comorbid multiple disorders.

6. Conclusion

In summary, several representative twin studies to demonstrate the heritability of each personality disorder are presented in this paper. Then, symptoms of borderline personality disorder, major depression disorder, bipolar disorder and schizophrenia are being compared, and an overlap of symptoms is identified. Follow up, genome-wide association studies of the four personality disorders are discussed and the possible correlation of genes and pathological mechanisms are investigated. Through this study, possible common pathological mechanisms that cause the shared symptoms of the four personality disorders have been identified, including mood swings, irritability and depressive mood. These symptoms may due to the brain secretory malfunction of a certain neurotransmitter. This possible association of pathological mechanisms provides a new insight to the comorbidity study of personality disorders, which physiological factors should also be considered as well as genetic factors. More studies are needed in the future to determine the exact influence of mutated genes on the process of intercellular communication. With a better understanding of the comorbidity of personality disorders, doctors can assign treatment in a more well-considered way that gives a better outcome and response.

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