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Childhood trauma interacted with *BDNF* Val66Met influence schizophrenic symptoms

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Abstract

The gene – environment (G × E) interaction effect is involved in severe mental disorders. However, whether the brain-derived neurotrophic factor (*BDNF*) Val66Met polymorphism participates in the childhood-abuse influenced schizophrenic symptoms remains unclear. We examined the interaction between *BDNF* Val66Met, and childhood trauma (ChT) on psychotic symptoms in a Chinese Han population.

To estimate the G × E interaction, psychiatric interviews, self-report questionnaires for ChT, and genotyping for *BDNF* Val66Met were carried out on 201 schizophrenic patients. G × E interactions were analyzed by generalized multifactor dimensionality reduction (GMDR).

Among all patients, 11.9%, 19.4%, 23.4%, 26.4%, and 73.6% reported emotional abuses, physical abuses (PA), sexual abuses (SA), emotional neglects (EN), and physical neglects (PN), respectively. Significant negative correlations were observed between anxiety/depression factors, and ChT total scores. Patients with 3 different BDNF genotypes showed significant differences in anxiety/depression scores. Significant 2-way interactions were found for Val66Met × PN, 3-way interactions were found for Val66Met × PN × PA, and four-way interactions were found for Val66Met × PN × PA × EN with regard to the excitement scores.

Our findings suggested an involvement of *BDNF* Val66Met polymorphism after ChT in terms of risk for schizophrenia symptoms.

Abbreviations: BDNF = brain-derived neurotrophic factor, ChT = childhood trauma, CRHR1 = corticotropin-releasing hormone receptor 1 gene, CTQ-SF = Childhood Trauma Questionnaire-Short Form, EN = emotional neglects, GMDR = generalized multifactor dimensionality reduction, PA = physical abuses, PANSS = Positive and Negative Syndrome Scale, PN = physical neglects, SA = sexual abuses.

Keywords: *BDNF* Val66Met, childhood trauma, gene-environment interactions, schizophrenia, symptoms

1. Introduction

Both genetic disposition, and environmental exposures play important roles in the development of severe mental illness.[1] Several researchers have identified specific gene–environment (G × E) interactions may play a role in the causation of psychoses, for example: the corticotropin-releasing hormone receptor 1 gene (*CRHR1*), and childhood maltreatment are both associated with some protections playing roles in depressive symptoms,[2] catechol-Methyl-transferase gene, and childhood abuse are related to psychosis-induced effects of cannabis,[3] and the brain-derived neurotrophic factor gene (*BDNF*) interacts with stressful life events (and the relative autism spectrum disorders) in the etiology of depression.[4]

According to the neurodevelopmental hypothesis, schizophrenia could be caused by both genetic, and environmental factors, and manifested by a disruption in cognition, and emotion along with negative, and positive symptoms.[5] Over the last decade, the relationship between *BDNF,* and schizophrenia has been widely, studied in both BDNF protein expression, and genetic polymorphism, and many results implicated that *BDNF* was involved in the pathophysiology of schizophrenia.[6]

Recently, a functional polymorphism (Val66Met) in the *BDNF* gene was reported to interact with childhood maltreatment in the development of psychotic-like experiences,[7] and those patients with schizophrenia, or bipolar disorder, and Met carriers of the *BDNF* Val66Met who experienced high level of childhood abuse; developed severer cognitive, and brain abnormalities.[8] Nevertheless, the above reports have some deficiencies: one was limited by the recruiting methods (from the campus but not the hospital), and the other limited by the sample size. To our knowledge, whether *BDNF* Val66Met in ChT patients, influences psychotic symptoms interacted has remained largely elusive.

We suppose that G × E interaction may be partially, responsible for schizophrenic symptoms, and this work is to investigate if the functional *BDNF* Val66Met variant interacts with childhood abuse experience, and modulates the schizophrenic symptoms in a Chinese Han population.

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X B and X L are the first authors.

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2. Methods

2.1. Participants

The participants were recruited from the Shandong Mental Health Center. All participants were Han nationality in Shandong province. For the present study, 201 hospitalized schizophrenic patients (18–65 years old, meeting the International Statistical Classification of Diseases, and Related Health Problems 10th Revision, ICD-10 criteria for schizophrenia) were recruited between 2012 to 2014. The diagnosis, along with a review of psychiatric case records, was independently checked, and verified by 2 senior psychiatrists. Patients with serious physical diseases, or those who fulfilled ICD-10 criteria for other mental disorders, and schizoaffective disorders were excluded. All participants were informed of the purpose of the study, and provided with written notice consent. The present study was approved by the Ethical Committee of Shandong Mental Health Center.

3. Clinical assessment

3.1. Childhood trauma questionnaire-short form (CTQ-SF)

A short CTQ-SF form was used to assess the maltreatment histories. The CTQ-SF consists of 28 items measuring 5 types of childhood traumas (ChTs): emotional abuse (EA), physical abuse (PA), sexual abuse (SA), emotional neglect (EN), and physical neglect (PN). Reliability, and validity of the CTQ have both been demonstrated.[9] Moreover, the reliability, and validity of the Chinese version of CTQ-SF were analyzed [10,11] Their results suggested that Chinese version of CTQSF (the Chinese version of the Childhood Abuse Questionnaire was revised in 2004 by Zhao Xingfu et al) is a good psychometric instrument for the evaluation of Chinese childhood abuse.

3.2. The positive and negative syndrome scale (PANSS)

The PANSS[12] scores were obtained by trained psychiatrists within a week after the patient was admitted to hospital. PANSS consists of 16 items that make up 3 subscales (positive, negative, and general, with the inter-rater reliability, higher than 80%), and further factor analyses in China yielded 5 components: positive, negative, excitement, anxiety/depression, and cognitive.[13] We used the 5 components for each symptom complex, and the summary score to indicate the severity of schizophrenia symptoms.

4. Genotyping

Venous blood (5 mL) was collected in EDTA-containing tubes. Genomic DNA was extracted from leukocytes using the improved potassium iodide method. SNP genotyping was performed using the TaqMan probe system.[14] Polymerase chain reaction (PCR), and fluorescent signals analyzing were performed by BioRad iQ5 Real Time PCR Detection System (Bio-Rad, California,). Allele-specific probes, and primers were designed, and produced by Shanghai GeneCore BioTechnologies Company Limited. The PCR reaction volume was 10μl, and the thermal cycling conditions were: 1 cycle at 95°C for 30 seconds, 45 cycles of 95°C for 5 seconds, 58°C for 5 seconds, and 72°C for 10 seconds.

5. Statistical analysis

Ages, years of education, scores of PANSS, and CTQ-SF of participants were analyzed as continuous variable. These continuous variables were presented as mean ± standard deviation, and tested by 1-way analysis of variance using SPSS 16.0 (SPSS Inc, Chicago, IL). The demographics factors of patients grouped by genotypes were compared by $\chi 2$ performed using SPSS 20.0 software (SPSS Inc, Chicago, IL). Spearman correlation analysis between CTQ and PANSS scores were also performed by SPSS 20.0 software. G × E interactions were analyzed by generalized multifactor dimensionality reduction (GMDR Software Beta version 0.7, Department of Psychiatry and Neurobehavioral Sciences, University of Virginia, Charlottesville, VA), which is a free open source accessible at http://www.healthsystem.virginia.edu/internet/Addiction-Genomics/.[15] Age, and gender were included as covariates in G × E interaction analyses. As the selected traits used for score calculation are quantitative ones, we selected linear regression method to calculate the statistic scores. All interactions were tested using 10-fold cross-validations in an exhaustive search considering all possible combinations. The model with the highest testing balance accuracy, and cross-validation consistency was selected as the best model. $P < 0.05$ was considered as statistically significant.

6. Results

6.1. Demographics and sample characteristics

All the 201 patients were investigated with CTQ-SF, and PANSS. Of the 201 patients, 83% of them were Met carriers (31% Met/Met, and 52% Val/Met), and 17% were Val homozygous, 49 men, and 152 women. The demographic, and clinical characteristics of patients in the present study were available in Table 1. There were no significant differences among groups divided by

Table 1

Demographic, and clinical characteristics in patients with schizophrenia.

Variable	Val/Val (34)	Val/Met (104)	Met/Met (63)	Statistics
Age(mean ± SD)	31.41 ± 10.77	32.79 ± 11.43	32.86 ± 10.60	F= .228, P= .797
Years of education (mean ± SD)	5.12 ± 1.25	4.89 ± 1.09	4.63 ± 1.07	F=2.253, P= .108
Gender(n)				
Male	6	25	18	χ^2=1.443, P= .486
Female	28	79	45	
Family history (n)				
Positive	20	67	41	χ^2= .560, P= .756
Negative	14	36	21	
Psychotic course (n)				
First-episode	8	33	18	χ^2=0.858, P=0.651
Recurrent	26	71	45	

SD = standard deviation

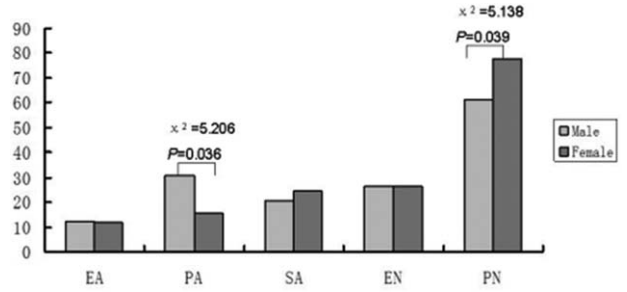

Figure 1. Gender differences in different types of abuse.

three types of genotypes. Using cut-off criteria previously described,[16] 11.9%, 19.4%, 23.4%, 26.4%, and 73.6% of the 201 patients reported EA, PA, SA, EN, and PN, respectively. We did not find statistical differences between psychosis course, and forms of trauma. However, as shown in Figure 1, more male experienced PA, and more women suffered from PN.

6.2. Correlation between childhood trauma and schizophrenia symptoms

Using the Spearman correlation analysis, we found that significant negative correlations existed between the anxiety/depression factor, and CTQ total scores ($r = -.160$, $P = .023$). No significant differences were observed among the other factors. However, the cognitive defect level, and scores of SA showed a trend of correlation ($r = .137$, $P = .053$). (Table 2)

6.3. Association of BDNF Val66Met polymorphisms with PANSS and CTQ

To analyze whether the *BDNF* Val66Met polymorphism has an effect on the clinical characteristics of schizophrenic patients, we compared 3 genotypic groups through 1-way analysis of variance. Three genotypes showed significant differences in anxiety/depression scores ($F = 3.726$, $P = .026$) but no significant association was observed between the other four factors of PANSS, and the polymorphism. With respect to the associations between the polymorphism, and ChT, no significant association was observed which suggested that the genetic, and environmental factors are independent. (Table 3)

6.4. G × E interactions between BDNF Val66Met and childhood trauma influences psychotic symptoms

We used GMDR software to analyze the interactions between *BDNF* Val66Met, and ChT on clinical symptoms of schizophrenia. Five components of PANSS (positive, negative, excitement, anxiety/depression, cognitive) were associated with 2 to 6-way interactions of each genotype and the 5 environmental factors. As summarized in Table 4, we found different types of ChTs interacted with BDNF Val66Met, particularly PN, which was associated with excitement symptom of schizophrenia. Significant 2-way interactions were found for *BDNF* Val66Met × PN,

Table 2

Correlation between scores of CTQ, and PANSS (Pearson correlation coefficient R and *P* value).

	EA	PA	SA	EN	PN	CTQ total
Positive	.057, .421	.041, .564	−0.014, .847	−0.086, .227	−0.036, .613	−0.036, .613
Negative	.035, .625	.049, .492	.081, .253	.087, .221	.122, .084	.074, .295
Excitement	.024, .739	.078, .268	−0.022, .760	−0.051, .469	−0.043, .543	−0.026, .714
Cognitive defect	−0.002, .979	.028, .698	.137, .053	−0.021, .765	−0.022, .759	.078, .271
Anxiety/depression	−0.127, .072	−0.076, .282	−0.023, .747	−0.115, .105	−0.109, .122	−0.160, .023*

CTQ = childhood trauma questionnaire, PANSS = positive and negative syndrome scale, EA = emotional abuse, PA = physical abuses, SA = sexual abuses, EN = emotional neglects, PN = physical neglects
* $P < .05$.

Table 3

Association of genotype frequencies of the *BDNF* Val66Met polymorphisms with CTQ, and PANSS.

	Val/Val (34)	Val/Met (104)	Met/Met (63)	F	*P*
CTQ (mean ± SD)					
EA	8.82 ± 3.78	8.46 ± 3.07	7.98 ± 3.71	.742	.477
PA	7.47 ± 3.82	7.06 ± 3.10	6.84 ± 3.69	.374	.689
SA	7.00 ± 3.643	6.56 ± 2.57	6.49 ± 2.78	.393	.675
EN	12.71 ± 4.75	12.92 ± 4.69	12.32 ± 4.29	.343	.71
PN	11.06 ± 1.97	10.80 ± 2.22	11.60 ± 4.45	1.352	.261
PANSS (mean ± SD)					
Positive	31.24 ± 3.93	32.74 ± 4.88	32.60 ± 4.42	1.432	.241
Negative	31.53 ± 8.14	32.34 ± 7.97	33.35 ± 6.48	.700	.498
Excitement	14.76 ± 5.58	13.86 ± 3.85	13.76 ± 3.56	.756	.471
Cognitive defect	9.21 ± 2.06	9.08 ± 2.00	9.21 ± 2.24	.096	.908
Anxiety/depression	12.91 ± 4.22	11.90 ± 2.29	13.17 ± 3.51	3.726	.026*

BDNF = brain-derived neurotrophic factor . CTQ = Childhood Trauma Questionnaire, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation, EA = emotional abuse, PA = physical abuses, SA = sexual abuses, EN = emotional neglects, PN = physical neglects
* $P < 0.05$.

Table 4

GMDR analyses on gene-environment interactions in schizophrenia patients.

Modes	Training accuracy	Testing accuracy	Cross-validation consistency	*P*
Val66Met × PN	.6314	.6463	10/10	.001*
Val66Met × PN × PA	.6505	.5744	6/10	.0107*
Val66Met × PN × PA × EN	.6854	.5917	8/10	.0107*

GMDR = generalized multifactor dimensionality reduction
* $P < 0.05$.

3-way interactions were found for *BDNF* Val66Met × PN × PA, and 4-way interactions were found for *BDNF* Val66Met × PN × PA × EN associated with the excitement scores.

7. Discussion

Of all the mental diseases, *BDNF* Val66Met as a functional polymorphism has been reported to interact with stressful life events, or childhood maltreatment in the development of depression,[4] bipolar disorder[1,17] but hardly with schizophrenia. Our research aims to find whether the interaction between *BDNF* Val66Met, and ChT affect the clinical symptoms targeted on schizophrenic patients. Patients with 3 different BDNF genotypes showed significant differences in anxiety/depression scores. Significant 2-way interactions were found for Val66Met × PN, 3-way interactions were found for Val66Met × PN × PA, and 4-way interactions were found for Val66Met × PN × PA × EN with regard to the excitement scores. The findings highlight the importance of the interaction between gene, and environment in schizophrenia, and reveal that *BDNF* Val66Met polymorphism, and childhood traumatic experiences both play a part of role in the clinical symptoms of schizophrenia.

Three forms of childhood abuse the schizophrenia patients experienced are PN > EN > SA in occurrence. This rank order is similar to some known reports in China, South Korea, and Western countries.[18–20] In addition, the number of patients experienced PA, and PN statistically differ in gender, which is a novel finding in childhood abuse.

ChT, and bullying account for 33% of cases of schizophrenia;[21] and emerging studies have shown that ChT is associated with schizophrenia. Consistently, our results suggested that anxiety/depression correlated with ChT, and the cognitive defect showed a tendency. However, which specific type of abuse corresponds to which symptom has been controversy. In Western countries, EA, and PA were associated with suicidal behavior.[22] In Chinese schizophrenic samples, PA, EN, PN, and total abuse were significantly related to aggressive behavior.[20] In India, persecutory delusion was linked to PA, while anxiety was linked to EN, and depression to EA.[23] These differences may be due to their inconsistent geographical, culture, and practices.

It was accepted that *BDNF* Val66Met polymorphism decided clinical symptoms. In this study, and our previous study,[24] we demonstrated that anxiety/depression was association with *BDNF* Val66Met polymorphism. Meanwhile, patients with Met/Met presented the highest score of anxiety/depression factor. Previous studies showed that *BDNF* Met/Met carriers not only showed an increased risk of schizophrenia (19%)[25] but was also associated with increased aggressive behaviors than other genotypes.[26] Moreover, Met allele carriers presented lower serum *BDNF* levels, and higher PANSS negative scores as compared to homozygote Val/Val schizophrenic patients.[27] In short, *BDNF* Val66Met related with the symptoms of schizophrenia but the association between genotypes, and specific symptoms is not consistent, and this needs further research.

Importantly, our results suggested that 3 G × E interaction models significant associated with the excitement factor. As the aforementioned explanation, we inferred that *BDNF* Val66Met polymorphism as a genetic factor, and ChT as an environmental factor jointly drive schizophrenia. Furthermore, an emerging body of evidence has been suggested that ChT is probably the most important environmental factor affecting schizophrenia, through the interplay of genes, and environment.[28] In a general population, Met carriers were reported more positive psychotic-like experiences when exposed to childhood abuse than individuals carrying Val/Val.[7] Similarly, Met carriers with high level of childhood abuse have more cognitive, and brain abnormalities than other schizophrenia patients.[8] On the molecular level, BDNF levels were found lower in the victims who experienced multiple sexual assaults.[29] Reduced BDNF mRNA levels, and hippocampal volume may be associated with both ChT experience, and Met carriers of *BDNF* val66met variants.[30] Besides, serum levels of BDNF in depressed patients were also reported relating to schizophrenia.[31] The pathway changes in brain suggested that BDNF played a pivotal role effecting by methylation, and glucocorticoid receptor.[32]

Our case-only study found models of *BDNF* Val66Met interacted with some ChT types on the excitement factor by GMDR. The case-only test has been proposed as a more powerful approach to detect G × E interactions. In this study, the excitement factors include items of excitement, hostility, noncooperation, and impulsive behavior according to previous study.[13] GMDR is a method that could identify contributors to gene variation on quantitative variables.[15,33] By running GMDR, we found *BDNF* Val66Met × PN, *BDNF* Val66Met × PN × PA, and *BDNF* Val66Met × PN × PA × EN had influences on excitement factors. When we changed the quantitative variables such as positive, negative, anxiety/depression, and cognitive, no significant differences were found. Although we found some new results in BDNF Val66Met polymorphism, the conclusions are consistent that the observed G × E interactions may be partially responsible for schizophrenic symptom.

The present study does have some limitations. First, our results were still limited by the sample size. The second was the scale, or questionnaire we used. Take PANSS for example, it is a state-related measure to assess the severity of psychiatric symptoms. We cannot get the long term psychiatric symptoms dynamically which may be associated with the ChT psychotherapy.

8. Conclusion

Our findings provide evidence in support of a gene-environment interaction between the BDNF Val66Met polymorphism, and childhood traumatic experiences in terms of risk for clinical symptoms in schizophrenia. A complex interplay between BDNF Val66Met polymorphism, childhood abuse, and psychotic symptom has been arisen but larger additional investigations in other populations are needed to better clarify the observed associations.

Author contributions

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