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ORIGINAL RESEARCH

The Interaction Between Family Functioning and the *PCDH9* rs9540720 Polymorphism on Major Depressive Disorder in Chinese Freshmen

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Objective: Unhealthy family functioning and Protocadherin 9 (*PCDH9*) have been recognized as potential environmental and genetic risk factors for major depressive disorder (MDD). This study examined the effects of the interaction between *PCDH9* and family functioning on MDD in first-year university students.

Methods: A cohort of 6985 first-year university students in China was established in 2018 and was followed for one year. The blood samples from 4866 of these participants (38.88% males, mean age:18.42) were genotyped. MDD was assessed using the Composite International Diagnostic Interview-3.0 (CIDI-3.0), while family functioning was evaluated with the Family Assessment Device (FAD). Logistic regression was used to examine the interaction of these two risk factors.

Results: The one-year prevalence of MDD was 2.4%. Among first-year university students, the AA genotype of rs9540720 (*PCDH9*) was a protective factor for MDD (OR=0.47, 95% CI: 0.23–0.88, *P*=0.025). Affective responsiveness was a risk factor for MDD (OR=1.77, 95% CI: 1.13–2.78, *P*=0.013). The interaction between AA genotype of rs9540720 and general functioning was statistically significant for MDD (OR=6.83, 95% CI: 1.16–39.27, *P*=0.031), indicating that unhealthy family functioning may exacerbate the risk of MDD in carriers of this genotype.

Conclusion: University students carrying the AA genotype of rs9540720(*PCDH9*) may have a higher probability of developing MDD when they have unhealthy family functioning. The etiological mechanism of depression in university students is explained from the perspective of gene-environment interaction and provides a theoretical basis for subsequent effective identification and screening of high-risk groups for depression in university students.

Keywords: depression, family functioning, gene-environment interaction, *PCDH9* rs9540720, freshman

Introduction

Mental disorders, notably depression, are prevalent among university students.[1] The lifetime prevalence of major depression among adolescents between the ages of 10–19 can reach as high as 19%.[2] Depression has become a major psychological problem in Chinese university students.[3,4] This adolescent stage (10–19 years) represents a time of important social, emotional and life transitions, and depression at this stage can have serious adverse consequences including recurrence of depression and long-term impairment of interpersonal, social, educational, and occupational functioning.[5] Many mental disorders begin in adolescence/young adulthood (12–24 years), and three-quarters of lifetime mental disorders appear before the age of 25.[6] Furthermore, one of the severe consequences of having depression is

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suicide.[7] And university students are in early adulthood with accelerated brain development and increased sensitivity to external stressors.[8] In addition, university freshmen are exposed to a variety of risk factors for depression, such as financial stress, being away from their families, and adjusting to new learning styles and greater academic pressures.[9,10] Thus, focusing on and investigating depression and its determinants in first-year university students have significant clinical and public health implications.

Innate genetic and acquired environmental factors have a significant impact on the development of depression.[11] The procalcitonin (*PCDH*) family is the largest subgroup family of the procalcitonin superfamily, which is mainly expressed in the nervous system and plays specific roles as receptors in synaptic connectivity and signal transduction.[12] A subset of non-clustered protocadherins (*PCDHs*) have been shown to be associated with neuronal disorders such as schizophrenia,[13] with some variants of *PCDH9* being implicated in major depressive disorder.[14,15] The lack of *PCDH9* may lead to a decrease in positive emotions.[16] *PCDH17*, another gene encoding a homologous protein located on the same chromosome as *PCDH9*, has been shown to increase the risk of developing depression.[17] Furthermore, *PCDH17* has been shown to significantly affect synapse development.[17,18] The short distance between these two genes on the chromosome and the similarity in the structure of the proadhesin product suggest that their biological roles may be similar. On the other hand, a meta-analysis reported that the previously unidentified single nucleotide polymorphism (SNP) *PCDH9* rs9540720 was significantly associated with MDD on a genome-wide basis.[19] G+ in *PCDH9* rs9540720 was found to be a risk allele for major depressive disorder (MDD) in a GWAS study.[20] However, the relationship between *PCHD9* and the development of MDD is poorly studied and the mechanism is still not clear.

Consistent with the McMaster Model of Family Functioning,[21] family functioning, within the context of illness, is conceptualized as the degree to which family members embrace family practices and procedures, fulfil roles, communicate, cope with stressors, and engage with one another.[22] A meta-analysis showed that a significant positive association was observed between family dysfunction and depression.[23] Family dysfunction may increase the incidence of depression when it is severely dysfunctional.[24,25] Parental rejection increases the risk of psychological distress in first-year university students.[26] Moreover, family stress can lead to depression among university students, affecting academic performance and learning outcomes.[27]

However, the interaction between genetics and the environment, known as the gene-environment interaction (G-by-E effect), also contributes to the complexity of the etiology of depression.[28] Potential genetic and environmental risk factors and interactions between them may drive abnormal epigenetic mechanisms targeting stress response pathways, neuronal plasticity, and other behaviorally relevant pathways associated with depression.[29] A systematic review suggests that epigenetic changes constitute a key mechanism by which stress-related exposures interact with the genome, leading to stable changes in DNA structure and gene expression.[30] Vulnerability stress theory suggests that genetic liability depends on the severity and frequency of stressors.[31] Several studies have also revealed this mechanism. For example, the interaction of genes (*5-HTTLPR, BDNF val66met*) with the quality of the home environment was found to predict depression.[32] The interaction of CRHR1 and the home environment may affect depression in a sex-specific manner.[33] TaqIA polymorphisms interacting with negative parenting styles predicted concurrent depressive symptoms in childhood.[34] Therefore, there is a need for a more in-depth investigation on the interactions between the two and their potential impact on the risk of MDD, especially in young adult population.

This study aimed to examine the interaction of family functioning and *PCDH9* rs9540720 polymorphism among first-year university students. This study tested the following three hypotheses: (1) the *PCDH9* rs9540720 polymorphism is associated with MDD among university first-year university students; (2) unhealthy family functioning may increase the risk of MDD among first-year university students; and (3) the *PCDH9* rs9540720 polymorphism may interact with family functioning to increase the risk of MDD.

Methods

Participants

All first-year university students enrolled at Jining Medical University and Weifang Medical University in Jining, Rizhao, and Weifang, Shandong Province, China, were invited for this study in 2018 and followed one year later.

Between April and October 2018, all first graders were included in the study using whole cohort sampling, and 8079 students provided baseline data. An assisted survey system for data collection with logic checking and voice prompts was installed on 365 computers in the libraries of the three campuses. Six trained investigators were assigned to assist in answering participants' questions. In this analysis, 437 participants with lifetime MDD at baseline were excluded. The remaining 7642 participants were followed for one year. Among them, 6985 participants provided follow-up data, and 4866 participants provided blood samples.

This study complied with the Declaration of Helsinki. All participants signed a written informed consent form before the start of the study, and the study protected the privacy of all participants, and all data were managed confidentially.[35] The study was reviewed and approved by the Health Committee of Jining Medical University (2019-JS-004).

Measurements

MDD was measured using the Chinese adapted version of the comprehensive international diagnostic interview-3.0 (CIDI-3.0) and completed by trained interviewers.[36,37] The Chinese adaptation of the CIDI-3.0 has been validated in a community-based Chinese population, and it has specificity, sensitivity, and test-retest reliability of 89.0%, 71.1%, and 0.74 for major depressive disorder, respectively.[36]

Family functioning was assessed by the Family Assessment Device (FAD) in seven domains: Problem Solving (PS), Communication (CM), Roles (RL), Affective Responsiveness (AR), Affective Involvement (AI), and Behavior Control (BC), as well as General Functioning (GF).[38] The Chinese version of the FAD was used in the present study, which has good reliability and validity.[39] FAD is a self-reported scale comprising 60 questions, and scores range from 1 to 4 to indicate an increase in the degree of disagreement. Higher scores indicate poorer family functioning. Cronbach's α, which reflects internal consistency, was 0.915.

Other Measures

The Beck Depression Inventory was used to assess baseline levels of depression. The self-rating scale, which measures the severity of depression in the past two weeks, is divided into 21 items on a 4-point Likert scale.[40] The higher the score indicates more severe depression. The Chinese version of The Beck Depression Inventory was used in this study. In a study of China Medical University students, the scale's Cronbach's α is 0.912.[41]

The baseline severity of anxiety of the participants in the past week was assessed using the Beck Anxiety Inventory. The scale was a 4-point Likert scale consisting of 21 items. The Chinese version of BAI was used in this study. The Cronbach's α for the Chinese version of the BAI was 0.950.[42] The scale's Cronbach's α was calculated to be 0.931 in this study.

Adolescent Self-rating Life Events Check List (ASLEC) was used to assess the subject's exposure to adverse life events in the last 12 months and consisted of 26 items. The Chinese version of ASLEC was used in this study. Each life event was evaluated on a 5-point Likert scale.[43] The calculations show that Cronbach's α is 0.810 for this scale.

A self-reported, self-administered version of the Chinese questionnaire was used to understand the status of Lifetime Severe Traumatic Events. The questionnaire consists of 23 questions, each corresponding to two answers of "Yes" or "No". A complete list of the questions can be found in Appendix Table 1.

DNA Extraction and Genotyping

With informed consent, 5 mL blood samples were collected from the participants. Genomic DNA was isolated from blood samples using the QIAamp96DNA QIAcube HT Kit and stored at −80°C. Sequenom Mass Array time-of-flight mass spectrometry biochip technology detected the genotype of each SNP site,[44] and the detection company issued a detailed detection report.

Statistical Analysis

All statistical analyses were performed using R (version 4.3.0).[45] The genetic balance test was performed using the Hardy-Weinberg equilibrium test (HWE) in the R package "Hardy Weinberg".[46,47] The R packages "ggplot2" and

"forestploter" were used for the mapping. The R package 'pwr' was used for efficacy analyses to ensure that the sample size was sufficient to support the interaction of interest.[48]

Statistical analyses were performed by grouping the study participants according to whether they had a new onset of major depressive disorder or not. Descriptive statistics were employed to examine the distribution of demographic characteristics and outcome variables across groups. Descriptive analyses were conducted using chi-square tests and Mann–Whitney *U*-test. Logistic regression was used to analyze the association of a genetic polymorphism (*PCDH9* rs9540720) and different dimensions of family functioning with MDD in first-year university students. Using the GA genotype, which has the highest proportion of distribution in the population, as a reference group,[49] the study further analyzed the multiplicative interactions between the *PCDH9* rs9540720 polymorphism and different dimensions of family functioning. In addition, the probability of MDD occurrence in *PCDH9* rs9540720 carriers of different genotypes under changes in family functioning (general functioning) was visualized.

Covariates included continuous variables: age, Beck anxiety score, Beck depression score; and categorical variables: only child, city, adolescent self-rating life events and lifetime severe traumatic events.

Results

Of the 6985 respondents who completed the one-year follow-up, 4866 (69.76%) provided a blood sample and completed genotyping. Of these, a total of 115 respondents 2.36% (95% CI:1.96%-2.83%) had new onset MDD. Table 1 shows the

Table 1 Comparison of Baseline Demographic Characteristics and Family Functioning of 4866 First-Year University Students With and Without New-Onset Major Depressive Disorder

Variables	Total	Non-MDD	New-onset MDD	χ^2/U	*P*
	N=4866(%)	N1=4751(%)	N2=115(%)		
Age(M±SD)	18.39 (0.84)	18.39 (0.84)	18.30 (0.89)	−1.213[a]	0.225
Beck anxiety score(M±SD)	25.14 (6.27)	25.08 (6.23)	27.74 (7.09)	−5.946[a]	<0.001
Beck depression score(M±SD)	3.11 (5.27)	3.01 (5.08)	7.17 (9.63)	−6.665[a]	<0.001
Number of Adolescent Self-rating Life Events	6.68 (4.14)	6.63 (4.12)	8.75 (4.43)	−5.255[a]	<0.001
Number of Lifetime Severe Traumatic Events	1.22 (1.26)	1.20 (1.24)	1.87 (1.83)	−3.740[a]	<0.001
One Child					
No	3020 (62.1)	2948 (62.1)	72 (62.6)	0.015	0.903
Yes	1846 (37.9)	1803 (37.9)	43 (37.4)		
City					
Jining	2179 (44.8)	2135 (44.9)	44 (38.3)	9.289	0.010
Weifang	2041 (41.9)	1978 (41.6)	63 (54.8)		
Rizhao	646 (13.3)	638 (13.4)	8 (7.0)		
Rs9540720 genotypes					
GA	2341 (48.1)	2280 (48.0)	61 (53.0)	4.693	0.096
GG	1695 (34.8)	1652 (34.8)	43 (37.4)		
AA	830 (17.1)	819 (17.2)	11 (9.6)		
Sex					
Male	1888 (38.8)	1848 (38.9)	40 (34.8)	0.800	0.371
Female	2978 (61.2)	2903 (61.1)	75 (65.2)		
Family functioning(M±SD)					
Problem Solving	2.14 (0.42)	2.14 (0.42)	2.19 (0.40)	−1.897[a]	0.058
Communication	2.11 (0.39)	2.11 (0.39)	2.24 (0.38)	−3.230[a]	0.001
Roles	2.17 (0.28)	2.17 (0.28)	2.24 (0.29)	−2.633[a]	0.008
Affective Responsiveness	2.2 (0.44)	2.19 (0.44)	2.38 (0.41)	−4.139[a]	<0.001
Affective Involvement	2.04 (0.41)	2.04 (0.41)	2.13 (0.42)	−2.302[a]	0.021
Behavior Control	2.29 (0.27)	2.29 (0.27)	2.32 (0.27)	−1.784[a]	0.074
General Functioning	2.06 (0.34)	2.06 (0.34)	2.12 (0.38)	−1.817[a]	0.069

Notes: [a]mann–Whitney *U*-test.

Table 2 Hardy-Weinberg Balance Test for PCDH9 rs9540720

Rs9540720 genotypes	Observations (%)	Expectations (%)	χ^2	*P*
GA	2341(48.11)	2356(48.42)	0.200	0.905
GG	1695(34.83)	1687(34.68)		
AA	830(17.06)	822(16.90)		

differences between baseline demographic characteristics and family functioning among respondents with and without new-onset major depressive disorder in the group of students who obtained genetic samples (n=4866). Results showed that the *PCDH9* rs9540720 genotype difference was not significant ($P>0.05$). Among the seven dimensions of family functioning, there were significant differences ($P<0.05$) in communication, roles, affective responsiveness, and affective involvement, whereas there were no significant differences ($P>0.05$) in problem solving, behavior control, and general functioning. Through comparative analysis of basic demographic characteristics and family functions between genetic samples and non-genetic samples, the study found that there was no significant difference in the prevalence of major depression and family functions between the two groups (see Appendix Table 2).

Table 2 shows the observed and expected distribution of *PCDH9* rs9540720 genotypes in the population providing genetic samples. The Hardy-Weinberg test showed that the sample ($\chi^2=0.200$, $P=0.905$) was genetically balanced.

Table 3 shows the effect of *PCDH9* rs9540720 genotype and family functioning on MDD among first-year university students. The AA genotype of *PCDH9* rs9540720 was a protective factor for MDD in first-year university students (OR=0.50, 95% CI:0.25–0.92) without covariate adjustment. As for the seven dimensions of family functioning, communication (OR=2.47, 95% CI:1.49–4.14), roles (OR=2.78, 95% CI:1.41–5.54), affective responsiveness (OR=2.71, 95% CI:1.75–4.21), affective involvement (OR=1.70, 95% CI:1.10–2.59), and general functioning (OR=1.79, 95% CI:1.03–3.14) were risk factors for MDD in first-year university students. After adjusting for the inclusion of covariates, AA genotype of *PCDH9* rs9540720 was a protective factor for MDD in first-year university students (OR=0.47, 95% CI:0.23–0.88). In contrast, only one dimension of family functioning, affective responsiveness (OR=1.77, 95% CI:1.13–2.78), was a risk factor for MDD in first-year university students.

Before conducting the interaction analysis, this study analyzed the correlation between family functioning and *PCDH9* rs9540720 gene polymorphisms using linear regression models, and the results showed that there was no significant correlation between the dimensions of family functioning and the polymorphisms of the *PCDH9* rs9540720 gene ($P>0.05$) (see Appendix Table 3).In Table 4, the interaction between AA genotype of *PCDH9* rs9540720 and general functioning in family functioning significantly increased the risk of MDD prevalence among first-year university

Table 3 Association of PCDH9 rs9540720 Genotypes and Family Functioning on Major Depressive Disorder in First year University Students

Variables	Crude OR (95% CI)	*P*	Adjusted* OR (95% CI)	*P*
Rs9540720 genotypes				
GA	Ref		Ref	
GG	0.97 (0.65, 1.44)	0.892	0.99 (0.66, 1.47)	0.961
AA	0.50 (0.25, 0.92)	0.037	0.47 (0.23, 0.88)	0.025
Family functioning				
Problem Solving	1.31 (0.85, 1.98)	0.215	1.08 (0.68, 1.71)	0.746
Communication	2.47 (1.49, 4.14)	0.001	1.40 (0.83, 2.38)	0.212
Roles	2.78 (1.41, 5.54)	0.003	1.40 (0.69, 2.88)	0.351
Affective Responsiveness	2.71 (1.75, 4.21)	<0.001	1.77 (1.13, 2.78)	0.013
Affective Involvement	1.70 (1.10, 2.59)	0.016	1.21 (0.76, 1.93)	0.414
Behavior Control	1.56 (0.78, 3.11)	0.210	0.85 (0.43, 1.71)	0.639
General Functioning	1.79 (1.03, 3.14)	0.040	1.13 (0.63, 2.04)	0.673

Notes: *Adjusted by sex, age, city, beck anxiety score, beck depression score, number of adolescent self-rating life events, number of lifetime severe traumatic events.

Table 4 Interaction Between PCDH9 Rs9540720 Genotypes and Family Functioning on Major Depressive Disorder in First year University Students

Rs9540720 genotypes × Family functioning	Crude OR (95% CI)	*P*	Adjusted* OR (95% CI)	*P*
GA×Problem Solving	Ref		Ref	
GG×Problem Solving	1.55 (0.62, 3.78)	0.341	1.85 (0.70, 4.83)	0.211
AA×Problem Solving	3.80 (0.81, 15.46)	0.074	4.60 (0.86, 22.17)	0.066
GA×Communication	Ref		Ref	
GG×Communication	2.09 (0.70, 6.30)	0.190	1.83 (0.64, 5.29)	0.263
AA×Communication	7.03 (1.21, 40.57)	0.029	5.35 (0.97, 30.43)	0.055
GA×Roles	Ref		Ref	
GG×Roles	0.83 (0.19, 3.67)	0.807	0.82 (0.19, 3.55)	0.785
AA×Roles	5.76 (0.63, 48.70)	0.110	3.95 (0.43, 34.79)	0.222
GA×Affective Responsiveness	Ref		Ref	
GG×Affective Responsiveness	1.47 (0.57, 3.82)	0.426	1.34 (0.53, 3.43)	0.543
AA×Affective Responsiveness	2.45 (0.51, 11.66)	0.262	1.92 (0.42, 9.25)	0.411
GA×Affective Involvement	Ref		Ref	
GG×Affective Involvement	0.72 (0.29, 1.83)	0.491	0.66 (0.25, 1.77)	0.412
AA×Affective Involvement	0.59 (0.13, 2.48)	0.490	0.43 (0.09, 1.99)	0.286
GA×Behavior Control	Ref		Ref	
GG×Behavior Control	1.66 (0.37, 7.47)	0.507	1.46 (0.33, 6.49)	0.619
AA×Behavior Control	5.61 (0.54, 56.36)	0.147	3.40 (0.34, 35.50)	0.305
GA×General Functioning	Ref		Ref	
GG×General Functioning	1.43 (0.44, 4.75)	0.554	1.37 (0.42, 4.55)	0.603
AA×General Functioning	9.57 (1.57, 54.94)	0.012	6.83 (1.16, 39.27)	0.031

Notes: *Adjusted by sex, age, city, beck anxiety score, beck depression score, number of adolescent self-rating life events, number of lifetime severe traumatic events.
Abbreviations: GA: *PCDH9* rs9540720 GA genotype; GG: *PCDH9* rs9540720 GG genotype; AA: *PCDH9* rs9540720 AA genotype.

students (OR=9.57,95% CI:1.57–54.94) without covariate adjustment. After adjustment for covariates, the interaction of AA genotype and general functioning in *PCDH9* rs9540720 remained a risk factor for MDD in first-year university students (OR=6.83, 95% CI: 1.16–39.27).

Following the interaction analyses, this study conducted power analyses based on the results of the interactions to test whether the sample size of this study was sufficient to support the statistical analyses. Visualization of the results of the power analyses showed that when the sample size reaches 1634, the power is infinitely close to 1 (see Appendix Figure 1). The final sample size of this study is 4866, which is much more than 1634, and therefore the sample size is sufficient to support the interaction of interest. Figure 1 shows a forest plot of the multifactorial logistic regression results. Figure 2 shows the effect of the interaction between family functioning and *PCDH9* rs9540720 genotype on MDD risk.

Discussion

The findings of this study indicated that among Chinese first-year university students, dysfunctional family functioning significantly increased the risk of MDD. Additionally, there was a significant interaction between the *PCDH9* rs9540720 polymorphism and family functioning in relation to the risk of MDD in this population. Specifically, carriers of the AA genotype of *PCDH9* rs9540720 with poor family functioning had a higher risk of developing MDD.

Family dysfunction was further demonstrated to be a risk factor for the development of MDD in this study, including poor communication and parental conflict.[50] Children who are exposed to unhealthy home environments such as parental psychopathology and family relationship problems (eg, limited communication) are more likely to experience childhood adversity.[51] Whereas childhood adversity has been linked to an elevated risk of depression and suicide attempts in university students.[52] Family psychosocial functioning plays an important role in maintaining adolescent mood.[53] Good family functioning is an important external resource for adolescent development and can promote the development of

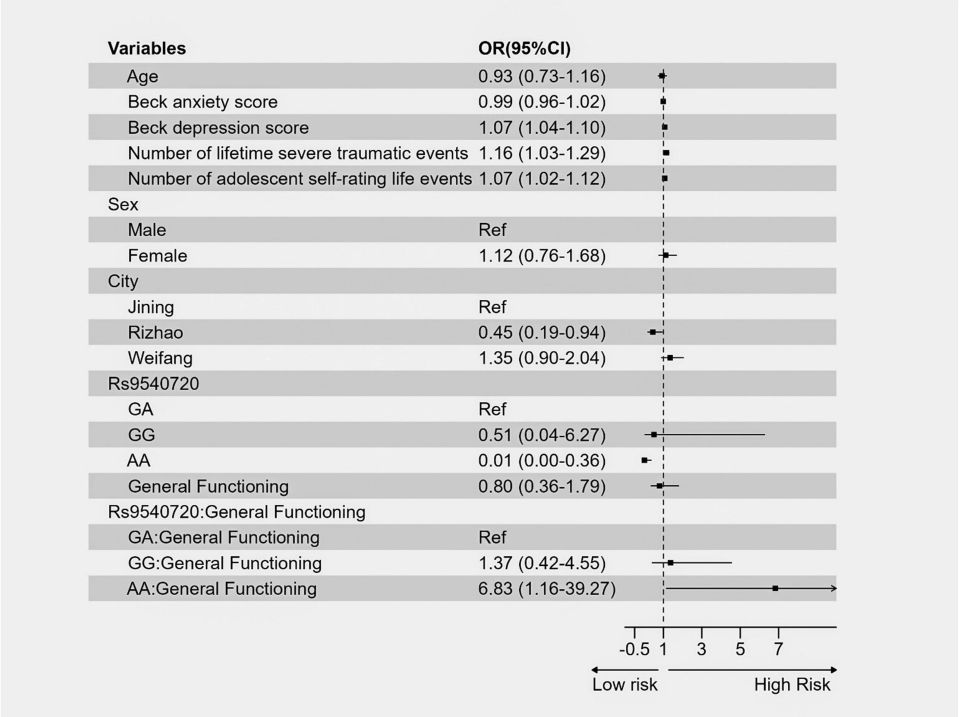

Figure 1 Association of interaction between Family functioning and *PCDH9* rs9540720 genotypes on major depressive disorder.

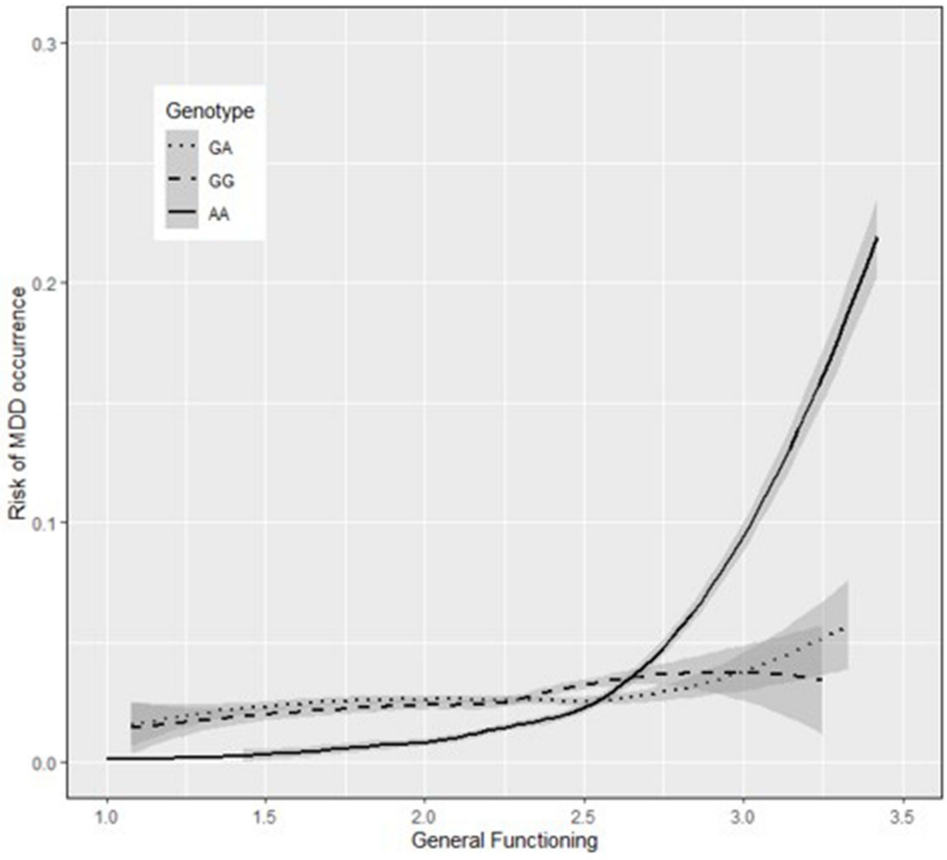

Figure 2 Risk of major depressive disorder in different *PCDH9* rs9540720 genotypes with different scores on General Functioning.

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internal resources (eg, resilience) that enable individuals to recover and adapt to life in the face of adversity, stress, and other negative pressures.[54,55] Family dimensions (eg, communication, etc.) strongly predict children's and adolescents' well-being.[56] Systematic family therapy can reduce the psychological stress of university students, decrease the level of depression, and improve their social adaptability.[57] In summary, a focus on family functioning for university freshmen is warranted.

The AA genotype of *PCDH9* rs9540720 was found to be a protective genotype for the development of MDD in this study, which is consistent with the G+ genotype shown by GWAS to be a risk factor for the development of MDD.[20] Previous studies have identified important roles in the development of *PCDH* neurons, particularly in the hippocampus and dentate gyrus.[58] Another study revealed a regional dependence of *PCDH* expression in other brain regions including the basal ganglia.[18] And the onset and development of MDD is closely related to the hippocampus and basal ganglia.[59,60] This shows that there is a strong link between *PCDH* and the development of MDD.*PCDH9* mRNA has been reported to be expressed in subregions of the olfactory bulb, cerebral cortex, hippocampus, and caudate shell nucleus.[61] Furthermore, the *PCDH9* gene has a putative role in specific neuronal linkages and signal transduction[62] and may be involved in the formation of specific neural circuits during neurodevelopment.[63] Although *PCDH9* is restrictedly expressed in the amygdala, it still provides a potential adhesion cue code for understanding the functional organization of the amygdala.[64] In addition, the amygdala is associated with many neuropsychiatric disorders such as depression and sleep deprivation,[65] and changes in the amygdala can be used as a biomarker for major depression.[66] Despite the lack of direct evidence, the above-mentioned studies suggest that the *PCDH9* rs9540720 polymorphism is associated with the pathogenesis of depression.

The effect of the interaction of *PCDH9* rs9540720 with family functioning on MDD found in the present study is similar to the prediction of depression by the interaction of genes such as *5-HTTLPR* and *DRD2 TaqIA* with parenting styles in previous studies,[34,67] which further suggests that there is a significant genetic correlation between the family environment and depressive symptoms.[68] Underlying genetic and environmental risk factors and the interactions between the two may align with aberrant epigenetic mechanisms targeting stress-response pathways, neuronal plasticity, and other behaviorally relevant pathways associated with major depressive disorder.[29] The synaptic complex *DPP6-DPP10-PCDH9* has been identified as a susceptibility profile for autism disorder (ASD),[69] suggesting that expression of *PCDH9* may influence the emergence of autism symptoms, including features such as social deficits and communication disorders.[70] Notably, communication, a core aspect of family functioning, is pivotal in upholding family stability.[71] Animal studies have shown that *PCDH9*-deficient mice demonstrate distinct long-term social and object recognition deficits, coupled with diminished positive emotional behaviors.[16,72] There is evidence to suggest that mental illnesses and early-life experiences can modulate the expression of the *PCDH* gene in the brain via epigenetic alterations.[73] This implies that *PCDH9* may influence early social and affective responses, thereby impacting family functioning (eg, communication and affective responsiveness). Conversely, suboptimal family functioning in early life may also alter *PCHD9* gene expression.

Cultural differences clearly affect different aspects of mental health, including perceptions of health and illness, coping styles, and family, with communication and cultural competence also being important considerations for mental health practitioners.[74] A Meta-analysis found that the impact of family on individuals varies by culture, with children from East Asian cultures being more likely to experience psychological problems such as anxiety when exposed to negative family interactions, relative to children from European-acquired American cultures.[75] The selection of the population for this study was specific and homogenous, and the cultural specificity of the sample could affect the generalizability of the findings. Enriching the selection of the population and considering the impact of cross-cultural influences is necessary in future studies. In addition, a one-year follow-up may not be able to capture the long-term effects of family functioning and genetic factors on MDD, and longer follow-up studies are necessary to plan. Nevertheless, this study still confirms the existence of significant effects of *PCDH9* rs9540720 polymorphism and family functioning on major depressive disorder in Chinese freshmen students, respectively, and further elucidates the interaction between genetics and the environment (*PCDH9* rs9540720×family functioning) on major depression, which provides important information for the study the intricate pathogenesis of depression, providing important information.

This study possesses certain limitations. Firstly, it is a one-year cohort study, and the data collection depended on self-reports from the respondents. This approach may introduce recall bias and loss of subjects to follow-up. Future studies should use objective ratings to effectively reduce this self-report bias. Second, there are differences in the worldwide distribution of the *PCDH9* rs9540720 genotype,[49] and the sample consisted only of Chinese first-year university students, which is not representative of the broader population, thus limiting the generalizability of the study. The influence of family on an individual varies by culture, and the differences brought about by different cultures deserve to be considered in future studies. In addition, it is necessary to explore all the socio-economic factors that may lead to risk and control them in subsequent studies.

Conclusion

This study identifies a novel factor influencing the incidence of MDD in Chinese first-year university students: the interaction between *PCDH9* rs9540720 polymorphism and family functioning. This study suggests that the *PCDH9* rs9540720 gene polymorphism may affect the performance of family functioning by influencing early affective responses in carriers; and poor family functioning as a stressor also promotes new-onset depression in university students carrying the susceptibility gene. In addition, different cultural backgrounds limited extrapolation of this study, and it would be worthwhile to include consideration of culture-specific effects in future studies. Finally, for university students during sensitive periods of mental health, regular assessment of family functioning and screening for susceptibility genotypes may improve the efficiency of university mental health departments and counsellors in mitigating the onset of depression and reduce the likelihood of depression. Higher education institutions in China should priorities the understanding of family functioning of new students and provide targeted counselling to provide mental health services to improve family relationships and mental health of university students.

Ethics Statement

This study complied with the Declaration of Helsinki. This study was approved by the Research Ethics Committee in Jining Medical University, Jining, China (No:2019-JS-004). All participants voluntarily submitted written informed consent before participating in the study. All data were handled in a confidential manner.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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