Int J Clin Exp Pathol 2017;10(6):6189-6197
www.ijcep.com /ISSN:1936-2625/IJCEP0040816

Review Article

Polymorphisms in 5-HTR1A and coupled G-proteins in association with negative life events increase susceptibility to suicide attempt

Lin Wang[1*], Lu Chen[2*], Jingsong Ma[1], Zhengxue Qiao[1], Xiaohui Qiu[1], Xiuxian Yang[1], Jia Run Yang[1], Yan Zhao[3], Yanjie Yang[1], Deyu Fang[4]

[1]Department of Psychology, The Public Health Institute of Harbin Medical University, Heilongjiang Province, China; [2]Peking Union Medical College Hospital, Beijing, China; [3]The Second Affiliated Hospital of Harbin Medical University, Heilongjiang Province, China; [4]Northwestern University, USA. [*]Equal contributors.

Received April 1, 2016; Accepted December 16, 2016; Epub June 1, 2017; Published June 15, 2017

Abstract: Suicide refers to an individual in a complex psychological state who, under intentional or voluntary action, takes various means to end their life. Importantly, 50%-70% of suicide deaths associated with mental disorders are in patients that suffer from depression. In this study, we investigated whether there were correlations between negative life events and genetic polymorphisms in the 5-HT receptor 1A (HTR1A) and its coupled G-protein gene that contribute to the incidence of suicidal behavior in depression patients. The admission criteria for this study excluded patients with psychotic spectrum disorders and active substance use. Clinical depression was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. Single nucleotide polymorphism (SNP) genotyping was performed by the Taqman allelic discrimination assay among 449 patients with clinical depression (suicide attempts: 98 and non-suicide attempts: 351). The frequency and severity of negative life events were measured using the Life Events Scale. Individual SNP genotype and allele frequencies were compared between the groups by χ^2 test, and gene-environment interactions were analyzed by logistic regression models. There were no significant associations between the four SNPs and suicide attempts in depression patients. Analyses assuming a single contribution of each gene-environment interaction to suicide attempt risk in individuals carrying the C/C genotype of rs5443, the C/C genotype of rs6295 or the C/C genotype of rs878567, in combination with high-negative life events, showed a trend for an interaction between these SNPs and high negative life events impacting the history of suicide attempts among depression patients in the Chinese population. These results suggest that HTR1A and GNB3 variations interact with environmental factors to increase the risk of suicide attempt in depression patients in the Chinese population.

Keywords: Suicide attempt, correlations, high negative life events, gene-environment

Introduction

Worldwide, at least 500,000 people die each year from suicide, and 10%-40% of these cases are patients with mental illness; among the suicide deaths associated with mental disorders 50%-70% suffer from depression [1]. Suicide refers to an individual in a complex psychological state who, under intentional or voluntary action, take various means to end their life [2]. According to recent statistics, every year in China approximately 2 million patients with clinical depression attempt suicide and at least 250,000 take their lives [3]. Studies of suicide rates have raised much attention, but the causes of suicide are not yet fully understood.

The results of this study suggest that genetic factors play an important role in suicide incidence, in accordance with pedigree investigations, twin studies and research on adopted children, which have drawn similar conclusions [4]. Acting synergistically with genetic risks, negative life events can increase suicide risk by influencing the epigenetic regulation of genes involved in stress-response systems [5].

A previous study confirmed that depression patients have reduced serotonin (5-hydroxytryptamine, 5-HT) levels, activity and metabolic products in their cerebrospinal fluid, which at the lower level was proportional to the severity of symptoms [6]. These genetic findings were

corroborated by the observation of several biological abnormalities in brain neurotransmitter systems in suicide cadavers, mainly involving signs of reduced 5-HT function [7]. Therefore, it was hypothesized that candidate genes for suicide would include genes involved in 5-HT synthesis, processing and the activity of related enzymes and receptors.

Studies investigating candidate genes for suicide risk have strongly supported a role for genetic polymorphisms in the serotonergic pathway, primarily in genes that regulate 5-HT synthesis, turnover or receptor density and structure. The human 5-HT receptor 1A (5-HTR1A) is located in the chromosomal region q11.2-q13, and the encoded G-protein-coupled receptor (GPCR) is distributed in dendrites of pre-synaptic and post-synaptic neurons, as well as independent pre-synaptic and post-synaptic receptors. 5-HTR1A expressing neurons are one of the most common subtype of neurons in the mammalian brain [8]. The 421 amino acid 5-HTR1A protein belongs to the GPCR family and is thought to mainly regulate 5-HT release [9]. While developments in molecular biology technology have begun to clarify the role of 5-HTR1A genetic polymorphisms in the etiology of depression and the activity of antidepressants, the molecular mechanism that underlies the association of these polymorphisms to suicidal behavior is not yet clear. Human HTR1A expression is regulated by two transcriptional repressors deformed epidermal auto-regulatory factor-1 (DEAF-1) and Hairy and enhancer of split 5 (HES-5). Single nucleotide polymorphisms (SNPs) in the HTR1A promoter prevent DEAF-1 and HES-5 binding, increasing HTR1A expression, which results in decreased serotonin signal conduction; these alterations in neural signaling may be the reasons for suicide [10]. Therefore, 5-HTR1A has become a new subject of focus in the study of suicide etiology. Although extensive research into the association between 5-HTR1A polymorphisms and suicidal behavior has been conducted both in China and abroad, it has yet to yield conclusive results [11, 12].

GPCRs are cytoplasmically associated with G-proteins, which are a family of proteins that are active or inactive when bound to guanosine triphosphate (GTP) or guanosine diphosphate (GDP), respectively. Upon ligand binding, GPCRs activate their associated G-proteins, which causes the G-proteins to dissociate into α- and β/γ-subunits. These subunits then activate downstream enzymes to influence signaling cascades including cyclic adenosine monophosphate (cAMP) signaling. GPCR signaling plays important roles in 5-HT signal transduction, and specifically, 5-HTR1A inhibits adenylyl cyclase (AC) activity, which normally generates a second messenger to further propagate 5-HT signaling, eventually leading to changes in emotion and behavior [13].

In recent years, studies on depression have begun to focus on GPCR signaling, but there have yet to be any studies focused on GPCR signaling and suicide in depression patients. Yuqing et al. reported that both the expression and activity of G-proteins were altered in people with depression [14]. According to another study, untreated depression patients had significantly higher platelet membrane $G_{\alpha i}$ and $G_{\alpha q}$ levels compared with healthy controls. Unfortunately, current antidepressant treatment regimes are unable to change the high level of G-protein expression. Cerebral autopsy results of suicidal depression patients have shown that 5-HTR1A coupling with G-proteins and their related signaling molecules are decreased [15]. There are also studies that have shown G-protein polymorphisms to be associated with severe depression. For example, Zill et al. selected 78 patients with single-phase depression who had taken antidepressant treatment, and found a genetic polymorphism within a G-protein β-subunit (C825T), for which TT homozygosity was relevant to antidepressant efficacy [16].

However, studies have shown that genetic factors account for only 37% of depression cases; therefore, the impact of the individual's environment may reach up to 63% on the occurrence of the disease [17]. In recent years, gene-environment interaction studies have opened a new direction in the understanding of the pathological mechanisms of depression. In this study, both the individual's genetic and environmental factors were considered; thus, we investigated if a person's genotype made them more likely to suffer from depression and be more prone to suicide under the same environmental factors. When investigating the pathogenesis of depression, taking environmental factors into consideration is necessary. Therefore, this study further explored the combined influence

Table 1. Characteristics of the study participants

Variable	Suicide attempt MD (n = 98)	Non-suicide MD (n = 351)	χ^2/t	*P*-value
Age (mean ± SD)	45.16±14.05	43.99±13.54	-0.751	0.453
Gender (males/females)	30/68	96/255	0.404	0.525
Negative LES score	12.81±18.96	5.77±10.05	-4.915	0.000
HAMD score	33.13±5.98	30.02±5.66	-4.757	0.000

of genetic and environmental factors on the suicidal behavior of depression patients.

This study proposed the following hypotheses: 1) Polymorphisms in 5-HTR1A and its coupled G-protein may be related to suicidal behavior in depression patients, and 2) interactions between environmental factors and polymorphisms in 5-HTR1A and its coupled G-protein may contribute to the incidence of suicidal behavior in depression patients.

Materials and methods

Participants

This study was approved by the Ethics Committee for Medicine of Harbin Medical University, China, and all participants provided written informed consent. The study cohort included 449 patients with clinical depression (126 males and 323 females; mean age 42.47±12.24 years; range 18-60 years) from Northern China and all were of Chinese Han origin. Patient demographic and clinical information is summarized in **Table 1**. The admission criteria for this study excluded patients with psychotic spectrum disorders and/or active substance use. Clinical depression was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria [18]. Patients were interviewed by at least two trained psychiatrists using the Structured Clinical Interview for DSM-IV disorders (SCID-I). The inter-rater reliability kappa value of SCID was 0.82. Only subjects with a minimum score of 21 on the 24-item Hamilton Rating Scale for Depression (HAMD) entered the study. All patients were genotyped for the HTR1A polymorphisms (rs6295, rs878567 and rs1364043) and the GNB3 polymorphism (rs5443).

Suicidal thoughts and suicide attempts

Two items from a self-made questionnaire were used in this study to assess the presence of suicidal thoughts and suicide attempts: (1) "In the past 2 weeks, have you actually had any thoughts of killing yourself"? and (2) "In the past month, have you made a suicide attempt? Or did you do anything as a way to end your life"? Items were rated as yes (1) or no (0). These two items were taken from The Columbia Suicide-Severity Rating Scale (CSSRS) [19].

Assessment of negative life events

Negative life events were assessed using the Life Events Sale (LES) developed by Desen Yang and Yalin Zhang. The LES is composed of 48 items classified into three groups: family life (28 items), work (13 items), and social and other aspects (7 items) [20] and has been validated in a Chinese population. Negative events include serious illness, housing, relationship, and social difficulties, relationship breakdowns, unemployment, and financial crises. The scores for positive and negative events were determined by the interviewers to yield a total life events score. The scale considers four aspects of the event: time of occurrence (absent = 1, more than one year ago = 2, within the past year = 3, chronic = 4), character (good = 1, bad = 2), influence on mood (absent = 1, mild = 2, moderate = 3, severe = 4, extreme = 5), and duration of influence (≤3 months = 1, 3-6 months = 2, 6-12 months = 3, >12 months = 4). The 75% percentile (a score of 4) was used as a cutoff value for high- and low-level negative life events.

DNA extraction and genotyping

Genomic DNA was extracted from 250 μl EDTA-anticoagulated venous blood samples using the AxyPrep Blood Genomic DNA Miniprep Kit (Axygen, Union City, CA, USA). Genotyping was performed for one SNP in GNB3 (rs5443) and three SNPs in HTR1A (rs6295, rs878567, rs1364043). The primers used for PCR amplification were designed using Primer 5.0 software, and the specificity of each primer was checked using a BLAST search of the National

Table 2. Primer sequences and lengths of PCR products

Gene	SNP ID	Polymorphisms	Primer sequence (5'→3')	Product length (bp)
GNB3	rs5443	C/T	F: 5'-CCAATGGAGAGGCCATCTGCA-3'	250
			R: 5'-CTTCCAGCTGAGGAAGCAGCA-3'	
5-HT1AR	rs6295	C/G	F: 5'-TTGGAGACGGAGTCTCGCTCT-3'	211
			R: 5'-TAAATCGTGTCAGCATCCCAG-3'	
	rs878567	C/T	F: 5'-CAGCGGAGGAGCGTTGAGAGC-3'	247
			R: 5'-CAAGTTCTAGAAGTTGGGTGA-3'	
	rs1364043	G/T	F: 5'-ATATAAGGATCAAATAGGTCT-3'	309
			R: 5'-ACAATCTGCCATTTGGATGAG-3'	

Center for Biotechnology Information database (http://blast.ncbi.nlm.nih.gov). DNA samples were genotyped by the 5' nuclease assay using a 7900HT Fast Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). The SNP genotype of each tested sample was determined by computer software and confirmed manually. Primer sequences and lengths of PCR products are given in **Table 2**.

Statistical analyses

Haploview 4.2 was used to generate a linkage disequilibrium (LD) map and to test for Hardy-Weinberg equilibrium (HWE). Individual SNP allele frequencies were compared between the groups by χ^2 test, and the gene-environment interactions were analyzed by logistic regression models. Statistical significance was defined as $P<0.05$ (two-tailed). The SPSS package (version 20.0 for Windows) was used for statistical analyses (SPSS, Chicago, IL, USA).

A history of suicide attempts was the primary dependent variable. The independent variables were HTR1A genotype, GNB3 genotype, history of negative life events, and the combination of these variables. The subjects were divided based on HTR1A (rs6295, rs878567, rs1364043) and GNB3 (rs5443) genotype. Each genotype group was further subdivided based on history of negative life events (high or low) for statistical analysis. Finally, the interaction between history of negative life events and HTR1A and GNB3 genotype on suicide attempts was evaluated by a logistic regression model using the following variables. First, HTR1A rs6295 (C/C, G/G or C/G genotype): 1) a variable for high life events and C/C; 2) a variable for high life events but no C/C; 3) a variable for low life events and C/C. Those three variables were included in a logistic model, and the resulting odds ratios (ORs; including 95% confidence intervals (CIs)) and *P*-values were compared against the reference group with low life events and no C/C. Second, HTR1A rs878567 (C/C, T/T or C/T genotype): 1) a variable for high life events and C/C; 2) a variable for high life events but no C/C; 3) a variable for low life events and C/C. Those three variables were included in a logistic model, and the resulting three ORs and *P*-values were compared against the reference group with low life events and no C/C. Third, HTR1A rs1364043 (T/T, T/G or G/G genotype): 1) a variable for high life events and T/T; 2) a variable for high life events but no T/T; 3) a variable for low life events and T/T. Those three variables were included in a logistic model, and the resulting three ORs and *P*-values were compared against the reference group with low life events and no T/T. Fourth, GNB3 rs5443 (C/C, T/T or C/T genotype): 1) a variable for high life events and C/C; 2) a variable for high life events but no C/C; 3) a variable for low life events and C/C. Those three variables were included in a logistic model, and the resulting three ORs and *P*-values were compared against the reference group with low life events and no C/C.

Gene × environment interactions were analyzed using generalized multifactor dimensionality reduction (GMDR) software (version 0.7), which classifies and predicts disease risk using c ross-validation (CV). In the configuration file, 10-fold CV was defined and the threshold ratio set at 1.0. We ran the analysis 10 times using 10 different random number seeds and the results were averaged to avoid spurious outcomes due to chance divisions of the data. The model with the combination of loci and/or discrete environmental factors that maximizes the CV consistency and minimizes the prediction error (PE) was selected. The null hypothesis

Table 3. Distributions of genotypes and alleles in the study participants

Gene	Group	N	Genotype frequencies Number of Subjects (%)			*P*-value	Allele frequencies Number of Subjects (%)		*P*-value	OR (95% CI)
GNB3	rs5443		CC	CT	TT		C	T		
	Suicide attempt	98	22 (22.5)	55 (56.1)	21 (21.4)	0.293	99 (50.5)	97 (49.5)	0.315	1.176 (0.857-1.615)
	Non-suicide	351	106 (30.2)	171 (48.7)	74 (21.1)		383 (54.6)	319 (45.4)		
5-HT1AR	rs6295		CC	CG	GG		C	G		
	Suicide attempt	98	40 (40.8)	53 (54.1)	5 (5.1)	0.069	133 (67.9)	63 (32.1)	0.118	1.314 (0.932-1.853)
	Non-suicide	351	186 (53.0)	144 (41.0)	21 (6.0)		516 (73.5)	186 (26.5)		
	rs878567		CC	CT	TT		C	T		
	Suicide attempt	98	52 (53.1)	43 (43.9)	3 (3.0)	0.109	147 (75.0)	49 (25.0)	0.176	1.292 (0.891-1.873)
	Non-suicide	351	222 (63.2)	114 (32.5)	15 (4.3)		558 (79.5)	144 (20.5)		
	rs1364043		GG	GT	TT		G	T		
	Suicide attempt	98	26 (26.5)	59 (60.2)	13 (13.2)	0.073	111 (56.6)	85 (43.4)	0.228	1.218 (0.884-1.678)
	Non-suicide	351	132 (37.6)	167 (47.6)	52 (14.8)		431 (61.4)	271 (38.6)		

Table 4. Interaction between GNB3 and HT1AR genetic polymorphisms with negative life events

Variable	Suicide attempt	Non-suicide	OR (95% CI)	*P*-value
rs5443				
CC and LN	8	80	1	
CC and HN	14	26	5.385 (2.031-14.273)	0.001
CT or TT and LN	47	192	2.448 (1.107-5.414)	0.027
CT or TT and HN	29	53	0.415 (0.135-1.274)	0.415
rs6295				
CC and LN	18	141	1	
CC and HN	22	45	3.830 (1.887-7.770)	0.000
CG or GG and LN	37	131	2.212 (1.200-4.078)	0.011
CG or GG and HN	21	34	0.571 (0.218-1.498)	0.255
rs878567				
CC and LN	24	170	1	
CC and HN	28	52	3.814 (2.036-7.143)	0.000
CT or TT and LN	31	102	2.153 (1.197-3.871)	0.010
CT or TT and HN	15	27	0.479 (0.180-1.273)	0.140
rs1364043				
TT and LN	9	44	1	
TT and HN	4	8	2.444 (0.604-9.894)	0.210
GT or GG and LN	46	228	0.986 (0.450-2.160)	0.973
GT or GG and HN	39	71	1.114 (0.252-4.921)	0.887

LN: low negative life events; HN: high negative life events; OR: odds ratio; CI: confidence interval.

was rejected when the upper-tail Monte Carlo *p*-value given by the permutation test was ≤0.05.

To validate GMDR results, we computed the OR values (with 95% CI) of risk factors selected by GMDR analysis using SPSS for Windows (version 20.0). To narrow down the number of possible combinations, we analyzed dominant models only. We also corrected the *p*-value for multiple comparisons using the Bonferroni method.

Results

SNP association analyses

There were no significant differences in mean age or sex ratio between depression patients who had or had not attempted suicide. The genotypic distributions of all three HTR1A polymorphisms conformed to Hardy-Weinberg equilibrium for both the suicide attempt non-suicide attempt groups. The genotype distributions and allele frequencies of the four SNPs are summarized in **Table 3**. There was no significant association between all four SNPs and suicide attempts (P>0.05).

Gene-environment interaction

As shown in **Table 4**, analyses assuming a single contribution of each gene-environment interaction to suicide attempt risk showed an OR value of 5.385 (95% CI 2.031-14.273) in individuals carrying the C/C genotype of rs5443 combined with high-negative life events. In individuals with the C/C genotype of rs6295 or C/C genotype of rs878567, high-negative life

events gave OR values of 3.830 (95% CI 1.887-7.770) and 3.814 (95% CI 2.036-7.143), respectively. However, among individuals carrying the other genotypes of rs5443, rs6295 and rs878567, low-negative life events yielded OR values of 2.448 (95% CI 1.107-5.414), 2.212 (95% CI 1.200-4.078) and 2.153 (95% CI 1.197-3.871), respectively, which was indicative of higher susceptibility to clinical depression.

Among the group with a C/C genotype of rs5443 (GNB3), depression with a high history of negative life events had a significantly higher prevalence of suicide attempts than patients with low-negative life events (14/98, 14.29% versus 26/351, 7.41%, P = 0.001; OR 5.385, 95% CI 12.031-14.273). Depression with the T allele present (C/T or T/T) also showed statistically significant differences based on negative life events (47/98, 47.96% versus 129/351, 36.75%, P = 0.0027; OR 2.448, 95% CI 1.107-5.414).

Among the group with a C/C genotype of rs6295 (HTR1A), depression with a high history of negative life events had a significantly higher prevalence of suicide attempts than patients with low-negative life events (22/98, 22.45% versus 45/351, 12.82%, P = 0.000; OR 3.830, 95% CI 1.887-7.770). Depression with the G allele present (C/G or G/G) also showed statistically significant differences based on negative life events (37/98, 37.76% versus 131/351, 37.32%, P = 0.011; OR 2.212, 95% CI 1.200-4.078).

Among the group with a C/C genotype of rs878567 (HTR1A), depression with a high history of negative life events had a significantly higher prevalence of suicide attempts than patients with low-negative life events (28/98, 28.57% versus 52/351, 14.81%, P = 0.000; OR 3.814, 95% CI 2.036-7.143). Depression with the T allele present (C/T or T/T) also showed statistically significant differences based on negative life events (31/98, 47.96% versus 102/351, 36.75%, P = 0.010; OR 2.153, 95% CI 1.197-3.871).

The likelihood ratio test from the logistic model showed no trend for the interaction between the group with only rs1364043 (HTR1A) and high negative life events; however, significant results were obtained from other groups.

Discussion

We performed an association study with the polymorphisms rs6295, rs878567 and rs1364043 in HTR1A, and rs5443 in GNB3 and negative life events in a sample of 449 patients with clinical depression. The main finding of the study was that HTR1A and GNB3 genotype modulate the relationship between negative life events and history of attempted suicide in depression patients. We showed a trend for interactions between polymorphisms in the serotonin receptor gene HTR1A (rs6295 and rs878567) and its coupled G-protein GNB3 (rs5443) and a high incidence of negative life events impacting the history of suicide attempts among depression patients.

Independent of exposure to negative life events, the HTR1A polymorphisms rs6295, rs878567 and rs1364043, which can influence activity of the serotonin system, were not associated with suicide attempts, which is consistent with the observation by Wrzosek et al. [21]. However, our results differ from previous reports; Pitchot et al. [22] concluded that HTR1A is associated with self-aggression in suicide attempters, and Boldrinim et al. [23] reported that the rates of combination for HTR1A in the brainstem Dorsal Raphe Nucleus (DRN) of suicide attempters was lower than the psychiatric group. Additionally, they showed that the rates of combination for HTR1A in DRN cross-sections of suicide attempters was higher in the rostrum and lower in the tail compared with control samples. This suggests that HTR1As with high rates of combination may reduce electric discharge of cortical neurons in the ventral prefrontal cortex, causing insufficient 5-HT release. However, Lowther et al. [24] did not find a significant difference between suicide attempters and controls, or patients who committed suicide with or without violence. These discrepant results may be attributable to several variables. First, the reported study selected subjects with suicidal behaviors from different subgroups such as depression, bipolar disorder, schizophrenia, and alcoholics. Therefore, they cannot exclude the possibility that the positive association of HTR1A with suicidal behavior may be related to those specific psychiatric disorders. Second, previous reports selected a different batch of SNPs to conduct an association study with suicidal behavior. While we chose the SNPs most commonly

reported to be associated with suicidal behavior; all SNPs studied here showed no association with completed suicides alone.

Moreover, analyses of the allele frequency of rs5443 (GNB3) as well as the comparison of genotypes in our study did not demonstrate a significant association with suicide attempts in depression patients. These findings parallel the results of Serafini et al. who also did not find an association between suicidal behavior and SNPs in GNB3 [25]. Some groups have previously investigated an association between GNB3 and affective disorder using depressive patients and healthy controls. For example, Zill et al. reported that the GNB3 SNP (C825T) is a susceptibility factor only for major depression and possibly for bipolar disorder, but not for suicide [16, 26]. The sample size of this study was less than our study (10 bipolar patients, and 78 with clinical depression). Many studies have suggested that GNB3 is a susceptibility factor for depression [27-30]. But no study has reported an association between GNB3 and suicide, which is consistent with our results. These discrepant results may suggest that genetic factors are less attributable to pathogenesis of suicide than previously hypothesized. Alternatively, the sample size of these case-control studies was not sufficient to detect small genetic effects.

We observed increased OR values among the GNB3 (rs5443) and HTR1A (rs6295, rs878567, rs1364043) depression groups with a high history of negative life events, demonstrating a significantly higher prevalence of suicide attempts in these groups. Analyses assuming a single contribution of each gene-environment interaction to suicide attempt risk showed an association in individuals combined with high negative life events. These findings are in agreement with previous observations, which found the same effect for several other genes in patients with a worse probability of developing a major depressive episode [31, 32]. Thus, compared with the negative life events, serotonergic dysfunction may be a secondary and compensatory change for environmental factors in depression patients with suicidal behaviors. Genetic factors may be less attributable to the pathogenesis of suicide, which has also been postulated by Mouri et al. [33].

Although there were no associations between HTR1A or GNB3 SNPs and suicide attempts in depression patients in our study, we could not completely ignore the genetic factors. HTR1A and GNB3 expression may influence the relationship between negative life events and suicide, which are likely to involve the functional and structural coupling of amygdale, hippocampus and prefrontal cortico-limbic structures, which provide a neural basis for the cognitive control of emotions [34, 35]. The HTR1A polymorphisms effect its expression in presynaptic and postsynaptic neurons, resulting in decreased neural serotonin conduction, which will reduce the efficiency of the cortico-limbic feedback circuits in response to negative stimuli [36]. Increased activity in the hypothalamic-pituitary-adrenal axis in response to adverse or threatening stimuli [6] increases higher brain activation and subjective distress, which promotes behavioral anxiety and harm avoidance [37, 38]. Genetic and epigenetic programs are likely to interact with environmental stimuli to produce these effects.

Limitations

Our results are interesting, especially regarding the role of polymorphic variation in genes related to 5-HT signaling, including HTR1A and GNB3, in mediating suicidal behavior in depression patients. However, further investigation is warranted for reliable conclusions considering the following limitations. First, we had a limited sample size, which could limit the power to detect potential differences between each group. Second, the study only included subjects of Chinese Han origin from Northern China. Therefore, we cannot generalize our findings to other populations. Also, a limitation of the study is that the history of suicide attempts was obtained by self-report without corroboration from hospital records or third party interviews.

Conclusions

These results suggest that HTR1A and GNB3 variations interact with environmental factors to increase the risk of suicide attempt in Chinese depression patients. The main finding of this study is that HTR1A and GNB3 genotype modulate the relationship between negative life events and history of attempted suicide in patients affected by clinical depression.

Acknowledgements

This research was supported by the National Natural Science Foundation of China (8147-3054) to Prof. Yanjie Yang. We do not hold any stocks or shares in an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future.

Disclosure of conflict of interest

None.

Authors' contribution

Lin Wang and Lu Chen contributed equally to this work. They carried out the epidemiological investigations, conceived the conceptual design of the study, participated in its coordination, and drafted the manuscript. Xiao Hui Qiu participated in the design of the study and performed statistical analyses. Xiu Xian Yang carried out the epidemiological investigations and participated in the design of the study. Zheng Xue Qiao participated in the design of the study. Yan Jie Yang is the corresponding author of the article, and she conceived the design of the study, participated in its coordination, and helped draft the manuscript.

Address correspondence to: Yanjie Yang, Department of Psychology, The Public Health Institute of Harbin Medical University, No. 157, Baojian Road, Nangang District, Harbin 150081, Heilongjiang Province, China. Tel: +86 451 87502859; Fax: +86 451 87502885; E-mail: yanjie1965@163.com; Deyu Fang, Northwestern University, USA. E-mail: fangd@northwestern.edu

References

[1] Lu Z, Jia Z, Huang X, Gong Q. Current progress in researches on depression with suicidal behavior in neurobiology. Sheng Wu Yi Xue Gong Cheng Xue Za Zhi 2011; 28: 834-838.

[2] McGirr A, Renaud J, Séguin M, Alda M, Turecki G. Course of major depressive disorder and suicide outcome: a psychological autopsy study. J Clin Psychiatry 2008; 69: 966-970.

[3] Wang DW. The relief and prevention of suicide. Journal of Life and Disaster 2011; 32-34.

[4] Currier D, Mann JJ. Stress, genes and the biology of suicidal behavior. Psychiatr Clin North Am 2008; 31: 247-269.

[5] Turecki G, Ernst C, Jollant F, Labonte B, Mechawar N. The neurodevelopmental origins of suicidal behavior. Trends Neurosci 2012; 35: 14-23.

[6] Li SJ, Zhu FL, Li Z. Effects of topiramate on the cognitive function in immature rats and the changes of 5-hydroxy tryptanune and γ-aminobutyric acid expression in brain tissue. Chinese Journal of Brain Dieases and Rehabilitatin (electronic edition) 2011; 1: 145-151.

[7] Mann JJ. Neurobiology of suicidal behaviour. Nat Rev Neurosci 2003; 4: 819-828.

[8] Yan L, liu Z, Song DR. Menopausal depression and the sea horse, skin quality, and the 5-HTR1AmRNA correlation experimental study. When Jane National Physician Characters 2010; 21: 1898-1900.

[9] Song YJ. Han Chinese population serotonin transporter, serotonin 1 a receptor and tryptophan hydroxylase 2 gene polymorphism with depression and paroxetine hydrochloride efficacy correlation research. Lanzhou University 2008.

[10] Zai CC, de Luca V, Strauss J, et al. Genetic factors and suicidal behavior. In: Dwivedi Y, editor. The neurobiological basis of suicide. Boca Raton, FL: CRC Press; 2012: Chapter 11. Available from: http://www.ncbi.nlm.nih.gov/books/NBK107191.

[11] Li XM, Li K, himself. The serotonin transporter gene second introns and promoter region polymorphism associated with suicide attempts analysis. Journal of Chongqing Medical University 2010; 35: 568-571.

[12] Oquendo MA, Placidi GP, Malone KM, Campbell C, Keilp J, Brodsky B, Kegeles LS, Cooper TB, Parsey RV, van Heertum RL, Mann JJ. Positron emission tomography of regional brain metabolic responses to a serotonergic challenge and lethality of suicide attempts in major depression. Arch Gen Psychiatry 2003; 60: 14-22.

[13] Wilkie MJ, Smith D, Reid IC, Day RK, Matthews K, Wolf CR, Blackwood D, Smith G. A splice site polymorphism in the G-protein beta subunit influences antidepressant efficacy in depression. Pharmacogenet Genomics 2007; 17: 207-15.

[14] Song YQ, Zhou DF, Fan JH, etc. The curative and fluoxetine treatment of depression before and after the change of platelet membrane guanylic acid binding protein content. Chinese Journal of Mental Health 2004; 17: 783-786.

[15] Schreiber G, Avissar S. G proteins as a biochemical tool for diagnosis and monitoring treatments of mental disorders. Isr Med Assoc J 2000; 2 Suppl: 86-91.

[16] Zill P, Baghai TC, Zwanzger P, Schüle C, Minov C, Riedel M, Neumeier K, Rupprecht R, Bondy B. Evidence for an association between a G-Protein beta3-gene variant with depression

and response to antidepressant treatment. Neuroreport 2000; 11: 1893-897.
[17] Thimm M, Kircher T, Kellermann T, Markov V, Krach S, Jansen A, Zerres K, Eggermann T, Stöcker T, Shah NJ, Nöthen MM, Rietschel M, Witt SH, Mathiak K, Krug A. Effects of a CACNA1C genotype on attention networks in healthy individuals. Psychol Med 2011; 41: 1551-61.
[18] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition. 2000.
[19] Posner K, Brent D, Lucas C, Gould MS, Stanley B, Brown GK, et al. Columbia-suicide severity rating scale (C-SSRS), unpublished manuscript. New York State Psychiatric Institute 2008.
[20] Yang DS, Zhang YL. Life event scale (LES). Rating scales for mental health. Chinese Mental Health Journal 1999; 101-106.
[21] Wrzosek M, Łukaszkiewicz J, Wrzosek M, Serafin P, Jakubczyk A, Klimkiewicz A, Matsumoto H, Brower KJ, Wojnar M. Association of polymorphisms in HTR2A, HTR1A and TPH2 genes with suicide attempts in alcohol dependence: a preliminary report. Psychiatry Res 2011; 190: 149-151.
[22] Pitchot W, Hansenne M, Pinto E, Reggers J, Fuchs S, Ansseau M. 5-Hydroxytryptamine 1A receptors, major depression, and suicidal behavior. Biol Psychiatry 2005; 58: 854-858.
[23] Boldrini M, Underwood MD, Mann JJ, Arango V. Serotonin-1A autoreceptor binding in the dorsal raphe nucleus of depressed suicides. J Psychiatr Res 2008; 42: 433-442.
[24] Lowther S, De Paermentier F, Cheetham SC, Crompton MR, Katona CL, Horton RW. 5-HT1A receptor binding sites in post-mortem brain samples from depressed suicides and controls. J Affect Disord 1997; 42: 199-207.
[25] Serafini G, Pompili M, Innamorati M, Gentile G, Borro M, Lamis DA, Lala N, Negro A, Simmaco M, Girardi P, Martelletti P. Gene variants with suicidal risk in a sample of subjects with chronic migraine and affective temperamental dysregulation. Eur Rev Med Pharmacol Sci 2012; 16: 1389-1398.
[26] Susan G, Leckband, Jeffery R, Bishop, Vicki L, Elingrod. Pharmacogenomics in psychiatry. Pharmacy Practice 2007; 20: 252-264.
[27] Lee HJ, Cha JH, Ham BJ, Han CS, Kim YK, Lee SH, Ryu SH, Kang RH, Choi MJ, Lee MS. Association between a G-protein beta 3 subunit gene polymorphism and the symptomatology and treatment responses of major depressive disorders. Pharmacogenomics J 2004; 4: 29-33.
[28] Exton MS, Artz M, Siffert W, Schedlowski M. G protein beta3 subunit 825T allele is associated with depression in young, healthy subjects. Neuroreport 2003; 14: 531-3.
[29] Wilkie MJ, Smith D, Reid IC, Day RK, Matthews K, Wolf CR, Blackwood D, Smith G. A splice site polymorphism in the G-protein beta subunit influences antidepressant efficacy. Pharmacogenet Genomics 2007; 17: 207-15.
[30] Lin CN, Tsai SJ, Hong CJ. Association analysis of a functional G protein beta3 subunit gene polymorphism (C825T) in mood disorders. Neuropsychobiology 2001; 44: 118-121.
[31] Ma J, Xiao H, Yang Y, Cao D, Wang L, Yang X, Qiu X, Qiao Z, Song J, Liu Y, Wang P, Zhou J, Zhu X. Interaction of tryptophan hydroxylase 2 gene and life events in susceptibility to major depression in a Chinese Han population. J Affect Disord 2015; 188: 304-9.
[32] Wang P, Yang Y, Yang X, Qiu X, Qiao Z, Wang L, Zhu X, Sui H, Ma J. CREB1 gene polymorphisms combined with environmental risk factors increase susceptibility to major depressive disorder (MDD). Int J Clin Exp Pathol 2015; 8: 906-13.
[33] Mouri K, Hishimoto A, Fukutake M, Shiroiwa K, Asano M, Nagasaki Y, Ueno Y, Shirakawa O, Nishiguchi N, Maeda K. TPH2 is not a susceptibility gene for suicide in Japanese population. Prog Neuropsychopharmacol Biol Psychiatry 2009; 33: 1546-50.
[34] Bousman CA, Potiriadis M, Everall IP, Gunn JM. G-protein beta3 subunit genetic variation moderates five-year depressive symptom trajectories of primary care attendees. J Affect Disord 2014; 165: 64-68.
[35] Phillips JL, Batten LA, Tremblay P, Aldosary F, Du L, Blier P. Impact of monoamine-related gene polymorphisms on hippocampal volume in treatment-resistant depression. Acta Neuropsychiatr 2015; 27: 353-361.
[36] Forssman L, Peltola MJ, Yrttiaho S, Puura K, Mononen N, Lehtimäki T, Leppänen JM. Regulatory variant of the TPH2 gene and early life stress are associated with heightened attention to social signals of fear in infants. J Child Psychol Psychiatry 2014; 55: 793-801.
[37] Lemogne C, Gorwood P, Bergouignan L, Pélissolo A, Lehéricy S, Fossati P. Negative affectivity, self-referential processing and the cortical midline structures. Soc Cogn Affect Neurosci 2011; 6: 426-433.
[38] Fodor A, Kovács KB, Balázsfi D, Klausz B, Pintér O, Demeter K, Daviu N, Rabasa C, Rotllant D, Nadal R, Zelena D. Depressive- and anxiety-like behaviors and stress-related neuronal activation in vasopressin-deficient female Brattleboro rats. Physiol Behav 2016; 158: 100-11.