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ORIGINAL ARTICLE

Case Control Study

Haplotype analysis of long-chain non-coding RNA NONHSAT102891 promoter polymorphisms and depression in Chinese individuals: A case-control association study

Yue Li, Yi-Xi Wang, Xing-Ming Tang, Peng Liang, Jing-Jie Chen, Feng Jiang, Qiang Yang, Yun-Dan Liang

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Abstract

BACKGROUND

Our previous study reported that the single-nucleotide polymorphism (SNP) rs155979 GC in the promoter region of long-chain non-coding RNA (lncRNA) NONHSAT102891 affects depression susceptibility in a Chinese population.

AIM

To explored associations of two SNPs and haplotypes in the lncRNA NONHSAT102891 promoter region with depression susceptibility in Chinese population.

METHODS

This this case-control association study was approved by the Ethics Committee of Chengdu Medical College (approval number: 201815). Patient diagnosis was based on DSM-IV criteria. We selected a total of 480 patients with depression and 329 healthy controls with no history of psychopathology, and performed genotyping of two SNPs by extracting peripheral venous blood samples from the subjects. The function of the two lncRNA NONHSAT102891 promoter G/C and A/T haplotypes was detected by dual-luciferase reporter assays of human embryonic kidney 293T transfected cells.

RESULTS

Stratified analysis of clinical and genotypic characteristics of our cohort showed that the degree of mild depressive episodes associated with the rs6230 TC/CC genotype increased by 1.59 times [TC/CC *vs* TT: odds ratio (OR) = 1.59, 95%

confidence interval (CI): 1.08-2.35, P = 0.019]. The haploid analysis revealed linkage disequilibrium between rs3792747 and rs6230, and the double SNP CG haplotype was more common in the control group compared to case group, indicating that this haplotype significantly reduced the risk of depression (C/G *vs* T/A: OR = 0.42, 95%CI: 0.21-0.83, P = 0.01). There was no significant difference in the dual-luciferase reporter activity of the G/C and A/T haplotypes compared with the control group (P > 0.05), indicating that the double SNP haplotype has no transcriptional activity.

CONCLUSION

The rs3792747 and rs6230 CG haplotypes of the lncRNA NONHSA T102891 promoter may be related to a reduced risk of depression in the Han Chinese population.

Key Words: Long-chain non-coding RNA NONHSAT102891; Depression; Susceptibility; Single-nucleotide polymorphisms; Haplotype; Transcriptional activity

Core Tip: Depression has risen to the top of the global burden of non-fatal diseases. Recently, emerging evidence supports long-chain non-coding RNA (lncRNA) may be involved in the occurrence and development of depression, and may serve as potential diagnostic and prognostic markers. Our previous study showed lncRNA NONHSAT102891 rs155979 GC affects depression susceptibility; this study genotyped 480 depression patients and 329 healthy controls for the two single-nucleotide polymorphisms and made dual-luciferase reporter assays to explore and elucidate the function of the two lncRNA NONHSAT102891 promoter G/C and A/T haplotypes. We found the rs6230 and rs3792747 CG haplotypes may reduce the risk of depression, which expanded our knowledge about this disease.

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INTRODUCTION

Depression is a highly heterogeneous and multifactorial mental illness with symptoms spanning domains of emotion and behavior, including changes in mood, anhedonia, sleep, and psychomotor activity[1]. With an estimated 5% of adults worldwide suffering from depression each year, depression has risen to the top of the global burden of non-fatal diseases [2]. In the post-coronavirus disease 2019 era, the global burden of mental disorders has become heavier, and has brought greater challenges to the diagnosis and treatment of depression. In China, health service utilization for depressive disorders is very low, with only 9.2% of depressed patients receiving adequate treatment[3]. Depression can also occur in patients with other underlying diseases, including Alzheimer's disease, stroke, multiple sclerosis and cardiovascular disease[4-6].

Long-chain non-coding RNAs (lncRNAs) are the most abundant class of ncRNAs in the human genome. Characteristically, lncRNAs are more than 200 bp in length and do not encode a protein, but may interact with DNA, RNA or protein molecules at multiple levels (epigenetic, transcriptional and post-transcriptional) to control the expression of related genes and participate in many biological processes, especially differentiation and development[7,8]. Approximately 40% of the lncRNAs in the mammalian genome are expressed in the brain[9]. LncRNAs are involved in regulation of neuronal function and play an important role in neuropsychiatric diseases. Through alternative splicing or binding to NRG1, v-erb-a erythroblastic leukemia viral oncogene homolog 4 gene expression inhibits downstream neurons, reduces the release of the neurotransmitter gamma-aminobutyric acid, and has negative effects on brain functions, such as cognition and working memory, in addition to an association with an increased risk of depression and schizophrenia[10-12]. LncRNAGm^{2}694 destroys endoplasmic reticulum homeostasis, significantly reduces expression of the A-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor on the postsynaptic membrane of neurons, reduces the excitatory synaptic transmission function of neurons, increases stress susceptibility in mice, and mediates the pathogenesis of depression[13]. In addition, some single-nucleotide polymorphisms (SNPs) in lncRNAs are associated with the risk of depression. A human-specific Alu insertion polymorphism (rs70959274) in the 5' flanking region of the lncRNA LINC01360 is in strong linkage disequilibrium with the major depression SNP rs12129573[14]. Identifying functional variants of non-coding SNPs is essential for understanding the molecular mechanism and biological basis of depression [15]. Changes in lncRNAs can be detected in cerebrospinal fluid as well as the circulatory system and brain, therefore, providing important prospects for use as biomarkers for disease identification or risk prediction. These biomarkers can also be employed to provide new insights into the genetic structure and biological etiology of neuropsychiatric diseases.

The term "haplotype" refers to several closely linked SNPs that determine the same trait on the same chromosome or in a certain region, either as two loci or the entire chromosome. CONVERGE consortium conducted sparse whole-genome sequencing on Chinese female patients with recurrent major depression and found two depression-related mutations, both located on chromosome 10, one near SIRT1, and the other in an intron of the *LHPP* gene[16]. LncRNA NONHSA T102891, which is located on chromosome 5 (CHR5): 95768987-95770845, has a transcript length of 1860 bp. A recent genome-wide association study (GWAS) revealed five genomic domains on CHR5 that were significantly associated with depression. The underlying background of these regions also includes LINC00461, MEF2C, and LOC101927421[17]. In human tissues, lncRNA NONHSAT 102891 is expressed in the thyroid, brain, adrenal glands and placenta[18]. Downregulated expression of lncRNA NONHSAT102891 in peripheral blood mononuclear cells of major depressive disorder (MDD) patients has been explored previously[19]. Furthermore, changes in the expression of NONHSA T102891 may be a potential non-invasive biomarker for the diagnosis of MDD[20].

In our previous study, we investigated the diagnostic and differential diagnostic value of lncRNA NONHSAT10289 (rs155979, rs3762983, rs3762984 and rs102891) SNPs in severe depression[21]. Because the polymorphism of a single locus in a gene often cannot reveal its true association with disease, haplotype analysis of multiple loci has become an effective means to find complex disease genes. Therefore, in this study, we compared the expression of the other two SNP (rs6230 and rs3792747) in the lncRNA NONHSAT102891 promoter region in patients with depression to further assess the association of lncRNANONHSAT102891 promoter SNPs and/or haplotypes with risk of depression in a Chinese population and to determine the functional correlation of risk haplotypes.

MATERIALS AND METHODS

Study subjects

From March 2018 to December 2019, a total of 480 patients with depression and 329 healthy individuals from three hospitals in China (Sichuan Provincial People's Hospital, Jining Psychiatric Hospital and Yunnan Provincial Mental Health Center) were recruited to the case and control groups, respectively. All participants were Han Chinese adults. The study protocol was approved by the Ethics Committee of Chengdu Medical College (No. 201815). All participants provided written informed consent. Patient diagnosis was based on the DSM-IV criteria, and the symptom severity was scored using the 24-item Hamilton Depression Rating Scale (HAMD-24). Patients with neurological diseases or other mental disorders, acute or chronic infections, thyroid dysfunction, being pregnant, or breastfeeding at the time of the study were excluded. Control subjects were volunteers with no history of self-reported mental illnesses and who participated in physical examination in the research hospitals. The following clinical data were collected from medical records: Age, sex, age of onset, HAMD-24 score, pulse rate, degree of depression, family history, suicide attempt/behavior and first episode.

The average age of the healthy control group (105 males and 224 females) was 44.0 ± 16.9 years. The case and control groups were matched according to sex, age and place of residence. Details of the participants can be found in our previous report[21].

SNP selection

The UCSC Genome Browser was used to explore SNPs of the lncRNA NONHSAT102891 promoter region (3-kb region upstream of the transcription initiation site)[22]. The SNPs rs6230 and rs3792747 were selected as loci with minor allele frequencies > 10% in the Asian population to study their correlation with depression susceptibility and clinical characteristics in a Han Chinese population.

Genotyping

Genomic DNA was extracted from peripheral venous blood samples using the whole blood genomic DNA extraction kit [Shenggong Bioengineering (Shanghai) Co., Ltd.]. The concentration of the DNA was determined as a measure of the quality by using a NanoDrop 2000/2000C [Thermo Fisher (China) Co., Ltd.]. The lncRNA NONHSAT102891 promoter region containing the rs6230 and rs3792747 polymorphisms was amplified by two-step polymerase chain reaction (PCR) to prepare an Illumina compatible library using the following primer sequences: rs3792747-F: *5'-TCAATGCAGCAGCATCATCAGATCCAAG-3'*, rs3792747-R: *5'-CGGGCAAAGTTATGAAGCTTGGACT-3'*, rs6230-F: *5'-GATCCCAGCAAACAGTTCCT-3'*; rs6230-R: *5'-CCAGCCAGAATGGAAATGAG-3'*.

The first-step PCR (25 μL reaction volume) amplification was performed under the following reaction conditions: 98 ℃, 3 min; 98 ℃, 30 s; 50 ℃, 30 s; 72 ℃ 30 s; 98 ℃, 30 s; 66 ℃ 30 s; 25 cycles for 30 s at 72 ℃, and 72 ℃ for 5 min. Using the first-step PCR product as the template, the Illumina sequencing library was obtained by the second round of PCR (30 μL reaction volume) amplification performed under the following reaction conditions: 98 ℃, 5 min; 94 ℃, 30 s; 55 ℃, 20 s; 5 cycles of 72 ℃, 30 s. The sizes of the two PCR products were confirmed by 1% agarose gel electrophoresis and then recovered using AMPure XP magnetic beads. Equal amounts of the two PCR products were then mixed and sequenced using HiSeqXTen platform (Illumina, San Diego, CA, United States).

Construction of luciferase reporter gene plasmids

The DNA fragments containing the haplotypes of the lncRNA NONHSAT102891 promoter region were amplified and different SNP sites (rs6230 and rs3792747) were selected as described above using the following primers sequences: upstream: *5'-GCTAGCAGCCAAGGAAAGGAAAGCTC-3'* (for-ward), downstream: *5'-TAAGCAGCAGGATTAG-*

GACTCGAG-3' (reve-rse). The target fragments were inserted into the PmirGLO-Vector (Promega) to construct the recombinant plasmids designated pmirGLO-AT and pmirGLO-GC, respectively, and sent to Chengdu Qingke Company for plasmid DNA synthesis. The recombinant plasmids were transfected into HEK-293T cells and the difference in the amount of luciferase protein expressed by the A-T and G-C haplotypes consisting of rs6230 and rs3792747 was detected.

Cell lines and cell culture

HEK-293T cell lines, provided by the National collection of authenticated cell cultures, were used for recombinant vector transfection and assessed by routine PCR and microscopic analysis to ensure that no cells were contaminated with mycoplasma during the research process. HEK-293T cells were cultured at 37 ℃ under 5% CO_2 in Dulbecco's Modified Eagle's Medium (Gibco) containing 10% fetal bovine serum (Gibco), 1% GlutaMAX (Invitrogen, Carlsbad, CA, United States) and 1% sodium pyruvate (Invitrogen) were added.

Transfection and luciferase reporter gene assays

HEK-293T cells were seeded into 24-well plates (2×10^5 cells per well) and cultured for 24-36 h to 90% confluence before transfection in serum-free medium with equal amounts of plasmid-free enzyme-free water (as blank control group), pmirGLO-AT, pmirGLO-GC, and the empty PmirGLO-Vector (no promoter) using the LipofectamineTM 2000 kit (Invitrogen). pRL-TK Luciferase Control Reporter Vectors (Promega, Madison, WI, United States) were co-transfected into HEK-293T cells for 24-48 h as a normal control. Luciferase activity in equal numbers of cells from each group was then measured using the dual-luciferase reporter gene assay system (Promega, Madison, WI, United States) according to the manufacturer's instructions. After adding the LAR II reagent (Promega) and cell lysis solution, the optical signal was detected by BioTek PowerWave XS2 full-wavelength scanning spectrophotometer. the measurement reading was recorded as The fluorescence value F (Firefly luminescence) was measured and after adding the Stop and Glo ®Reagent, the fluorescence value R (Renilla luminescence) was measured. Relative luciferase activity was calculated as the ratio of fluorescence value F to fluorescence value R. All samples were analyzed in triplicate and experiments were repeated in three independent occasions.

Statistical analysis

Continuous variable data were expressed as mean ± SEM and the categorical variable data were expressed as numbers (percentages). Moreover, for comparison between groups, *t*-tests were used for continuous variables, and χ^2 tests were used for categorical variables. The genotype frequencies of rs6230 and rs3792747 were obtained by direct counting. The χ^2 test was used to analyze the distribution and Hardy-Weinberg equilibrium of rs6230 and rs3792747 genotypes in the two groups. The correlation between gene polymorphisms and disease was evaluated using odds ratio (OR) and 95% confidence interval (CI), with the OR values adjusted based on age and sex data. Codominant, dominant and recessive genetic models were used for comparative analysis.

In the haplotype correlation analysis, the luciferase activity corresponding to each configuration was expressed as the mean ± SD, and the differences among the experimental data were analyzed by one-way analysis of variance. $P < 0.05$ was considered to indicate statistical significance. All data were analyzed using SPSS 25.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

LncRNA NONHSAT102891 promoter genotypes and risk of depression

We first investigated the association of the rs6230 and rs3792747 variants of the lncRNA NONHSAT102891 promoter with the risk of depression. For this purpose, we summarized the frequency distribution of genotypes and alleles of lncRNA NONHSAT102891 SNP rs6230 and rs3792747 in depressed patients and controls. In the control group, the genotype frequencies of the two polymorphisms were both in Hardy–Weinberg equilibrium (rs6230 $P = 0.101$; rs3792747 $P = 0.104$). There were significant differences in genotype and allele frequencies between the case and control groups (Table 1).

After further stratification by degree of depressive episode, suicide attempt, first episode patient and family history, we observed a correlation between depressive episode stratification and depressive risk in the rs6230 polymorphism group. The frequency of the TC/CC genotype was 69.3% in patients with moderate depression, which was higher than that in patients with severe depression (60.3%) (TC/CC *vs* TT, 95%CI: 1.59 (1.08-2.35), $P = 0.019$). These findings indicated that the rs6230 TC/CC genotype is associated with an increased risk of moderate depression; however, there was no significant correlation between rs3792747 polymorphism and the four variables used for stratification ($P > 0.05$) (Table 2).

LncRNA NONHSAT102891 promoter haplotypes and the risk of depression

We also evaluated the association of the two SNP haplotypes (rs3792747 and rs6230) of the lncRNANONHSAT102891 promoter with the risk of depression. LD analysis showed that these two common polymorphisms had higher D' values and lower R2 values ($D' = 0.71$, $r^2 = 0.07$) in the control, indicating the existence of gene recombination between the two SNP and that both were suitable for haplotype reconstruction.

Haplotype reconstruction analysis based on the genotyping data of depressed patients and controls revealed that the CG haplotype was more common in the control group than in the depressed patients These findings indicated that the CG haplotype is significantly associated with reduced risk of depression [CG *vs* TA: 95%CI: 1.59 (0.21-0.83], $P = 0.01$. There was no significant correlation between other haploid types and risk of depression (Table 3).

Table 1 Genetic model genotype and allele frequencies of two long-chain non-coding RNA NONHSAT102891 promoter polymorphisms among depressed patients and controls and association with risk of depression, *n* (%)

Models	Polymorphisms	Control (*n* = 329)	Patients (*n* = 480)	Adjusted OR (95%CI)	*P* value
	rs6230				
Codominant	TT	109 (33.1)	170 (35.4)	1	
	TC	173 (52.6)	250 (52.1)	0.91 (0.66-1.24)	0.53
	CC	47 (14.3)	60 (12.5)	0.82 (0.52-1.30)	0.41
Dominant	TT	109 (33.1)	170 (35.4)	1	
	TC/TT	220 (66.9)	310 (64.6)	0.79 (0.57-1.10)	0.17
Recessive	TT/TC	282 (85.7)	420 (87.5)	1	
	CC	47 (14.3)	60 (12.5)	0.77 (0.49-1.23)	0.28
Allele	T	391 (59.4)	590 (61.5)	1	
	C	267 (40.6)	370 (38.5)	0.92 (0.75-1.12)	0.40
	rs3792747				
Codominant	TT	208 (63.2)	326 (67.9)	1	
	TC	113 (34.3)	137 (28.5)	0.77 (0.57-1.05)	0.17
	CC	8 (2.4)	17 (3.5)	1.36 (0.57-3.20)	0.48
Dominant	TT	208 (63.2)	326 (67.9)	1	
	TC/CC	121 (36.8)	154 (32.1)	0.84 (0.60-1.17)	0.31
Recessive	TT/TC	321 (97.6)	463 (96.5)	1	
	CC	8 (2.4)	17 (3.5)	1.47(0.63-3.45)	0.36
Allele	T	529 (80.4%)	789 (82.2)	1	0.65
	C	129 (19.6)	171 (17.8)	0.89 (0.69-1.15)	0.36

Odds ratio was adjusted by age and sex. OR: Odds ratio; CI: Confidence interval.

Effects of different haplotypes of lncRNA NONHSAT102891 promoters on transcriptional activity

Next, we tested the hypothesis that the G/C and A/T haplotypes change the transcriptional activity of the lncRNA NONHSAT102891 by comparing the luciferase reporter activity of HEK-293T cells transfected with the pmirGLO-AT and pmirGLO-GC constructs. There was no significant difference in the dual-luciferase reporter activity of the G/C and A/T haplotypes compared with the control group ($P > 0.05$) (Table 4), indicating that the G/C and A/T haplotypes do not alter the transcriptional activity of the lncRNA NONHSAT102891.

DISCUSSION

After excluding organic brain lesions, clinicians mainly identify depression on the basis of the key symptoms of the disease. However, the most important basis for diagnosis is still based on the patient's clinical manifestations, which are affected by the patient's subjective experience and the clinical experience of the doctor. Finding objective and effective molecular indicators for the diagnosis of depression is the current focus of clinicians. Depression-related biomarkers in the peripheral blood or brain are attracting increasing attention for the development and exploration of clinical objective diagnostic indicators. LncRNAs are known to play an important role in the normal functions of cells and the pathological consequences of disorders, which lays a molecular foundation for understanding the similarities and differences in the pathophysiological mechanisms behind depression. Using targeted reverse transcription PCR analysis of lncRNA expression levels in peripheral blood and brain tissue of depression patients or a mouse model of depression, Seki *et al* [23] found that the expression levels of Y5, MER11C, PCAT1, and PCAT29, were upregulated in patients with major depressive disorder compared to healthy controls, while the expression level of RMRP was downregulated. Low expression of RMRP in peripheral blood leukocytes of depressed patients and mice correlated strongly with the severity of the symptoms. Thus, these findings implicate RMRP in peripheral blood leukocytes as a potential biomarker of depression. Zhou *et al*[24] performed RNA-sequencing in the rostral anterior cingulate cortex of 26 depressed suicidal individuals and 24 controls who died naturally or by accident with no history of psychopathology, and identified 23 differentially expressed lncRNAs, including SNORD3C and ZNF833P, and their differentially expressed overlapping and

Table 2 Stratified analyses of the rs6230 and rs3792747 polymorphisms in depressed patients

Variables	Frequency (%)		Adjusted OR (95%CI)	*P* value
rs6230				
Depressive episode	Severe	Mild		
TT	100 (39.7)	70 (30.7)	1.00 (Ref)	
TC	125 (49.6)	125 (54.8)	1.57 (1.05-2.36)	0.28
CC	27 (10.7)	33 (14.5)	1.69 (0.92-3.09)	0.088
TC/CC	152 (60.3)	158 (69.3)	1.59 (1.08-2.35)	0.019
Suicide attempt	Yes	No		
TT	102 (34.9)	68 (36.2)	1.00 (Ref)	
TC	154 (52.7)	96 (51.1)	1.06 (0.70-1.63)	0.78
CC	36 (12.3)	24 (12.8)	0.87 (0.45-1.68)	0.68
TC/CC	190 (65.1)	120 (63.8)	1.02 (0.68-1.54)	0.91
First-episode patient	Yes	No		
TT	88 (35.5)	82 (35.3)	1.00 (Ref)	
TC	131 (52.8)	119 (51.3)	1.07 (0.71-1.60)	0.75
CC	29 (11.7)	31 (13.4)	1.15 (0.63-2.10)	0.66
TC/CC	160 (64.5)	150 (64.7)	1.08 (0.73-1.58)	0.70
Family history	Yes	No		
TT	37 (39.4)	133 (34.5)	1.00 (Ref)	
TC	47 (50)	203 (52.6)	1.29 (0.79-2.11)	0.31
CC	10 (10.6)	50 (12.9)	1.44 (0.66-3.14)	0.35
TC/CC	57 (60.6)	253 (65.5)	1.30 (0.81-2.07)	0.28
rs3792747				
Depressive episode	Severe	Mild		
TT	176 (69.8)	150 (65.8)	1.00 (Ref)	
TC/CC	76 (30.2)	78 (34.2)	1.21 (0.82-1.80)	0.33
Suicide attempt	Yes	No		
TT	201 (68.8)	125 (66.5)	1.00 (Ref)	
TC/CC	91 (31.2)	63 (33.5)	1.14 (0.75-1.72)	0.54
First-episode patient	Yes	No		
TT	168 (67.7)	158 (68.1)	1.00 (Ref)	
TC/CC	80 (32.3)	74 (31.9)	0.98 (0.66-1.44)	0.9
Family history	Yes	No		
TT	64 (68.1)	262 (67.9)	1.00 (Ref)	
TC/CC	30 (31.9)	124 (32.1)	1.00 (0.62-1.63)	1.00

Odds ratio was adjusted by age and gender. OR: Odds ratio; CI: Confidence interval.

antisense protein-coding genes, several of which were associated with interferon signaling. Bioinformatics approaches have also been adopted to identify differential expression of depression-related genes. Liu *et al*[25] analyzed the genes for seven mental traits identified in large-scale GWAS and found that LINC00461 has a pleiotropic effect and is associated with five mental traits, including depression, schizophrenia, and Alzheimer's disease. Als *et al*[26], identified 243 risk loci in more than 1.3 million individuals through GWAS and found that depression is highly polygenic, which could help deepen depression research and precise treatment. This information provides a better understanding of the genetic associations of depression and could aid in the development of more effective treatments.

Table 3 Haplotype analysis of rs3792747 and rs6230 in depressed patients and controls, *n* (%)

Haplotype	Depressed patients	Controls	OR (95%CI)	*P* value
T/A	433 (45.1)	284 (43.2)	1.00	
T/G	356 (37.1)	245 (37.2)	0.95 (0.76-1.19)	0.67
C/A	157 (16.4)	107 (16.3)	0.96 (0.72-1.28)	0.79
C/G	14 (1.5)	22 (3.3)	0.42 (0.21-0.83)	0.01

OR: Odds ratio; CI: Confidence interval.

Table 4 Relative luciferase activity of control and case groups

Group	RFA	OR (95%CI)	*P* value
Control	1.58 ± 0.28	1.00	
EV	1.52 ± 0.22	0.080 (-0.526-0.542)	0.973
p-G/C	1.59 ± 0.27	-0.006 (-0.540-0.528)	0.979
p-A/T	1.57 ± 0.29	0.060 (-0.474-0.594)	0.802

Data represent the mean ± SEM. RFA value: The ratio of luciferase activity of recombinant plasmid to that of Renilla. EV: Empty vector; OR: Odds ratio; CI: Confidence interval.

In this study, we explored the possible association of other SNPs and haplotypes in the lncRNANONHSAT102891 promoter region with susceptibility to depression in a Chinese population. Our results suggest that the TC/CC genotype of rs6230 in the lncRNA NONHSAT102891 promoter region may be associated with the risk of moderate depression. In the haplotype analysis of rs3792747 and rs6230, the frequency of the CG haplotype was more common in the patients with severe depression than in the control group, indicating that the haplotype was associated with a reduced risk of depression. However, no significant correlation was found between the two haplotypes and lncRNA NONHSAT102891 promoter transcriptional activity in dual-luciferase reporter assays.

In recent years, lncRNAs have provided significant advances in our understanding of the pathogenesis of severe depression as well as its diagnosis and treatment. Li *et al*[22] suggested that nine lncRNA, including NONHSAT102891, TCONS_00019174, and ENST00000566208, may be biomarkers of MDD. LncRNAs can participate in the epigenetic, transcriptional, and post-transcriptional regulation of the pathogenesis of depression. LncRNA XR351665 has been reported to promote the development of chronic pain-induced depression by upregulating DNMT1 *via* sponge miR-152-3p[27]. Long-intergenic non-coding RNA (Linc) 01360 expression is affected by rs70959274Alu polymorphism, and the Alu insertion induces DNA methylation, which significantly reduces the transcriptional activity of linc01360 compared with the control group, thus reducing the genetic risk of human MDD[14]. Differentially expressed lncRNAs also affect the pathogenesis of depression by participating in the regulation of a variety of signaling pathways. Microdeletion of FAAH-OUT lncRNA expressed in the brain and dorsal root ganglia led to downregulation of FAAH expression and a sharp increase in BDNF levels, thereby reducing the risk of depression and anxiety[28]. Decreased levels of lncRNAMIR155HG were shown to induce increased microRNA (miR)-155 expression in the hippocampus and inhibit BDNF expression, leading to depression-like behavior in a chronic unpredictable mild stress model of depression in mice. MiR-155HG/miR-155/BDND axis damage is a key cause of depression[29]. Low levels of linc00473 and upregulated expression of FEDORA in prefrontal cortex (PFC) neurons were detected in female depressed patients; the expression of linc00473 affected the pre-and postsynaptic features of mPFC pyramidal neurons and participated in regulation of the cAMP response element binding protein (CREB), and low levels of linc00473 in PFC neurons promoted stress recovery in female mice[30-32]. Selective expression of FEDORA in mouse mPFC neurons or oligodendrocytes confirmed its role as a sex-specific regulator of anxiety and depression-like behavior, since this phenomenon occurred only in female mice. Abedpoor *et al*[33] found that exercise and leucine consumption can alleviate depression-related behaviors by increasing the expression of four lncRNAs (MEG3, HOTAIR, GAS5 and TUG1 related to KDR/VEGF-α/PTEN/BDNF) in the lncRNA network of the brain-gut axis in depression-like mice. KEGG enrichment analysis revealed the involvement of important signaling pathways such as hippo, MAPK, Wnt, PI3K/Akt, cGMP-PKG, RAS, and IL-17 in the regulation of hippocampal function or pathological processes associated with depression[34-38]. For example, overexpression of lncRNA TCONS_00019174 can activate the Wnt classical pathway in mice, inactivating GSK3β phosphorylation, while also upregulating β-catenin protein expression, thereby exerting antidepressant effects in mice[39]. Silencing lncRNA GAS5 can activate the PI3K/AKT pathway to protect hippocampal neurons from depression-like injury by regulating the miR-26a/EGR1 axis[40]. LncRNA84277 ameliorated chronic pain-associated depressive-like behavior by upregulating SIRT1 expression *via* the competitive sponge miR-128-3p[41]. Thus, there is accumulating evidence that these biomarkers play a key role in the pathogenesis of depression and provide new targets for the treatment of depression.

The limitations of current research should be noted. First, the case group comprised 71% females and only 29% males. The incidence of depression is sex-biased, and the higher heritability of women than men may lead to a higher incidence of depression in women[42]. Therefore, the role of epigenetic factors in the occurrence and development of depression represents an important focus of future research. Evaluating the effect of lncRNA on depression and targeted control of the phenotype of depression in a research population will promote the discovery of new and more effective treatments. Second, due to the limited sample size, the results of this study may be biased, and further studies with a larger sample size are required to determine the reference expression range of biomarkers. Third, existing evidence suggests that patients with late-onset depression have more severe and frequent patchy lesions in the deep frontal white matter and basal ganglia detected by magnetic resonance imaging as compared with the control groups or patients with early-onset depression[43]. Due to barriers such as the lack of scientific basis for diagnostic systems and structures, uncertainty in brain function, indeterminate time-course of recovery in patients with functional mental disorders, and lack of diagnostic tools, no causal relationships have been identified for functional mental disorders such as depression[44]. In the future, we aim to explore a multidimensional framework that incorporates epigenetic and neurological impact data, thereby enhancing the practical ability of clinicians to diagnose[45].

CONCLUSION

Our results indicate that the rs3792747 and rs6230 CG haplotypes of the lncRNA NONHSA T102891 promoter are related to a reduced risk of depression in the Han Chinese population.

ARTICLE HIGHLIGHTS

Research background

Depression is a common life-threatening and disabling mental illness, and long-chain non-coding RNA (lncRNA) abnormal expression may affect the pathophysiological processes of depression. Our previous study reported that the single-nucleotide polymorphism (SNP) rs155979 GC in the promoter region of lncRNA NONHSAT102891 affects depression susceptibility in a Chinese population.

Research motivation

The complex interplay of species between major depressive disorder and lncRNA remains unclear.

Research objectives

To explored associations between two SNPs and haplotypes within lncRNA NONHSAT102891 promoter region and depression susceptibility in Chinese population.

Research methods

We conducted a case-control study in a cohort of 480 patients with depression and 329 healthy controls, and performed genotyping by gene sequencing. The function of the two lncRNA NONHSAT102891 promoter G/C and A/T haplotypes was detected by dual-luciferase reporter assays of human embryonic kidney 293T transfected cells.

Research results

The degree of mild depressive episodes associated with the rs6230 TC/CC genotype increased by 1.59 times. The haploid analysis revealed linkage disequilibrium between rs3792747 and rs6230, and the double SNP CG haplotype was more common in the control group compared to case group, indicating that this haplotype significantly reduced the risk of depression (C/G *vs* T/A: odds ratio = 0.42, 95% confidence interval: 0.21-0.83, P = 0.01). There was no significant difference in the dual-luciferase reporter activity of the G/C and A/T haplotypes compared with the control group (P > 0.05).

Research conclusions

The rs3792747 and rs6230 CG haplotypes of the lncRNA NONHSA T102891 promoter may be associated with a reduced risk of depression in the Chinese population. However, further studies with a larger sample size are required to determine the reference expression range of biomarkers.

Research perspectives

This study provides insights into the early prediction and diagnosis of depression and important clues for development of tools that will facilitate more accurate diagnosis and treatment of depression in the clinic.

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FOOTNOTES

Author contributions: Liang YD designed the study and corrected the manuscript; Li Y performed the majority of experiments and wrote the manuscript; Wang YX, Tang XM, Liang P, Chen JJ, Jiang F, Yang Q participated to the data collection and analysis of human material, and commented on previous versions of the manuscript; all authors contributed to the study conception and design. All authors read and approved the final manuscript.

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