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Research article

The interaction of miR-34b/c polymorphisms and negative life events increases susceptibility to major depressive disorder in Han Chinese population

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HIGHLIGHTS

- The significance of miR-34b/c gene polymorphisms in MDD was evaluated.
- The rs4938723 and rs2187473 polymorphisms were associated with stratified MDD by discarding subjects with severe negative life events in the dominant models.
- C-G haplotype (rs4938723/rs28757623) showed the strongest association with stratified MDD.
- Significant gene–environment interaction between the C-G haplotype (rs4938723/rs28757623) and negative life events associated with MDD risk.

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ABSTRACT

Background: Previous studies have shown that microRNAs(miRNAs) are involved in the pathogenesis of MDD; in particular, miR-34b/c has been implicated in MDD risk and found to exert antidepressant effects. However, the effects of miR-34b/c polymorphisms on MDD risk have not been investigated.
Methods: In this study, we evaluated the effect of miR-34b/c gene polymorphisms and their interaction with negative life events in relation to MDD, using data from 381 Han Chinese patients with MDD and 291 healthy volunteers. Allelic, genotypic, haplotypic, and gene-environment associations were analyzed using UNPHASED and SPSS software.
Results: After discarding data with extremely severe negative life events in our study population, we found an association between rs4938723, rs2187473 polymorphisms and MDD in the dominant models (TC/CC vs. TT, OR = 1.45, P = 0.027; TC/CC vs. TT, OR = 3.32, P = 0.030). In haplotype analysis, the C-G haplotype (rs4938723/rs28757623) showed the strongest association with MDD (OR = 1.95, P = 0.026). Additionally, we found significant gene-environment combination rs4938723 C allele, rs28757623 G allele and high level of negative life events (C-G-HN) was significantly associated with MDD (OR, 3.85; 95% CI, 1.62–9.13). In addition, the combination of (C-C-HN) is of significance (OR, 2.99; 95% CI, 1.36–6.60), indicating that the rs28757623 C allele may contribute to the risk of MDD as well.
Limitations: The sample size was small and the role of miR-34b/c polymorphisms for MDD should be assessed using independent samples from other ethnic populations. Conclusions: Our results suggest that miR-34b/c is a susceptibility factor for MDD stratified by negative life events and that rs4938723 is a significant association locus for gene-environment interaction in relation to MDD risk.

1. Introduction

Major depressive disorder (MDD) is one of the most prevalent psychiatric diseases, with a 12-month prevalence of 6.6% and a lifetime prevalence of 16.2% [1]. The etiology of MDD is multifactorial, and genetic risk is an important factor accounted for

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37% of the risk of developing MDD [2,3]. Epigenetic modifications are one of the principal mechanisms by which gene expression is regulated. MicroRNAs (miRNAs), which play an important role in the epigenetic modulation of gene expression, regulate various biological functions such as cell proliferation, differentiation, and apoptosis [4]. Recent studies have demonstrated that miRNAs are involved in several aspects of neural plasticity, neurogenesis, and stress responses [5,6]. Moreover, accumulated evidence shows that miRNAs play a critical role in the pathogenesis of MDD and the modulation of gene expression by miRNAs mxay represent novel avenues for the development of therapeutic targets [7,8].

The miR-34 family, which is involved in cell proliferation, differentiation, and apoptosis, consists of three miRNAs: miR-34a, which is encoded by its own transcript, and miR-34b and miR-34c, which share a common primary transcript. We included them as a unique gene as the overlap extensively. Previous studies have suggested that miR-34b/c may be involved in stress response and exert antidepressant effects [9,10]. Consistent with these reports, we have previously found that the expression levels of miR-34b-5p and miR-34c-5p in the peripheral blood leukocytes of Chinese patients with MDD were significantly higher than those in normal controls [11].

Several lines of evidence have shown that genetic variants located within mature precursors or primary miRNAs may exhibit altered miRNA expression, maturation, or binding to target sites [12,13]. Over the last five years, a number of findings linking miRNA variants to MDD have been reported. Saus et al. found a significant association between the T allele of the rs76481776 polymorphism in the pre-miR-182, which targets the CLOCK gene, and late insomnia in patients with MDD [14]. Liang et al. found that the rs10877887 and rs13293512 polymorphisms of the let-7 family were associated with MDD [15]. Moreover, our group have reported the occurrence of the rs112439044 polymorphism in pre-miR-30e, which has been implicated in elevated MDD risk in the Han Chinese population [16]. Recently, a potentially functional polymorphism rs4938723 was discovered in the promoter region of miR-34b/c. The T → C variation of the rs4938723 polymorphism is thought to influence the GATA-X binding sites, which affect the miRNA transcription activity [17].

In view of these findings, we hypothesize that polymorphisms of the miR-34b/c gene are associated with a higher risk of MDD. Accordingly, we conducted a case–control study in the northern Han Chinese population to elucidate the potential association of miR-34b/c gene polymorphisms with MDD risk. First, we investigated whether an association between the miR-34b/c polymorphysms and MDD exists, when data related to severe negative life events were discarded to exclude the effects of environmental factors. Second, MDD is a complex disease, many studies revealed significant gene-environment (GxE) interactions in relation to MDD for negative life events and genetic factors including polymorphisms in the serotonin transporter, brainderived neurotrophic factor (BDNF), and HPA axis-related genes [18–20]. So we attempted to determine whether the interaction between the miR-34b/c gene and negative life events play a role in the development of MDD.

2. Materials and methods

2.1. Subjects

In total, 381 patients with MDD (male, n = 158; female, n = 223; mean age 32.04 ± 10.77 years, range 18–60 years) were recruited from the clinical settings of the Department of Psychiatry, First Hospital of Shanxi Medical, Taiyuan, China. The diagnosis was made by at least two consultant psychiatrists according to the criteria for MDD specified by the "Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV)" (American Psychiatric Association, 1994). All patients were also diagnosed using the Chinese Version of the Modified Structured Clinical Interview for DSM-IV TR Axis I Disorders Patient Edition (SCID-I/P, 11/2002 revision). The 17-item Hamilton Depression Rating Scale (HAMD-17) and the Hamilton Anxiety Rating Scale (HAMA) were used to assess clinical characteristics. Among these patients, 85.3% were suffering their first depressive episode (n = 325), whereas the other 14.7% were experiencing a relapse episode (n = 56) at the time of recruitment. Pregnant patients and those with significant medical conditions, unstable psychiatric features (e.g., suicide ideation), a history of alcoholism or drug abuse, neurological illness, or concomitant additional Axis I psychiatric disorders were excluded. 291 healthy volunteers (male, n = 133; female, n = 158; mean age 32.81 ± 11.65 years, range 18–60 years) who did not have a history of neuropsychiatric disorders were recruited from the community or during regular health screening visits to form the control group.

All subjects were from the same geographical areas in Northern China and were of Chinese Han origin. All participants provided written informed consent. This study was approved by the Ethical Committee for Medicine of the First Hospital of Shanxi Medical University, China.

2.2. Assessment of negative life events

Negative life events were assessed using the life events scale (LES) of Desen

Yang and Yalin Zhang, in which 48 items related to positive and negative life events are classified into two aspects [21]. The LES is based on the premise that life changes require an effort to adapt and regain stability. Event scores derived using the LES show high reliability and validity. All participants carefully read the questionnaires and described life events occurring in the previous 1-year period. These life events included serious illness, adverse relationships, social difficulties, unemployment, and financial crises. Each life event is given a score that indicates the level of readjustment a person has to make as a result of the event. The data showed a skewed distribution; the 95% percentile (score of 39) in the control sample was selected as the cutoff value for categorizing results as severely or moderately negative life events.

2.3. Genotyping

The sequences of the miR-34b/c gene and ± 2000 bp were acquired from UCSC Genome Bioinformatics (http://genome.ucsc.edu/). SNPs were selected from the NCBI SNP database (http://www.ncbi.nlm.nih.gov/SNP) and the HapMap database (http://www.hapmap.org). We found two tag SNPs (rs4938723 and rs28690953) located in miR-34b/c using the HaploView program [22], based on the HapMap database for a Chinese Han population of Beijing (CHB) (Fig. 1). However, the minor allele frequency (MAF) of rs28690953 was 0.012, with a very low level of heterozygosity. Therefore, this SNP was not selected for further analysis. Another criteria applied to select the genotyped SNPs based on whether they were located upstream or downstream of the precursor or primary miR-34b/c gene where have been thought to affect the miRNA transcription activity [17]. Therefore, four SNPs (rs4938723, rs11606481, rs2187473, and rs28757623) were analyzed in the present study. Among these four SNPSs, rs4938723 is a tag SNP and associated with cancer risk, and the other SNPs (rs11606481, rs2187473, and rs28757623) were located upstream or downstream of the precursor or primary miR-34b/c gene. The rs4938723 polymorphism is located within the CpG island of pri-miR-34b/c.The rs11606481 and rs2187473 polymorphisms are located 43 bp and 100 bp downstream of pre-miR-34b,