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***Case Control Study***

***Glutamate decarboxylase 1* gene polymorphisms are associated with respiratory symptoms in panic disorder**

Zou *et al*. *GAD1* gene polymorphisms in PD

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**Abstract**

BACKGROUND

Genetic factors play an important role in the pathogenesis of panic disorder (PD). However, the effect of genetic variants on PD remains controversial.

AIM

To evaluate the associations between *glutamate decarboxylase 1 (GAD1)* gene polymorphisms and PD risk and assess the effect of GAD1 gene polymorphisms on the severity of clinical symptoms in PD.

METHODS

We recruited 230 PD patients and 224 healthy controls in this study. All participants were assessed for anxiety and panic symptom severity using the Hamilton Anxiety Rating Scale (HAM-A) and Panic Disorder Severity Scale (PDSS). *GAD1* gene polymorphisms (rs1978340 and rs3749034) were genotyped and assessed for allele frequencies.

RESULTS

There were no significant differences between cases and controls in the genotype distributions or allele frequencies of *GAD1* (rs1978340 and rs3749034). In addition, the effect of *GAD1* (rs1978340 and rs3749034) on PD severity was not significant. However, regarding respiratory symptoms, patients with the *GAD1* rs1978340 A/A genotype had significantly higher scores than those with the A/G or G/G genotype.

CONCLUSION

Here, we showed that the A/A genotype of *GAD1* rs1978340 was associated with increased severity of respiratory symptoms in patients with PD.

**Key Words:** Panic disorder; Gene polymorphisms; Respiratory symptoms; Allele frequencies; Pathogenesis; Chinese population

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**Core Tip:** The study found that the A/A genotype of *glutamate decarboxylase 1 (GAD1)* rs1978340 was associated with increased severity of respiratory symptoms in patients with panic disorder (PD). However, there were no significant differences between cases and controls in the genotype distributions or allele frequencies of *GAD1* (rs1978340 and rs3749034), and neither did *GAD1* (rs1978340 and rs3749034) have a significant effect on the severity of PD symptoms. These findings suggest that genetic factors may play a role in the pathogenesis of PD, particularly in respiratory symptoms, but further studies with larger sample sizes are needed to confirm these results.

**INTRODUCTION**

Panic disorder (PD), the most common anxiety disorder, is characterized by recurrent and unexpected panic attacks and has an estimated 12-mo and lifetime prevalence rates of 2.4% and 3.8%, respectively[1,2]; the lifetime prevalence rate of panic attacks is 13.2%[3]. PD typically occurs in young adults, and women are more likely to be affected than men. However, the etiology of PD is multifactorial and complex, involving genetic, environmental, psychological and neurobiological factors[2,3]. Recent studies examining twins and family shows that the heritability of panic disorder is 30%-40%, suggesting strong evidence for a genetic etiology[4]. To date, genetic studies have reported several susceptibility genes for PD such as *neuropeptide Y*, *catechol-O-methyltransferase* and particularly 5-HT system-related genes[5,6]. For example, a previous study found that patients with PD were characterized by significantly higher frequencies of the LL genotype and L allele variant of the 5-HT transporter-linked promoter region (5-HTTLPR)[7]. However, few of these findings have been replicated by other researchers, and the pathogenesis of PD remains unclear[8-12]. Therefore, other candidate gene polymorphisms in PD should be explored.

γ-Aminobutyric acid (GABA) is an important inhibitory neurotransmitter in the mammalian brain, and abnormalities in the GABAergic system have long been implicated in the pathophysiology of PD[13-15]. For example, a significant decrease in *GABA* has been detected in the anterior cingulate and medial prefrontal cortices of patients with PD[16]. The *GAD1* gene encodes the 67-kDa glutamic acid decarboxylase isoform (GAD67) and is the rate-limiting enzyme responsible for GABA biosynthesis from glutamic acid. The *GAD1* gene might play an important role in the GABAergic system. A previous study found a significant effect of rs1978340 on cingulate cortex GABA concentrations[17]. In addition, previous studies have indicated that *GAD1* rs3749034 is associated with mRNA expression[18]. Therefore, *GAD1* may be an important candidate gene in PD. Incidentally, previous reports have suggested that the *GAD1* single nucleotide polymorphisms (SNPs) rs3749034 or rs1978340 are significantly related to several psychiatric disorders such as bipolar disorder[19], schizophrenia[20], attention-deficit/hyperactivity disorder[21], and heroin dependence[22]. For instance, the allelic or genotypic frequencies of the rs1978340 polymorphism in heroin addicts significantly differ from those in normal controls[23]. However, few studies have examined the relationship between *GAD1* and PD, particularly in Chinese populations.

Previous genetic and chromosomal studies have yielded inconsistent results. It is likely that most cases of PD have a complex genetic basis. In addition, current data suggest that the genetic architecture underlying PD is heterogeneous and differs among cases[24]. PD is accompanied by various symptoms, including palpitations, accelerated heart rate, dyspnea, sweating, and chest pain. These symptoms may be linked to distinct genetic mechanisms, and genetic polymorphisms have been speculated to be linked to the discrete symptoms of PD. Hence, to test the hypothesis that the GAD1 polymorphism could be associated with PD, we have conducted a case-control study comparing the frequency of these SNPs (rs1978340 and rs3749034) in PD patients and healthy controls. Additionally, we examined the relationship between the presence of PD symptoms and these polymorphisms.

**MATERIALS AND METHODS**

***Participants***

A total of 230 patients with PD were recruited as in- and outpatients at the Departmentof Psychosomatics, Sichuan Provincial People’s Hospital, from July 2012 to January 2016. Patients were qualified based on the following criteria: A primary diagnosis of PD performed by professional psychiatrists according to the standardized structured clinical interview of the diagnostic and statistical manual of mental disorders, fourth edition axis I disorders (SCID-I)[25], and no episodes of other psychiatric disorders in the past or at present. Additionally, 224 healthy controls (HCs) among community volunteers were recruited for the study during the same period. SCID-I was also performed by a trained clinical psychiatrist, and the HCs had no history of any psychiatric disorder or major psychiatric condition in their first-degree relatives. All participants in this study were Han Chinese, aged 18–60 years. None of the patients had acute or chronic somatic disorders, head trauma, or neurological illnesses. The study was approved by the Ethics Committee of the Sichuan Provincial People’s Hospital [reference number: (2016) Ethics Review (29)]. All participants provided written informed consent before the initiation of study procedures.

***Measures***

**PDSS:** The 7-item PDSS was used to assess the severity of panic symptoms for all patients, and participants were instructed to rate each item from 0 to 4 based on the severity of each symptom, with possible responses ranging from “none” to “extremely severe”[26]. The scale was translated into Chinese by Xiong[27], and the PDSS-Chinese version had good internal consistency (Cronbach’s alpha) with an overall score of (0.83).

***Hamilton anxiety rating scale***

The Hamilton anxiety rating scale (HAM-A) scale comprises 14 items (anxious mood, tension, fear, insomnia, cognitive function, depressed mood, somatic anxiety (muscular system), somatic anxiety (sensory system), cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, autonomic symptoms, and behavior at interview) with 5-level responses for each item, *i.e.*, scores 0, 1, 2, 3, and 4 indicating not present, mild, moderate, severe, and very severe, respectively[28]. A total score > 17 indicates mild anxiety symptoms; 18-24, mild-to-moderate anxiety symptoms; and 25-30, moderate-to-severe anxiety symptoms.

***DNA extraction and SNP genotyping***

For each participant, 3 mL of peripheral blood was collected in EDTA tubes. An automatic nucleic acid extractor (TGuide M16; Tiangen Biotech, Beijing, China) was used to extract genomic DNA. SNP genotyping was performed using an improved multiplex ligation detection reaction (iMLDR) technique developed by Genesky Bio-Tech (Shanghai, China). The multiplex polymerase chain reaction (PCR) reaction volume included 1 μL GC-I buffer (Takara Bio Inc., Shiga, Japan), 3.0 mmol/L Mg2+, 0.3 mmol/L dNTP, 1 U HotStar Taq Polymerase (Qiagen, Hilden, Germany), 1 μL genomic DNA (5–10 ng/μL), and 1 μL Multiplex-PCR primer mix. The cycling program for PCR was 95 °C for 120 s, followed by 11 cycles of 94 °C for 20 s, 65 °C for 40 s, and 72 °C for 90 s, and each cycle decreased by 0.5 °C. The third step comprised 24 cycles at 94 °C for 20 s, 59 °C for 30 s, and finally, 72 °C for 2 min, and a hold at 4 °C. The PCR product was purified with 5 U SAP and 2 U Exonuclease I at 37 °C for 1 h and then inactivated at 75 °C for 15 min. The primer and probe information is provided in Supplementary Tables 1 and 2, respectively. The ligation reaction included 1 μL of 10× ligation buffer, 0.4 μL 3′ ligation primer (2 μM), 0.25 μL Tag DNA ligase, 6 μL ddH2O mixture, 0.4 μL 5′ ligation primer (1 μM), and 2μL purified multiplex PCR product. The ligation cycling program comprised 38 cycles at 94 °C for 60 s, 56 °C for 4 min, and a hold at 4 °C. Sequencing was conducted in 0.5 μL 500 LIZ Size Standard, 0.5 μL ligation product, and 9 μL Hi-Di mixture (ABI3730XL; Applied Biosystems, Waltham, MA, United States). Raw data were analyzed using GeneMapper v4.1 software (Applied Biosystems). A random sample accounting for approximately 5% of the total DNA samples was directly sequenced using Big Dye-terminator version 3.1 and an ABI3730XL automated sequencer (Applied Biosystems) to confirm the iMLDR results.

***Statistical analysis***

SPSS version 13.0 software (SPSS Inc., Chicago, IL, United States) was used to analyze the data. Student’s *t*-test was used for intergroup comparisons of continuous variables, and Pearson’s chi-square test was used for categorical variables. The Hardy-Weinberg equilibrium (HWE) *P* values were tested using Pearson’s chi-square test. Associations between SNPs and PD were determined based on the distribution of allelic frequencies and genetic models (additive, dominant, and recessive models). Odds ratios and 95% confidence intervals were calculated by unconditional logistic regression analysis using PLINK v1.07. Analysis of variance was performed to compare the clinical variables with different *GAD1* SNPs (rs1978340 and rs3749034). Bonferroni’s correction was used to avoid Type I errors. For all analyses, statistical tests were two-tailed, and an alpha level of 0.05 was used to define statistical significance.

**RESULTS**

***Demographic data and clinical manifestations***

The analyzed sample comprised 230 PD cases (92 men and 138 women; mean age, 35.38 ± 9.55 years) and 224 controls (100 men and 124 women; mean age, 36.57 ± 8.43 years). Of these patients, 54% (*n* = 124) resided in urban locations, and 46% (*n* = 106) resided in rural locations. No statistically significant differences were found between the cases and controls in terms of sex, age, or residential location (*P* > 0.05). For the PD patients, the mean course of PD was 2.80 ± 1.68 years, the mean PDSS score was 14.13 ± 3.74, and the mean HAM-A score was 22.07 ± 6.86 (Table 1).

***Association of GAD1 (rs1978340 and rs3749034) polymorphisms with PD risk***

HWE was measured in all genotyped individuals. *GAD1* (rs1978340 and rs3749034) polymorphisms fulfilled the HWE (*P* > 0.05) in both patients and HCs. The linkage disequilibrium evaluated in patients with PD and HCs for variants rs1978340 and rs3749034 of *GAD1* is shown in Figure 1 (*R*2 > 0.9). The genotype and allele distributions of *GAD1* (rs1978340 and rs3749034) did not significantly differ between PD patients and HCs (*P* > 0.05) (Table 2).

***Association of GAD1 (rs1978340 and rs3749034) polymorphisms with clinical manifestations in PD patients***

There were no statistically significant differences in the total PDSS and sub-item scores among the three genotype groups of *GAD1* polymorphisms (rs1978340 and rs3749034; all *P* > 0.05) (Table 3).

However, there was a significant difference among the three groups with different *GAD1* rs1978340 genotypes in item 10 of the HAM-A score for PD (*P* < 0.01). In addition, post hoc analyses indicated that patients with the *GAD1* rs1978340 A/A genotype had significantly higher scores than those with the A/G or G/G genotypes (all *P* < 0.001), and the results remained significant after Bonferroni’s multiple comparison adjustment (*P* < 0.01), reflecting a higher score for respiratory symptoms in patients with the *GAD1* rs1978340 A/A genotype than in those with the A/G or G/G genotype. However, there was no statistically significant difference among the three groups with different *GAD1* rs1978340 genotypes for the remaining items or HAM-A total scores (*P* > 0.05). Moreover, there was no significant association between *GAD1* rs3749034 and anxiety severity in PD patients (all *P* > 0.05) (Table 4).

**DISCUSSION**

In this study, regarding respiratory symptoms, which include chest tightness, choking, and breathing difficulty, we found that patients with the *GAD1* rs1978340 A/A genotype had significantly higher scores than those with the A/G or G/G genotypes. In other words, the present study showed that the *GAD1* rs1978340 A/A genotype was associated with increased severity of respiratory symptoms in patients with PD and demonstrated that the *GAD1* genotype might be related to symptomatic profiles rather than vulnerability to developing PD. In addition, our findings imply that different clinical features in PD patients are closely related to the heterogeneity of heredity. Compared with PD patients of the non-respiratory subtype (non-RS), previous studies have shown that patients with the RS subtype have a more extensive family history of PD[29]. Moreover, experimental animal research has provided evidence of the important role of GABAergic neurotransmission in the amygdala in modulating anxiety-related behaviors. For example, diminished GAD67 expression in the amygdala blunts the anxiolytic-like effects of diazepam in adult mice[30]. Furthermore, *GAD1* SNP rs1978340 is potentially functional because it affects GABA concentrations in the cingulate cortex[22]. In addition, the presence of *GAD1* rs1978340 allele A has been associated with a higher Glu/GABA ratio[31]. Clinical trials have shown that patients with PD and RS have a more rapid response to antidepressants and benzodiazepines than that of non-RS PD patients[32]. These findings contribute to our understanding of the mechanism linking *GAD1* rs1978340 with respiratory-related symptoms.

Similar findings suggest that patients with PD carrying the 5-HTTLPR s-allele experience the most severe panic and depressive symptoms[33]. Another study showed higher anxiety levels among A/G carriers than those among A/A carriers in patients[34]. It is evident that molecular genetics showed inconsistent results across different studies. This may be due to different sample sizes and ethnic differences. In addition, different clinical symptoms may be partly attributed to different genetic backgrounds, leading to difficulties in reaching a consensus on the etiology of PD. Further studies with larger populations are needed to obtain precise results based on different symptom subtypes.

In this case-control study, we examined two SNPs (rs1978340 and rs3749034) in a Chinese population. The results revealed that there was no association between *GAD1* and PD. In addition, we did not observe a modulatory effect of *GAD1* (rs1978340 and rs3749034) on PD severity. Much evidence has indicated that *GAD1* gene polymorphisms may be involved in the etiology of several psychiatric disorders. However, only one study has found that *GAD1* variation is associated with PD in females[35]. The different results of these studies might be partly attributable to differences in sample size and sex. Moreover, samples from different ethnicities and meta-analyses are required to further test this association. The SNP coverage in the present study was limited, and other gene polymorphisms should be considered. In addition, the pathogenesis of PD may involve the interaction of multiple genes and signal pathway regulation, which may incorporate the combined effects of genetic and environmental factors. For example, a previous study suggested the effect of the interaction between 5-HTTLPR and separate life events on PD[36].Finally, epigenetic mechanisms have been suggested to play important roles at the intersection of genetic and environmental factors[37]. Environmental factors may influence biological processes through epigenetic mechanisms, particularly DNA methylation[38]. For instance, patients with PD exhibit significantly lower average *GAD1* methylation levels than those of HCs[39]. Another study showed that patients had significantly lower methylation of the *GAD1* promoter region on cytosine-phosphate-guanine 7 than that of HCs, and a significant negative association was found between the cg171674146 site and clinical severity[40]. Therefore, epigenetic modifications may play an important role and should be further investigated in future studies.

**CONCLUSION**

In conclusion, the present study showed that the A/A genotype of GAD1 rs1978340 is associated with increased severity of respiratory symptoms in patients with PD. However, the results of our study should be considered in light of the following limitations: Since this was a small sample investigating the associations between *GAD1* gene polymorphisms and PD, it would be valuable to replicate our findings in a larger cohort. In addition, SNP coverage in the present study was limited, and other gene polymorphisms should be considered.

**ARTICLE HIGHLIGHTS**

***Research background***

Genetic factors are known to play a significant role in the development of panic disorder (PD). However, the impact of genetic variants on PD is still a subject of controversy.

***Research motivation***

γ-Aminobutyric acid (GABA) is an important neurotransmitter that inhibits brain activity. Previous reports have linked the *glutamate decarboxylase 1 (GAD1)* genetic variants to various psychiatric disorders, including bipolar disorder, schizophrenia, attention-deficit/hyperactivity disorder, and heroin dependence. However, few studies have examined the relationship between *GAD1* and PD, particularly in Chinese populations.

***Research objectives***

The main objectives of this study were to examine the associations between *GAD1* gene polymorphisms (rs1978340 and rs3749034) and PD risk, and to determine the effect of these polymorphisms on the severity of clinical symptoms, specifically respiratory symptoms, in individuals with PD.

***Research methods***

The study included a total of 230 PD patients and 224 healthy controls. All participants underwent assessments for anxiety and panic symptom severity using the Hamilton Anxiety Rating Scale (HAM-A) and Panic Disorder Severity Scale (PDSS). The GAD1 gene polymorphisms (rs1978340 and rs3749034) were genotyped, and allele frequencies were analyzed.

***Research results***

The study findings revealed no significant differences in the genotype distributions or allele frequencies of *GAD1* (rs1978340 and rs3749034) between the PD cases and the control group. Furthermore, the *GAD1* gene polymorphisms (rs1978340 and rs3749034) did not exhibit a significant effect on the overall severity of PD. However, in relation to respiratory symptoms, PD patients with the *GAD*1 rs1978340 A/A genotype demonstrated significantly higher scores compared to those with the A/G or G/G genotype.

***Research conclusions***

In conclusion, this study demonstrated that the A/A genotype of *GAD1* rs1978340 is associated with increased severity of respiratory symptoms in individuals with PD. However, no significant associations were found between *GAD1* gene polymorphisms and the risk of developing PD or the overall severity of the disorder.

***Research perspectives***

Further research is needed to explore other potential genetic factors involved in the development and severity of PD. Additionally, investigating the underlying mechanisms through which *GAD1* gene polymorphisms affect respiratory symptoms in PD patients could provide valuable insights for future studies.

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**Footnotes**

**Institutional review board statement:** The study was approved by the Ethics Committee of the Sichuan Provincial People’s Hospital [reference number: (2016) Ethics Review (29)]. All participants provided written informed consent before the initiation of study procedures.

**Conflict-of-interest statement:** The authors report no conflict of interest.

**Data sharing statement:** Data is available on request due to privacy/ethical restrictions

**STROBE Statement:** The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

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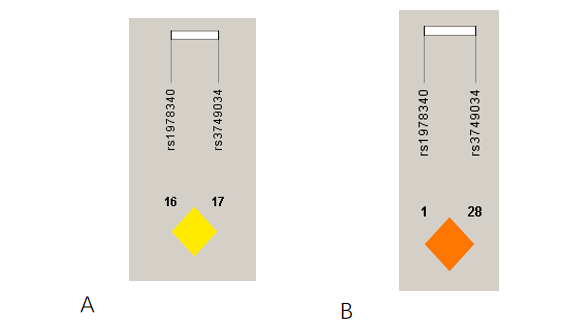
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**Figure Legends**



**Figure 1 Linkage disequilibrium in *glutamate decarboxylase 1* polymorphisms (rs1978340 and rs3749034).** A: Data from this study; B: Data from 1000 genomes.

**Table 1 Demographic and clinical characteristics in patients with panic disorder and controls, *n* (%)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** | **PD (*n* = 230)** | **Controls(n=224)** | **t/*χ*2-value** | ***P* value** |
| **Sex** |  |  |  |  |
| Male | 92 (40.0) | 100 (44.6) | 1.002 | 0.317 |
| Female | 138 (60.0) | 124 (55.4) |  |  |
| **Age**, **yr** | 35.38 ± 9.55 | 36.57 ± 8.43 | 1.410 | 0.159 |
| **Educational level** |  |  |  |  |
| <J[unior](file:///D:\A-MYJ\科编\Administrator\AppData\Local\Yodao\DeskDict\frame\20150807001456\javascript:void(0);) [high](file:///D:\A-MYJ\科编\Administrator\AppData\Local\Yodao\DeskDict\frame\20150807001456\javascript:void(0);) [school](file:///D:\A-MYJ\科编\Administrator\AppData\Local\Yodao\DeskDict\frame\20150807001456\javascript:void(0);) | 49 (21.3) | 43 (19.2) |  |  |
| High school | 95 (41.3) | 92 (41.1) | 0.412 | 0.814 |
| College and above | 86 (37.4) | 89 (39.7) |  |  |
| **Resident location** |  |  |  |  |
| Urban | 124 (53.9) | 126 (56.3) |  |  |
| Rural | 106 (46.1) | 98 (43.7) | 0.250 | 0.617 |
| Total duration of PD, yr | 2.80 ± 1.68 |  |  |  |
| PDSS score | 14.13 ± 3.74 |  |  |  |
| HAMA score | 22.07 ± 6.86 |  |  |  |

PDSS: Panic Disorder Severity Scale; HAMA: Hamilton Anxiety Rating Scale.

**Table 2 *Glutamate decarboxylase 1* gene polymorphisms of patients with panic disorder *vs* controls in the Chinese population, *n* (%)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **SNP** | **Alleles and genotypes** | **PD (*n* = 230)** | **Controls (*n* = 224)** | **Model** | **OR (95%CI)** | ***P* value** |
| rs1978340 | A | 122 (26.5) | 116 (25.9) | Allelea | 1.003 (0.769-1.389) | 0.829 |
| G | 338 (73.5) | 332 (74.1) |
| A/A | 17 (7.4) | 20 (8.9) | Additiveb | 1.031 (0.774-1.373) | 0.835 |
| A/G | 88 (38.3) | 76 (34.8) | Dominantb | 1.120 (0.773-1.622) | 0.549 |
| G/G | 125 (54.3) | 128 (57.1) | Recessiveb | 0.814 (0.415-1.598) | 0.550 |
| rs3749034 | A | 131 (28.5) | 129 (28.8) | Allele | 0.985 (0.738-1.313) | 0.916 |
| G | 329 (71.5) | 319 (71.2) |
| A/A | 17 (7.4) | 15 (6.7) | Additive | 0.984 (0.732-1.323) | 0.914 |
| A/G | 97 (42.2) | 99 (44.2) | Dominant | 0.948 (0.656-1.370) | 0.777 |
| G/G | 116 (50.4) | 110 (49.1) | Recessive | 1.112 (0.541-2.286) | 0.773 |

SNP: [Single Nucleotide Polymorphism](javascript:;), “A” represent wild type and “a” represent mutant type: allele, a *vs* A; additive, aa *vs* Aa *vs* AA; dominant, aa + Aa *vs* AA, recessive, aa *vs* Aa +AA.

aChi-square test;

bLogistic regression analyses.

OR: Odds ratios; CI: Confidence interval.

**Table 3** **Panic disorder severity scale subdimension scores of panic disorder with different *glutamate decarboxylase 1* rs1978340 and rs3749034 polymorphisms**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **rs1978340** | | | ***F-*value** | ***P* value** | **rs3749034** | | | ***F-*value** | ***P* value** |
| **A/A (*n* = 17)** | **A/G (*n* = 88)** | **G/G (*n* = 125)** | **A/A (*n* = 17)** | **A/G (*n* = 97)** | **G/G (*n* = 116)** |
| PDSS1 | 2.12 ± 0.93 | 2.11 ± 1.09 | 2.14 ± 1.08 | 0.022 | 0.978 | 1.94 ± 0.97 | 2.06 ± 1.04 | 2.22 ± 1.10 | 0.837 | 0.434 |
| PDSS2 | 2.41 ± 1.00 | 2.32 ± 1.00 | 2.44 ± 1.10 | 0.349 | 0.706 | 2.35 ± 1.41 | 2.28 ± 1.07 | 2.49 ± 0.97 | 1.099 | 0.335 |
| PDSS3 | 2.41 ± 1.18 | 2.08 ± 0.89 | 2.14 ± 1.05 | 0.786 | 0.457 | 2.18 ± 1.13 | 1.99 ± 1.00 | 2.26 ± 0.98 | 1.934 | 0.147 |
| PDSS4 | 1.59 ± 1.28 | 1.57 ± 1.04 | 1.66 ± 1.06 | 0.218 | 0.804 | 1.41 ± 1.12 | 1.76 ± 1.12 | 1.53 ± 1.00 | 1.590 | 0.206 |
| PDSS5 | 1.71 ± 1.26 | 1.91 ± 1.01 | 1.76 ± 1.10 | 0.581 | 0.560 | 2.12 ± 1.22 | 1.67 ± 0.93 | 1.89 ± 1.63 | 1.818 | 0.165 |
| PDSS6 | 2.33 ± 1.22 | 2.15 ± 0.97 | 2.11 ± 1.03 | 0.417 | 0.660 | 2.18 ± 1.33 | 2.09 ± 1.03 | 2.18 ± 0.97 | 0.206 | 0.814 |
| PDSS7 | 1.59 ± 0.94 | 1.83 ± 1.01 | 1.97 ± 1.18 | 1.087 | 0.339 | 2.00 ± 1.06 | 1.85 ± 1.05 | 1.91 ± 1.15 | 0.174 | 0.841 |
| PDSS total | 14.18 ± 4.68 | 13.97 ± 3.39 | 14.23 ± 3.86 | 0.132 | 0.877 | 14.18 ± 4.99 | 13.70 ± 3.54 | 14.47 ± 3.69 | 1.134 | 0.323 |

PDSS1: Panic attack frequency, PDSS2: Panic distress, PDSS3: Severity of anticipatory anxiety, PDSS4: Agoraphobic fear/avoidance, PDSS5: Fear/avoidance of panic-related sensations, PDSS6: Work impairment, PDSS7: Social impairment, PDSS: Panic Disorder Severity Scale.

**Table 4 Hamilton Anxiety Rating Scale subdimension scores of panic disorder with different *glutamate decarboxylase 1* rs1978340 and rs3749034 polymorphisms**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **rs1978340** | | | ***F-*value** | ***P* value** | **rs3749034** | | | ***F-*value** | ***P* value** |
| **A/A (*n* = 17)** | **A/G (*n* = 88)** | **G/G (*n* = 125)** | **A/A (*n* = 17)** | **A/G (*n* = 97)** | **G/G (*n* = 116)** |
| HAMA1 | 1.59 ± 1.06 | 1.88 ± 1.16 | 1.81 ± 1.18 | 0.439 | 0.645 | 1.82 ± 1.33 | 1.81 ± 1.14 | 1.82 ± 1.17 | 0.001 | 0.999 |
| HAMA2 | 2.00 ± 1.00 | 2.06 ± 0.94 | 2.17 ± 1.11 | 0.402 | 0.669 | 2.24 ± 1.30 | 2.07 ± 1.01 | 2.13 ± 1.03 | 0.206 | 0.814 |
| HAMA3 | 1.94 ± 1.09 | 1.66 ± 1.07 | 1.98 ± 1.08 | 2.295 | 0.103 | 2.24 ± 1.25 | 1.78 ± 1.01 | 1.85 ± 1.11 | 1.260 | 0.286 |
| HAMA4 | 1.71 ± 1.11 | 1.43 ± 1.11 | 1.58 ± 1.02 | 0.728 | 0.484 | 1.47 ± 0.87 | 1.48 ± 1.02 | 1.58 ± 1.12 | 0.231 | 0.794 |
| HAMA5 | 1.59 ± 1.06 | 1.58 ± 1.04 | 1.65 ± 1.03 | 0.121 | 0.886 | 1.65 ± 1.17 | 1.55 ± 1.06 | 1.67 ± 0.99 | 0.402 | 0.670 |
| HAMA6 | 1.53 ± 1.01 | 1.25 ± 1.05 | 1.54 ± 0.99 | 2.255 | 0.107 | 1.65 ± 1.32 | 1.38 ± 1.07 | 1.44 ± 0.94 | 0.498 | 0.747 |
| HAMA7 | 1.76 ± 1.03 | 1.34 ± 0.99 | 1.62 ± 1.01 | 2.459 | 0.088 | 1.59 ± 1.06 | 1.46 ± 1.01 | 1.56 ± 1.02 | 0.277 | 0.759 |
| HAMA8 | 1.06 ± 0.83 | 1.38 ± 1.10 | 1.37 ± 1.12 | 0.644 | 0.526 | 1.41 ± 0.94 | 1.34 ± 1.10 | 1.34 ± 1.11 | 0.032 | 0.969 |
| HAMA9 | 2.06 ± 1.20 | 1.91 ± 0.99 | 1.94 ± 1.03 | 0.154 | 0.858 | 1.82 ± 1.13 | 2.08 ± 1.07 | 1.84 ± 0.97 | 1.647 | 0.195 |
| HAMA10 | 2.88 ± 0.93 | 1.94 ± 0.98 | 1.90 ± 1.02 | 7.445 | 0.001 | 2.41 ± 1.00 | 1.94 ± 0.96 | 1.97 ± 1.08 | 1.601 | 0.204 |
| HAMA11 | 0.76 ± 0.66 | 0.86 ± 0.79 | 0.97 ± 0.91 | 0.672 | 0.512 | 1.00 ± 0.94 | 0.89 ± 0.87 | 0.92 ± 0.82 | 0.143 | 0.867 |
| HAMA12 | 1.00 ± 1.00 | 1.20 ± 0.96 | 1.34 ± 0.92 | 1.214 | 0.299 | 1.41 ± 1.00 | 1.22 ± 0.93 | 1.28 ± 0.95 | 0.340 | 0.712 |
| HAMA13 | 1.12 ± 0.93 | 1.35 ± 0.87 | 1.30 ± 1.03 | 0.427 | 0.653 | 1.29 ± 1.11 | 1.25 ± 0.99 | 1.36 ± 0.92 | 0.377 | 0.687 |
| HAMA14 | 1.59 ± 1.06 | 1.48 ± 0.98 | 1.35 ± 0.98 | 0.693 | 0.501 | 1.53 ± 1.28 | 1.44 ± 0.99 | 1.38 ± 0.94 | 0.229 | 0.796 |
| HAMA total | 22.59 ± 5.22 | 21.34 ± 6.94 | 22.50 ± 6.97 | 0.799 | 0.451 | 23.53 ± 7.13 | 21.70 ± 6.93 | 22.16 ± 6.75 | 0.535 | 0.587 |

HAMA1: Anxious mood; HAMA2: Tension; HAMA3: Fears; HAMA4: Insomnia; HAMA5: Intellectual; HAMA6: Depressed mood; HAMA7: Somatic complaints muscular; HAMA8: Somatic complaints sensory; HAMA9: Cardiovascular symptoms; HAMA10: Respiratory symptoms; HAMA11: Gastrointestinal symptoms; HAMA12: Genitourinary symptoms; HAMA13: Autonomic symptoms; HAMA14: Behavior at interview; HAMA: Hamilton Anxiety Rating Scale.