Neurosci. Bull. February, 2017, 33(1):107–110
DOI 10.1007/s12264-016-0088-8

www.neurosci.cn
www.springer.com/12264

LETTER TO THE EDITOR

# Associations Between *PPP1R1B* Gene Polymorphisms and Anxiety Levels in the Chinese Population

**Hui Ma[1,2] · Xin Li[2] · Ailu Lin[2] · Zhen Yuan[2] · Jing Zhou[2] · Xueping Yang[2] · Zhengtu Cong[2] · Yinglin Huang[2] · Gang Zhu[2]**

Received: 30 June 2016 / Accepted: 7 November 2016 / Published online: 19 December 2016


**Dear Editor:**

Early in 1983, DARPP-32, a phosphoprotein regulated by dopamine (DA) and cAMP, encoded by the *PPP1R1B* gene, was identified as a mediator of postsynaptic DA receptor signaling in striatal neurons [1]. Later, studies on postmortem brains using the quantitative polymerase chain reaction, immunohistochemical staining, and immunoblotting demonstrated significantly changed expression of DARPP-32 in the dorsolateral prefrontal cortex (DLPFC) of patients with mental disorders such as schizophrenia and bipolar disorder [2, 3]. At the same time, several gene association studies demonstrated that *PPP1R1B* polymorphisms or their haplotypes are associated with schizophrenia and substance dependence [4, 5]. However, no studies have tested for an association between *PPP1R1B* polymorphisms and anxiety levels or anxiety disorders. It has been demonstrated that the *PPP1R1B* gene is expressed in brain regions closely associated with anxiety, such as the amygdala and hippocampus [6, 7]. Moreover, DARPP-32 is closely associated with the DA and glutamine neurotransmitter systems that mediate anxious emotion and behavior. The *PPP1R1B* gene and DARPP-32 may thus play a role in anxiety through these neural pathways.

Here, we investigated in a healthy Han Chinese population whether genetic variants in the *PPP1R1B* gene are associated with state anxiety (a current emotional state) and trait anxiety (a consistent emotional state) using the 40-item State-Trait Anxiety Inventory (STAI). A previous study by our team has demonstrated significant associations between the *PPP1R1B* intron single nucleotide polymorphisms (SNPs) rs12601930C/T, rs879606A/G, and rs3764352A/G, and personality traits measured by the Tridimensional Personality Questionnaire in healthy Han Chinese [8]. Because anxiety, especially trait anxiety, is considered to be an important and enduring dimension of personality, we examined its association with the above three SNPs based on their previously-established association with personality traits. A total of 571 unrelated healthy Han Chinese volunteers (272 males, 299 females) were recruited. The age range was 19–58 years ($30.20 \pm 7.82$ years). All protocols were approved by the Ethics Committee of China Medical University. Written consent was given by all participants and venous blood samples were taken. The polymorphism genotyping experiments were performed according to the methods described in our previous studies [4, 8, 9].

The genotype counts and frequencies for the rs12601930C/T, rs879606A/G, and rs3764352A/G polymorphisms are shown in Table 1. The genotype distributions did not deviate from Hardy-Weinberg equilibrium. We did not find any statistical difference in the state-anxiety dimension for the rs12601930C/T, rs879606A/G, and rs3764352A/G genotypes, but statistical differences in the trait-anxiety dimension for the rs879606A/G ($F = 5.207$, $P = 0.006$) and rs3764352A/G ($F = 3.960$, $P = 0.020$) genotypes (Table 1). We also compared the anxiety scores among the three genotypes of each SNP between genders (Table 1). In the female participants, there were statistical associations of the rs879606A/G ($F = 4.977$, $P = 0.007$) and rs3764352A/G ($F = 3.404$, $P = 0.035$) genotypes with trait-anxiety levels, while no such associations were

✉ Gang Zhu
gzhu@mail.cmu.edu.cn

[1] Center for Mental Health, Yanshan University, Qinhuangdao 066004, China

[2] Department of Psychiatry, The First Affiliated Hospital of China Medical University, Shenyang 110001, China

**Table 1** Effects of *PPP1R1B* gene polymorphisms on STAI scores.

| SNP | Genotype | Total *n* (%) | State anxiety | Trait anxiety | Male *n* (%) | State anxiety Male | Trait anxiety Male | Female *n* (%) | State anxiety Female | Trait anxiety Female |
|---|---|---|---|---|---|---|---|---|---|---|
| rs12601930 | C/C | 287 (50.26%) | 37.51 ± 7.96 | 38.53 ± 6.97 | 117 (43.01%) | 37.59 ± 7.12 | 39.15 ± 6.59 | 170 (56.86%) | 37.45 ± 8.50 | 38.10 ± 7.20 |
| | C/T | 234 (40.98%) | 37.93 ± 7.69 | 38.86 ± 6.43 | 127 (46.69%) | 37.24 ± 7.82 | 38.43 ± 6.36 | 107 (35.79%) | 38.75 ± 7.49 | 39.37 ± 6.51 |
| | T/T | 50 (8.76%) | 37.22 ± 9.36 | 39.54 ± 7.69 | 28 (10.29%) | 36.71 ± 8.31 | 39.82 ± 6.48 | 22 (7.36%) | 37.86 ± 10.72 | 39.18 ± 9.16 |
| | *F* | | 0.259 | 0.515 | | 0.171 | 0.715 | | 0.793 | 1.120 |
| | *P* value | | 0.772 | 0.598 | | 0.843 | 0.490 | | 0.454 | 0.328 |
| rs879606 | A/A | 130 (22.77%) | 37.97 ± 8.48 | 38.85 ± 7.07 | 74 (27.21%) | 38.46 ± 8.60 | 39.23 ± 7.32 | 56 (18.73%) | 37.32 ± 8.37 | 38.34 ± 6.74 |
| | A/G | 291 (50.96%) | 38.12 ± 7.84 | 39.47 ± 6.84 | 140 (51.47%) | 37.27 ± 7.14 | 39.11 ± 6.16 | 151 (50.50%) | 38.90 ± 8.39 | 39.81 ± 7.41 |
| | G/G | 150 (26.27%) | 36.49 ± 7.70 | 37.28 ± 6.34 | 58 (21.32%) | 36.05 ± 7.01 | 37.90 ± 6.01 | 92 (30.77%) | 36.76 ± 8.13 | 36.89 ± 6.55 |
| | *F* | | 2.210 | 5.207 | | 1.669 | 0.865 | | 2.094 | 4.977 |
| | *P* value | | 0.111 | **0.006** | | 0.190 | 0.422 | | 0.125 | **0.007** |
| rs3764352 | A/A | 138 (24.17%) | 36.58 ± 7.86 | 37.36 ± 6.37 | 47 (17.28%) | 36.26 ± 7.09 | 37.89 ± 6.07 | 91 (30.43%) | 36.75 ± 8.26 | 37.09 ± 6.53 |
| | A/G | 286 (50.09%) | 37.78 ± 7.49 | 39.08 ± 6.34 | 143 (52.57%) | 37.10 ± 7.02 | 39.08 ± 6.10 | 143 (47.83%) | 38.45 ± 7.89 | 39.07 ± 6.60 |
| | G/G | 147 (25.74%) | 38.43 ± 8.89 | 39.43 ± 7.89 | 82 (30.15%) | 38.35 ± 8.62 | 39.10 ± 7.28 | 65 (21.74%) | 38.52 ± 9.28 | 39.85 ± 8.64 |
| | *F* | | 1.988 | 3.960 | | 1.294 | 0.663 | | 1.360 | 3.404 |
| | *P* value | | 0.138 | **0.020** | | 0.276 | 0.516 | | 0.258 | **0.035** |

Data of STAI scores are mean ± SD.

The values highlighted in bold indicate statistical significance $P < 0.05$.

found between the three genotypes of each SNP and state-anxiety levels. There were no associations between these genotypes and either state- or trait-anxiety levels in the male participants.

No previous studies have demonstrated a direct link between *PPP1R1B*/DARPP-32 and anxiety despite some indirect evidence. There is a large amount of anatomical, physiological, pharmacological, and behavioral evidence for the importance of DARPP-32 regulation in the DA system [1]. Clinical studies on the influence of gene variations in the DA system on anxiety have demonstrated that polymorphisms of the DA transporter catechol-O-methyl aminotransferase and monoamine oxidase type A genes are associated with anxiety spectrum disorders [10–12]. Therefore, the *PPP1R1B* gene and DARPP-32 may play a role in normal and/or pathological anxiety through DA neuronal pathways. Moreover, animal experiments have demonstrated that physiological or psychosocial stress induces anxious behaviors through altered *PPP1R1B* gene expression [13, 14]. It is known that psychological factors including cognition, reinforcement learning, emotion processing, personality traits, and defense mechanisms act as mediators or moderators of the effects of stressors on individual anxiety responses. Of interest, the rs879606 and rs3764352 genotypes, demonstrated to be associated with anxiety in the present study, are related to cognition [5], personality traits [8], and defense mechanisms [9], while the rs879606G/rs3764352T/rs907094A haplotype is involved in associative emotional learning [15]. Moreover, the rs907094 genotype of the *PPP1R1B* gene has been associated with reward learning [16] and the processing of anger [17]. The *PPP1R1B* gene and DARPP-32 may thus indirectly regulate stress-induced anxiety levels through the above mediation processes.

In the present study, we investigated the possible association between three *PPP1R1B* polymorphisms and trait- and state-anxiety dimensions in healthy Han Chinese participants, and demonstrated significant differences in the trait-anxiety dimension among the rs879606A/G and rs3764352A/G genotypes, especially in the female participants. Our results are consistent with previous findings and further complement them. Recently, Kunii *et al.* [2] found that the expression of a truncated DARPP-32 transcript (t-DARPP-32) is increased in the DLPFC of patients with schizophrenia or bipolar disorder and is strongly associated with the rs879606, rs90974, and rs3764352 SNPs, as well as the previously identified 7-SNP haplotype [5], indicating that variations in the *PPP1R1B* gene may affect the abundance of t-DARPP-32 mRNA and reflect the potential molecular mechanisms underlying some mental disorders. Therefore, further studies examining the expression of *PPP1R1B* mRNA as affected by variations in the *PPP1R1B* gene are necessary to gain a more complete understanding of the effects of *PPP1R1B* allelic variants on anxiety.

**Acknowledgements** This work was supported by grants from the Doctoral Fund Project of Yanshan University, China (B901 to HM) and the National Basic Research Development Program of China (2013CB531305). We thank all the volunteers for participating in this study.

## References

1. Walaas SI, Aswad DW, Greengard P. A dopamine- and cyclic AMP-regulated phosphoprotein enriched in dopamine-innervated brain regions. Nature 1983, 301: 69–71.
2. Kunii Y, Hyde TM, Ye T, Li C, Kolachana B, Dickinson D, *et al.* Revisiting DARPP-32 in postmortem human brain: changes in schizophrenia and bipolar disorder and genetic associations with t-DARPP-32 expression. Mol Psychiatry 2014, 19: 192–199.
3. Ishikawa M, Mizukami K, Iwakiri M, Asada T. Immunohistochemical and immunoblot analysis of Dopamine and cyclic AMP-regulated phosphoprotein, relative molecular mass 32,000 (DARPP-32) in the prefrontal cortex of subjects with schizophrenia and bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 2007, 31: 1177–1181.
4. Ma H, Huang Y, Li X, Lin A, Cong Z, Zhu G. A case-control study of the association between DARPP-32 gene polymorphisms and alcohol dependence in Chinese Han subjects. Psychiatry Res 2015, 229: 1052–1054.
5. Meyer-Lindenberg A, Straub RE, Lipska BK, Verchinski BA, Goldberg T, Callicott JH, *et al.* Genetic evidence implicating DARPP-32 in human frontostriatal structure, function, and cognition. J Clin Invest 2007, 117: 672–682.
6. Long H, Liu B, Hou B, Wang C, Li J, Qin W, *et al.* The long rather than the short allele of 5-HTTLPR predisposes Han Chinese to anxiety and reduced connectivity between prefrontal cortex and amygdala. Neurosci Bull 2013, 29: 4–15.
7. Engin E, Treit D. The role of hippocampus in anxiety: intracerebral infusion studies. Behav Pharmacol 2007, 18: 365–374.
8. Li J, Ma H, Zhou H, Huang Y, Wu L, Li J, *et al.* Association between DARPP-32 gene polymorphism and personality traits in healthy Chinese-Han subjects. J Mol Neurosci 2011, 44: 48–52.
9. Huang Y, Li J, Ma H, Zhao X, Wang Y, Jin Q, *et al.* Association between PPP1R1B polymorphisms and defense mechanisms in healthy Chinese-Han subjects. J Mol Neurosci 2013, 49: 618–624.
10. Segman RH, Cooper-Kazaz R, Macciardi F, Goltser T, Halfon Y, Dobroborski T, *et al.* Association between the dopamine transporter gene and posttraumatic stress disorder. Mol Psychiatry 2002, 7: 903–907.
11. Hettema JM, An SS, Bukszar J, van den Oord EJ, Neale MC, Kendler KS, *et al.* Catechol-O-methyltransferase contributes to genetic susceptibility shared among anxiety spectrum phenotypes. Biol Psychiatry 2008, 64: 302–310.
12. Samochowiec J, Hajduk A, Samochowiec A, Horodnicki J, Stepień G, Grzywacz A, *et al.* Association studies of MAO-A, COMT, and 5-HTT genes polymorphisms in patients with anxiety disorders of the phobic spectrum. Psychiatry Res 2004, 128: 21–26.
13. Yamamoto Y, Tanahashi T, Kawai T, Chikahisa S, Katsuura S, Nishida K, *et al.* Changes in behavior and gene expression induced by caloric restriction in C57BL/6 mice. Physiol Genomics 2009, 39: 227–235.

14. Jin HM, Shrestha Muna S, Bagalkot TR, Cui Y, Yadav BK, Chung YC. The effects of social defeat on behavior and dopaminergic markers in mice. Neuroscience 2015, 288: 167–177.
15. Curčić-Blake B, Swart M, Ter Horst GJ, Langers DR, Kema IP, Aleman A. Variation of the gene coding for DARPP-32 (PPP1R1B) and brain connectivity during associative emotional learning. Neuroimage 2012, 59: 1540–1550.
16. Frank MJ, Moustafa AA, Haughey HM, Curran T, Hutchison KE. Genetic triple dissociation reveals multiple roles for dopamine in reinforcement learning. Proc Natl Acad Sci U S A 2007, 104: 16311–16316.
17. Reuter M, Weber B, Fiebach CJ, Elger C, Montag C. The biological basis of anger: associations with the gene coding for DARPP-32 (PPP1R1B) and with amygdala volume. Behav Brain Res 2009, 202: 179–183.