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No Association of *Stathmin 1* Gene Polymorphism with Trait or State Anxiety in the Chinese Population

ABSTRACT

Objective: Stathmin 1 (Stmn1) is a neuronal growth-associated protein which was found to be involved in fear processing both in animals and humans. Moreover, it has been demonstrated that 2 single nucleotide polymorphisms (SNPs) of the *Stmn1* gene (rs182455 and rs213641) significantly impacted individual fear and anxiety responses in German. However, there have been no reports on the correlation between *Stmn1* SNPs and anxiety in Chinese. The present study thus aimed to explore such correlation.

Methods: A sample of 567 healthy Han Chinese adults were genotyped for the *Stmn1* SNP, namely rs182455, using polymerase chain reaction and restriction fragment length polymorphism analysis. Anxiety was assessed by the Chinese version of 40-item State-Trait Anxiety Inventory (STAI), which measures 2 anxiety dimensions, state and trait anxiety.

Results: The numbers of CC, CT, and TT genotypes of rs182455 polymorphism were 227 (40.0%), 263 (46.4%), and 77 (13.6%), respectively. The genotype distribution did not deviate from the Hardy–Weinberg equilibrium ($\chi^2 = 0.004$, $P = .953$). There were no significant differences in either state or trait anxiety among the 3 rs182455 genotype groups ($F = 0.457$, 0.415, $P = .634$, .660), between the 2 dominant model groups ($t = 0.865$, −0.195, $P = .388$, .845), or between the 2 recessive model groups ($t = 0.106$, 0.906, $P = .916$, .365). Moreover, no significant gender-specific differences in any STAI scores were found among the rs182455 genotype groups (all $P > .05$).

Conclusion: No evidence was demonstrated for the association of the *Stmn1* gene polymorphism rs182455 with either trait or state anxiety in Chinese adults.

Keywords: *Stmn1*, gene polymorphism, anxiety, state-trait anxiety inventory

Introduction

As a psychological construct, anxiety is considered a continuum from normal mild anxiety to pathologic anxiety. Mild anxiety experienced in everyday life is usually an appropriate response to stressors, whereas pathologic anxiety, which is also called anxiety disorders, is excessive or occurs in response to non-threatening or other inappropriate situations. Anxiety is only called an anxiety symptom if the clinical manifestations of an individual with anxiety do not reach the level of a diagnosis of an anxiety disorder. Many physical and psychiatric illnesses also accompany anxiety symptoms.[1-4] Because of the high occurrence rate of anxiety symptoms and the pain and harm they bring to the individual, it is important to investigate the potential risk factors for anxiety symptoms. Genetic, neuroanatomical, neurobiological, environmental, and psychological factors have been studied.[5,6] Our team has been focusing on the association of some transmitters and their genetic polymorphisms in the central neurotransmitter pathway with anxiety symptoms.[7,8]

Unlike neurotransmitters, Stathmin 1 (Stmn1) is a neuronal growth-associated protein which is involved in microtubule (MT) dynamics and plays an important role in synaptic outgrowth and plasticity.[9,10] In the present study, we planned to explore the possible association between *Stmn1* single nucleotide polymorphism (SNP) and anxiety symptoms on the basis of the evidence provided by previous studies.

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First, it has been demonstrated that anxiety and fear are genetically related and are modulated by overlapping neuroanatomical circuits.[11] Moreover, anxiety and fear symptoms are also intertwined in clinical settings. On an anatomical and cellular level, Stmn1 is highly expressed in the amygdala, hippocampus, and prefrontal cortex, the main brain regions that control and regulate emotions including fear and anxiety.[12-14] This is the first clue that Stmn1 may be related to anxiety.

Second, a number of studies have demonstrated that Stmn1 is involved in fear processing in experimental animals.[10,13,15,16] For example, by constructing a single prolonged stress rat model of post-traumatic stress disorder (PTSD), Shan et al[10] found that Stmn1 in the memory loop, especially in the hippocampus, regulates MT structure through its phosphorylation at Ser25 and Ser38 and thereby participates in the mediation of fear memory abnormalities in PTSD. Using *Stmn1* knockout (KO) mice, many studies have demonstrated that *Stmn1* KO could lead to abnormal spike-timing-dependent long-term potentiation (LTP) and defective memory on fear conditioning.[13,15,17] These results indicate that Stmn1 is required for the induction of LTP in afferent inputs to the amygdala and is essential in regulating both innate and learned fear in mice. Using *Stmn1* KO dogs, Ding et al[16] demonstrated that 2 SNPs, −327A > G and −125C > T, located in the *Stmn1* gene promoter region could affect canine fear behavior by altering *Stmn1* transcriptional activity.

Third, there are few human studies at the genetic level on the relationship of *Stmn1* with anxiety and fear, except *Stmn1* KO animal models mentioned above. Brocket et al[18] demonstrated that 2 SNPs of the *Stmn1* gene (rs182455 and rs213641) significantly impacted individual fear and anxiety responses in healthy Germans. Ehlis et al[9] found that *Stmn1* SNP rs182455 affected cognitive-affective processing in healthy Germans. All the results of these 2 studies indicate that the *Stmn1* SNPs impact anxiety response.

The above 3 aspects of research evidence support the *Stmn1* gene as a candidate for anxiety susceptibility. However, there have been no reports on the correlation between *Stmn1* gene polymorphisms and anxiety in Chinese. Therefore, the present study aimed to explore the correlation of SNP rs182455 of the *Stmn1* gene selected from previous related studies[9,18] with anxiety levels assessed by the State-Trait Anxiety Inventory (STAI) in the healthy Chinese population.

Material and Methods

Participants

G*Power version 3.0 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany), a free statistical software,[19] was used to calculate the sample size during the experimental design period. Considering the estimated sample size of G*Power (n = 210 or 252) as well as the sample size of previous studies on genetic polymorphisms of mental symptoms or disorders (n ≥ 300), a total of 567 healthy volunteers (271 males, 47.8%; 296 females, 52.2%) were recruited by a simple random sampling method from undergraduate students, graduate students, and staff of a university in China in the present study. All participants were unrelated Han Chinese. Individuals with a history of psychiatric, neurological, or severe/chronic physical illnesses were excluded. The age range of the participants was 19-58 years [mean (SD): 30.72 (SD = 7.80) years]. There were no significant differences in age ($t = 0.792$, $P = .428$) between male [mean (SD): 31.00 (SD = 7.85) years] and female participants [mean (SD): 30.48 (SD = 7.76) years]. Written informed consent was obtained from all participants. All protocols in this study were approved by the Ethics Committee of Hainan Provincial Anning Hospital (Approval No: 202206).

MAIN POINTS

- *The numbers of CC, CT, and TT genotypes of Stmn1 gene polymorphism rs182455 were 227 (40.0%), 263 (46.4%), and 77 (13.6%), which did not deviate from the Hardy–Weinberg equilibrium.*
- *There were no significant differences in state or trait anxiety scores among the 3 rs182455 genotype groups, between the 2 dominant model groups, or between the 2 recessive model groups.*
- *There were no significant gender-specific differences in state or trait anxiety scores among the rs182455 genotype groups.*

Psychological Assessment

The first edition of STAI (STAI-Form X) was originally introduced by Charles D. Spielberger et al in 1970. The authors revised the STAI-Form X in 1979 and began to apply the revised version (STAI-Form Y) in 1980, which was translated into Chinese in 1988. The Chinese version of the 40-item STAI, which has been shown to be a highly reliable measure of anxiety, was used in the present study. State-Trait Anxiety Inventory is a self-reporting scale with a total of 40 descriptive items. Each item is rated on a scale of 1-4. State-Trait Anxiety Inventory consists of 2 subscales that measure 2 kinds of anxiety: state anxiety (a current emotional state) and trait anxiety (an ordinary and consistent emotional state).

Polymorphism Genotyping

A 2 mL venous blood sample was obtained from each participant for genotyping. Genomic DNA was extracted from EDTA (ethylene diamine tetraacetic acid)-treated peripheral venous blood using the standard potassium iodide method. Amplification of gene fragments containing *Stmn1* SNP rs182455 was performed using polymerase chain reaction, and subsequent genotyping was carried out using restriction fragment length polymorphism analysis, as described in our previous studies.[7,20,21]

Statistical Analysis

Data are presented as the percent frequency or mean (SD). The genotype distribution of SNP rs182455 and Hardy–Weinberg equilibrium were assessed using the chi-square test. One-way analysis of variance (ANOVA) was used to compare the mean state and trait anxiety scores between the 3 genotype groups. The independent sample *t*-test was used to compare the mean age between male and female participants, and state and trait anxiety scores between the 2 dominant-model genotype groups or 2 recessive-model genotype groups. The Statistical Package for the Social Sciences version 22.0 for Windows (IBM SPSS Corp.; Armonk, NY, USA) was used to perform the above statistical analyses. The level of statistical significance was set at $P < .05$.

Results

Hardy–Weinberg Equilibrium Results

The genotype counts and frequencies for SNP rs182455 in the overall sample are shown in Table 1. The numbers of CC, CT, and TT genotypes of the rs182455 polymorphism were 227 (40.0%), 263 (46.4%), and 77 (13.6%), respectively. The genotype distribution did not

Table 1. Effects of *Stmn1* Gene rs182455 Polymorphism on State-Trait Anxiety Inventory Scores

		Overall Sample (n = 567)			Males (n = 271)			Females (n = 296)		
Groups		n (%)	State Anxiety	Trait Anxiety	n (%)	State Anxiety	Trait Anxiety	n (%)	State Anxiety	Trait Anxiety
Genotype	CC	227 (40.0%)	38.04 (SD = 7.75)	38.72 (SD = 6.84)	109 (40.2%)	38.17 (SD = 6.80)	39.34 (SD = 6.39)	118 (39.9%)	37.92 (SD = 8.57)	38.14 (SD = 7.21)
	CT	263 (46.4%)	37.36 (SD = 8.28)	38.65 (SD = 6.82)	127 (46.9%)	37.03 (SD = 8.38)	38.61 (SD = 6.89)	136 (45.9%)	37.66 (SD = 8.20)	38.70 (SD = 6.78)
	TT	77 (13.6%)	37.78 (SD = 7.60)	39.44 (SD = 6.81)	35 (12.9%)	35.91 (SD = 6.56)	38.51 (SD = 5.12)	42 (14.2%)	39.33 (SD = 8.13)	40.21 (SD = 7.92)
	F		0.457	0.415		1.393	0.441		0.654	1.308
	P		.634	.660		.250	.644		.521	.272
Dominant model	CC	227 (40.0%)	38.04 (SD = 7.75)	38.72 (SD = 6.84)	109 (40.2%)	38.17 (SD = 6.80)	39.34 (SD = 6.39)	118 (39.9%)	37.92 (SD = 8.57)	38.14 (SD = 7.21)
	CT + TT	340 (60.0%)	37.45 (SD = 8.12)	38.83 (SD = 6.82)	162 (59.8%)	36.79 (SD = 8.02)	38.59 (SD = 6.54)	178 (60.1%)	38.06 (SD = 8.19)	39.06 (SD = 7.07)
	t		0.865	−0.195		1.481	0.938		−0.134	−1.078
	P		.388	.845		.140	.349		.894	.282
Recessive model	TT	77 (13.6%)	37.78 (SD = 7.60)	39.44 (SD = 6.81)	35 (12.9%)	35.91 (SD = 6.56)	38.51 (SD = 5.12)	42 (14.2%)	39.33 (SD = 8.13)	40.21 (SD = 7.92)
	CT + CC	490 (86.4%)	37.68 (SD = 8.04)	38.68 (SD = 6.82)	236 (87.1%)	37.56 (7.70)	38.94 (6.66)	254 (85.8%)	37.78 (SD = 8.36)	38.44 (SD = 6.98)
	t		0.106	0.906		−1.201	−0.367		1.118	1.496
	P		.916	.365		.231	.714		.265	.136

Data for state and trait anxiety are mean (SD) values.

deviate from the Hardy–Weinberg equilibrium ($\chi^2 = 0.004$, $P = .953$), and showed no statistical difference from those observed in a previous sample of 160 Asian individuals ($T = 0.344$, $\chi^2 = 0.621$, $P = .431$) and 102 East Asian individuals ($T = 0.382$, $\chi^2 = 0.159$, $P = .690$) (https://www.ncbi.nlm.nih.gov/snp/rs182455). Therefore, the sample in the present study can be considered representative of the general Chinese population.

Association Between *Stmn1* Polymorphism and Anxiety in the Overall Sample

The state and trait anxiety scores in the overall sample are presented in Table 1. There were no significant differences in either state or trait anxiety among the 3 rs182455 genotype groups ($F = 0.457$, 0.415, $P = .634$, .660). Then the 3 genotype groups were divided into 2 groups based on recessive and dominant models. There were still no significant differences between the 2 dominant model groups ($t = 0.865$, −0.195, $P = .388$, .845), or between the 2 recessive model groups ($t = 0.106$, 0.906, $P = .916$, .365).

Association of *Stmn1* Polymorphism with Anxiety in Male and Female Samples

Subsequently, differences in state anxiety and trait anxiety scores were analyzed separately by sex among the rs182455 genotype groups, between the 2 dominant model groups and between the 2 recessive model groups (Table 1). No significant gender-specific differences in any STAI scores were found among the 3 genotype groups, between the 2 dominant model groups, or between the 2 recessive model groups (all $P > .05$).

Discussion

The present study investigated the association between *Stmn1* gene polymorphism and anxiety level assessed by STAI in a healthy Han Chinese sample. The results indicated no significant associations of the genotype, dominant model, or recessive model of the rs182455 polymorphism with the state or trait anxiety score of STAI in the overall sample and 2 subgroups of different genders.

Stathmin 1, also known as p17, p18, p19, 19k, metablastin, oncoprotein 18, LAP 18, and Op 18, is a 19 kDa cytosolic protein composed of 149 amino acids organized into 4 domains (I-IV) as defined by limited proteolysis.[22-24] Microtubule are protein polymers comprised of α/β tubulin heterodimers that contribute to and are essential for the structure and function of the cell. The functions include intracellular transport, cell motility, cell polarity, cell proliferation, neurite branch growth, and synaptic plasticity.[14,23,25,26] Unphosphorylated or hypophosphorylated *Stmn1* interacts with tubulin heterodimers and prevents them from forming MTs.[27] After phosphorylation, *Stmn1* releases tubulin, allowing MT formation.[25] That is to say, *Stmn1* is involved in MT dynamics by regulating both the formation of MTs and their disassembly, so it has a role in neural functions. Previous studies have thus investigated the relationship between *Stmn1* and some neural functions in experimental animals and humans.

Stathmin 1 was called a fear memory-related gene since it has been demonstrated to be closely related to fear level and memory in both animals and humans. Some animal experiments have demonstrated that Stmin1 is involved in fear processing in mice[10,13,15] and dogs.[16] However, the number of experimental studies on the association of the *Stmn1* gene with anxiety and fear in humans is limited. In 2010, Broke et al[18] used the acoustic startle paradigm and a standardized laboratory protocol for the induction of fear and psychosocial stress in 113 healthy German volunteers to investigate the impact of *Stmn1* gene polymorphisms (rs182455 and rs213641) on 2 fear- and anxiety-controlling effector-systems of the amygdala and found that *Stmn1* genotype interacting with individuals' gender significantly impacts fear and anxiety responses and cortisol stress response. In 2011,

Ehlis et al[9] used 3 experimental paradigms probing different aspects of cognitive-affective function in 59 healthy German volunteers to investigate the impact of *Stmn1* gene polymorphism rs182455 on executive functions and fear processing and found that carriers of the rs182455 C-allele showed altered cognitive-affective processing, which was more pronounced in females.

The results of the above 2 studies indicated that the *Stmn1* genotype has functional relevance for the acquisition and expression of basic fear and anxiety responses and cognitive-affective processing in healthy individuals, and such association was women specific. These 2 studies were precedents for investigating the influence of *Stmn1* gene polymorphisms on anxiety in humans and laid an empirical research foundation for further studies, including ours. However, they have 1 limitation in common, and that is the sample size is quite small for genetic association studies. The sample sizes are 113[18] and 59,[9] respectively. In the "Participants" section of this article, we have addressed the calculation of the sample size of our study, and the estimated sample size of G*Power is 210 or 252. Obviously, the sample sizes of both previous studies are much smaller than the estimated sample size, which can easily lead to sample bias and false positive rate (type I error), and increase the experimental effect of predictors. Therefore, the conclusions of the inherent risk in *Stmn1* genetic association studies using small size samples should be taken with caution. The present study thus uses a large sample of healthy Chinese people to minimize sample bias.

In the present study, we found no evidence for the possible association of the *Stmn1* gene SNP rs182455 with either trait or state anxiety dimensions in the total sample and 2 subgroups of different genders. Both the present study and the 2 previous studies[9,18] took samples of healthy adults. The main reason for the inconsistency might be the difference in sample size. The sample size of our study is sufficient to reduce the occurrence of false positives. Other reasons for the inconsistency might include differences in sample race, assessment tools, and study variables. The samples of the 2 previous studies were both Germans belonging to Caucasian ethnicity, while the sample of the present study was Han Chinese belonging to the Mongolian race. Race difference may explain the inconsistency of the results to some extent, as previous studies have found that different races have different influences on physical and psychological disorders or symptoms in associative gene studies.[20,28,29] On the other hand, the STAI, a self-reporting scale, was used to measure the state and trait anxiety levels in the present study, while the acoustic startle paradigm and a standardized laboratory protocol for the induction of fear and psychosocial stress were used in Brocke's study,[18] and 3 experimental paradigms probing different aspects of cognitive-affective function were used in Ehlis's study.[9]

It is well-known that pathologic anxiety is a complex disorder which includes phobic anxiety, generalized anxiety, panic, obsessive-compulsive, PTSD, and so on. In 2013, Cao et al examined the association between *Stmn1* rs182455 genotype and PTSD symptoms measured with the PTSD Checklist in 326 Chinese adults who suffered from a deadly 2008 Wenchuan earthquake and unexpectedly lost their children during the disaster and found that the *Stmn1* rs182455 genotype was not associated with severity of total PTSD symptoms in either females or males while it could significantly predict severity of PTSD's reexperiencing symptoms in females.[30] The result of this study indicated that the *Stmn1* genotype has a role in the development of PTSD.

Although the subjects of the present study and Cao's study were all Chinese, the results were not consistent. The reasons for the inconsistency might include differences in sample characteristics and study variables. The present study took a sample of 567 healthy Chinese adults, while Cao's study took a sample of 326 Chinese adults who suffered from a deadly 2008 Wenchuan earthquake and unexpectedly lost their children, which meant that they might be suspected PTSD patients. Moreover, the present study used the 40-item symptom STAI to measure state and trait anxiety levels, while Cao's study used the 17-item PTSD Checklist to assess PTSD symptoms.

In this study, we investigated the possible association between the *Stmn1* gene polymorphism rs182455 and both trait and state anxiety dimensions in healthy Han Chinese subjects for the first time. The results provided no evidence for the assumed association and contributed to the accumulation of evidence on the candidate gene for anxiety. The limitations of the present study should be fully considered when applying the findings in the future. First, although STAI is commonly used, the drawbacks of STAI, a self-rating scale used to evaluate anxiety symptoms, are obvious. When the subjects think about the questions of a self-rating scale, their answers are inevitably subjective, which is affected by the individual mental state, cognitive function, self-protection mechanism, and so on. The assessed anxiety levels may thus be exaggerated or reduced. Second, the studied SNP in the present research was only *Stmn1* polymorphism rs182455 and the sample included only Han Chinese. Third, the effect of gene–environment interaction was not studied in the present study. All of these limitations could increase the potential possibility of false negatives in the present study (type II error). Further studies with adequate sample sizes in other ethnic populations, or with additional SNPs of *Stmn1*, or by other methods to measure anxiety, or by investigating the interaction of gene and environment are necessary to confirm or refute the lack of association between the *Stmn1* gene and anxiety.

Availability of Data and Materials: *The raw data supporting the results and conclusions of this article are available upon request.*

Ethics Committee Approval: *This study was approved by the Ethics Committee of Hainan Provincial Anning Hospital (Approval No: 202206; Date: November 10, 2022).*

Informed Consent: *Informed consent was obtained from all participants who agreed to take part in the study.*

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Declaration of Interests: *The authors have no conflicts of interest to declare.*

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