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Genetic variations in the serotoninergic system and environmental factors contribute to aggressive behavior in Chinese adolescents

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HIGHLIGHTS

- With 478 healthy Chinese, we found that 12 serotonin-related SNPs were associated with aggression.
- *HTR2C* interacts with *HTR5A* as well as stressful life event on aggression.
- Gene, environment and their interactions together accounted for 1/5 of aggression variation.

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ABSTRACT

Aggressive behavior is a major public health problem worldwide and has been associated with many gene variants, especially those related to the serotonin (5-hydroxytryptamine, 5-HT) system, and environmental factors. However, the overall contribution of serotonin-related genes to aggressive behavior is not well understood. With a sample of 478 healthy Chinese volunteers, this study investigated the relation between aggressive behavior and genetic variations of the serotoninergic system (as characterized by 129 representative polymorphisms) interacting with environmental factors (parental warmth and acceptance; stressful life events). We adopted a system-level approach to identify SNPs and environmental factors associated with aggressive behavior, and estimated their overall contribution to aggressive behavior using multiple regression, which was then verified by permutation analysis. We identified 12 SNPs that made statistically significant contributions to aggressive behavior. Next, main effects, interactions among these SNPs, and interactions between these SNPs and environmental factors were assessed using multiple regression. The final model accounted for approximately 19% of the variance for aggressive behavior. Permutation analysis confirmed that the probability of obtaining these findings by chance was low ($p = 0.045$, permuted for 1000 times). These results showed that genetic variations in the serotoninergic system, combined with environmental risk factors, made a moderate contribution to individual differences in aggressive behavior among a healthy population sample.

1. Introduction

According to the World Health Organization [1], the number of people dying in interpersonal conflicts was almost twice the number of war victims in 2002 and aggressive behavior has been increasingly viewed as a public health issue. Identifying environmental and genetic risk factors is an important first step in preventing violence and has been the focus of decades of research.

Behavior genetic studies estimated the heritability of aggressive behavior to be about 50% [2,3]. Recent molecular genetic studies revealed that many genes are associated with aggression, including: (1) sex steroid-related genes; (2) serotonin- (5-HT) related genes; (3) dopamine-related genes; and (4) a variety of other genes (for reviews, see [4–7]). Of all these genes, serotonin-related genes were the most commonly studied [6,8,9], although the results have been inconsistent. Generally speaking, genotypes associated with lower levels

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or activity of serotonin or its metabolites were associated with increased levels of aggressive behavior and impulsivity [7,8], but exceptions were also often reported.

Tryptophan hydroxylase (TPH) is the rate-limiting enzyme for brain serotonin synthesis. *TPH1* and *TPH2* genes have been linked to impulsivity, aggressive behavior, and suicide [4,8]. MAOA and MAOB are enzymes that degrade serotonin and other neurotransmitters, and the *MAOA* gene was once called the "warrior gene". However, some studies found that low MAOA activity (thus high serotonin level) was associated with low aggression [10], but others reported no association [11,12] or reversed association [13]. The serotonin transporter pumps serotonin from the synaptic cleft back to presynaptic neurons. Knocking out the serotonin transporter gene in mice (thus increasing serotonin level in the synaptic cleft) resulted in reduced aggressive behavior [14]. The S allele of the well-studied *5HTTLPR* polymorphism (resulting in higher levels of serotonin) was also reported to be associated with decreased aggressive behavior [15], but others reported increased aggressive behavior [16–18]. For serotonin receptor genes, *5-HT1A*/*1B* receptors were extensively studied, with positive results in some studies [19–21], but negative results in others [22–25].

There may be several reasons for these inconsistencies. One most likely reason is polygenicity. All these genes mentioned above, as well as other genes, may contribute to aggressive behavior, each with a small individual effect. As early as 1918, Fisher proposed this polygenic model that combined many genes of small effects to yield the continuous variation for most quantitative traits [26]. Recently, some studies have successfully applied the polygenic model by combining effects from alleles throughout the whole genome [27] or effects of genes within a biochemical pathway [28,29]. Since the serotonin-related genes exert their effects at different stages of the serotonin pathway, their effects may be cumulative and/or interactive [30]. Another possible reason is that environmental factors are likely to make direct contributions to behavioral phenotypes, or interact with genetic factors [5,31]. Finally, other differences between studies such as subject characteristics (age, gender, health, ethnicity, sample size) and behavioral measures (verbal or physical aggression, suicide, antisocial behavior, etc.) may also have contributed to the inconsistencies in the literature on gene-aggression association.

The current study adopted a system-level approach to examine the role of the serotoninergic system and environmental factors as well as their interaction in aggressive behavior in a relatively homogenous sample (in terms of age, health status, and ethnicity). To do this, we enrolled a sample of young healthy Han Chinese college students, genotyped 129 polymorphic loci within the serotonin system, and assessed relevant environmental factors and aggressive behavior. Because gender has been found to be a potential confounding factor [32], we included it as a covariate.

2. Materials and methods

2.1. Participants

Four hundred and eighty healthy Chinese college students (mean age = 19.9 years, SD = 0.9) were recruited from Beijing Normal University, Beijing, China. They had normal or corrected-to-normal vision, and had no history of neurological or psychiatric problems according to self-report. None of them were identified to have alcohol or nicotine dependence according to the Alcohol Use Disorders Identification Test [33] and the Fagerström Test for Nicotine Dependence [34]. Two participants were excluded because of poor genotyping results. A written consent form was obtained from each subject after a full explanation of the study procedure. This study was approved by the IRB of the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University, China.

2.2. Behavioral measurements

2.2.1. Aggression Questionnaire

Aggression Questionnaire (AQ) [35] is a 34-item scale that measures aggression in five aspects: physical aggression, verbal aggression, anger, hostility, and indirect aggression. Sample items include "at times I feel like a bomb ready to explode" and "I may hit someone if he or she provokes me". Participants rated each item on a 5-point scale, 1 = "Disagree strongly" to 5 = "Agree strongly". The total score of all items was used for analysis.

2.2.2. Parental Warmth and Acceptance Scale

Parental Warmth and Acceptance Scale (PWAS) [36] measures perceived parental warmth with 11 items, such as "My parents really understand me" and "My parents like me the way I am; they don't try to 'make me over' into someone else". Participants rated each item on a 6-point scale, 1 = "Disagree strongly" to 6 = "Agree strongly". The total score of all items was used for analysis.

2.2.3. Stressful life events

This scale was adapted from similar measures used in Wills, Vaccaro, and McNamara [37]. The scale has been used with cross-cultural samples including Chinese [36]. It lists 24 possible stressful events such as the death of a relative, not passing an examination, and parents getting divorced. Participants in this study had to indicate whether they experienced each event or not during early childhood (primary school years), early adolescence (secondary school years), and within the past two years (i.e., college years for this sample of college sophomores). The stressful events were counted separately for the three periods. The total score of the stressful life events in three periods was used for analysis.

All scales were translated from English to Chinese by a team consisting of Chinese–English bilinguals and native English and Chinese speakers and double-checked with forward and backward translation. All scales had good reliability (Table 1) in this study. Reliability (or internal consistency) for stressful life events was not calculated because stressful life events are assumed to be relatively independent of one another, with no underlying latent factors, and only its cumulative effects are evident.

2.3. Genetic analysis

2.3.1. Gene selection

We selected 129 polymorphisms (127 SNPs and 2 VNTR polymorphisms) in the 24 known major genes distributed across the synthesis, degradation, transporter, and receptor subsystems of the 5-HT system. Tryptophan hydroxylase (TPH) is the main enzyme involved in 5-HT synthesis, so we included two TPH genes (*TPH1* and *TPH2*, with three SNPs each). For the degradation subsystem, released 5-HT is directly broken down at the synapse into inactive metabolites by MAO (including MAOA and MAOB). We included monoamine oxidase genes (*MAOA*, with 5 SNPs and 1 VNTR, and *MAOB* with 3 SNPs). The 5-HT transporter

Table 1
Means, standard deviations, Cronbach's alpha coefficients, and inter-scale correlations.

	Mean (SD)	Cronbach's alpha	Correlations	
			AQ	Parental warmth
Aggression Questionnaire (AQ)	68.57 (15.75)	0.855		
Parental warmth	53.00 (7.49)	0.827	−0.17*	
Stressful life events	9.72 (5.08)	–	0.29*	−0.17*

* $p < 0.01$.