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SHORT COMMUNICATION

Influence of *HTR2A* polymorphisms and parental rearing on personality traits in healthy Japanese subjects

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Genetic factors and environmental influences contribute to the determination of human personality traits. This study examined the influence of serotonin receptor 2A polymorphisms and parental rearing on temperament. Subjects included 1245 Japanese volunteers (592 males and 653 females). Three single-nucleotide polymorphisms (SNPs) (rs6311, rs6313 and rs643627) were selected for genotyping. All subjects completed the 125-item Japanese short version of the temperament and character inventory, and 572 completed the Japanese version of the Parental Bonding Instrument. All SNPs were in Hardy–Weinberg equilibrium. A significant association (P=0.0026) was observed between rs643627 and novelty seeking in females. On the other hand, significant effects of maternal overprotection to harm avoidance (HA) were seen for rs6311 (P=0.0005), rs6313 (P=0.0004) and rs643627 (P=0.0003) in males only. In terms of the interaction of genotype and maternal overprotection with HA, interaction was observed in rs6311 (P=0.0290) and rs6313 (P=0.0230) in females only. Our results indicate a relationship between the rs643627 polymorphism and novelty seeking in females. In terms of serotonin receptor 2A gene polymorphisms and maternal overprotection, our findings suggest the existence of a gene–environmental interaction that influences HA.
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INTRODUCTION

Serotonergic (*5-HT*) genes have been implicated in personality traits or temperament predisposition.[1] Among 5-HT candidates, serotonin receptor 2A (*HTR2A*) has received considerable attention. *HTR2A* is located on chromosome 13 (13q14-21), spans approximately 63 kb and consists of three exons interrupted by two introns.[2,3] Furthermore, molecules have an important role in cognitive function,[4] anxiety[5] and personality traits.[6]

The Temperament and Character Inventory (TCI), a self-rating scale that measures four dimensions of temperament (novelty seeking (NS), harm avoidance (HA), reward dependence (RD) and persistence (P)) and three dimensions of character (self-directedness (SD), cooperativeness (C) and self-transcendence (ST)) was developed by Cloninger *et al.*[7] HA was originally postulated to be influenced by the serotonergic system.[8] Several studies have examined the effects of parental rearing on personality traits using the Parental Bonding Instrument (PBI) developed by Parker *et al.*[9] and the TCI. They showed that parental rearing affects both temperament and character dimensions, particularly HA.[10,11] The primary aim of this study was to evaluate the influence of possible functional variants within *HTR2A* on the temperament of healthy Japanese subjects. The secondary aim was to examine the combined effect of parental rearing and possible functional variants within *HTR2A* on HA.

MATERIALS AND METHODS

Subjects were 1245 healthy Japanese volunteers (592 males and 653 females). The mean age was 27.8 ± 12.4 years. Subjects who had current or past psychiatric disorders were excluded based on brief unstructured interviews.

The total sample was used in genotyping of single-nucleotide polymorphisms (SNPs). A total of 1245 subjects completed the 125-item short version of the TCI. The abbreviated version of the questionnaire has been shown to be highly reliable.[12] In addition, 572 subjects (346 males and 226 females) completed the Japanese version of the PBI. It has been shown to be highly reliable.[13] The study was approved by the Ethics Committee of Nagoya University School of Medicine, Hirosaki University School of Medicine and Keio University School of Medicine.

Several studies have implicated four SNPs (rs6311, rs6313, rs594242 and rs643627) of *HTR2A* that may modulate personality traits.[2] However, as the minor allele frequency of rs594242 is very low in the Japanese population, three

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Table 1 Temperament and Character dimensions stratified for *HTR2A* genotypes

Male subjects (N=*592*)	*TCI scores, mean* ± *s.d.*			*One-way ANOVA*	
rs6311	*A/A* (N=*138*)	*A/G* (N=*322*)	*G/G* (N=*137*)	*F*	P-*value*
Novelty seeking	10.1 ± 3.2	10.3 ± 3.4	10.3 ± 3.3	0.175	0.8394
Harm avoidance	11.6 ± 4.2	11.2 ± 4.4	11.8 ± 4.6	0.974	0.3783
Reward dependence	9.8 ± 2.3	9.5 ± 2.7	10.0 ± 2.3	2.040	0.1310
Persistence	2.5 ± 1.5	2.5 ± 1.5	2.6 ± 1.6	0.173	0.8408
Self-directedness	16.0 ± 4.8	16.0 ± 5.0	16.0 ± 4.7	0.012	0.9879
Cooperativeness	17.8 ± 3.4	17.3 ± 3.4	17.2 ± 3.4	1.240	0.2903
Self-trascendence	3.5 ± 2.9	3.6 ± 2.9	3.4 ± 2.7	0.188	0.8286
rs6313	*T/T* (N=*139*)	*C/T* (N=*319*)	*C/C* (N=*137*)	*F*	P-*value*
Novelty seeking	10.0 ± 3.3	10.3 ± 3.4	10.3 ± 3.3	0.368	0.6923
Harm avoidance	11.6 ± 4.2	11.2 ± 4.4	11.8 ± 4.6	1.115	0.3288
Reward dependence	9.8 ± 2.3	9.5 ± 2.7	10.0 ± 2.3	2.312	0.1000
Persistence	2.5 ± 1.5	2.6 ± 1.5	2.6 ± 1.6	0.144	0.8663
Self-directedness	16.0 ± 4.8	16.0 ± 4.9	16.0 ± 4.6	0.001	0.9987
Cooperativeness	17.8 ± 3.4	17.3 ± 3.4	17.2 ± 3.4	1.343	0.2619
Self-trascendence	3.5 ± 2.9	3.6 ± 3.0	3.4 ± 2.7	0.216	0.8059
rs643627	*A/A* (N=*139*)	*A/G* (N=*312*)	*G/G* (N=*143*)	*F*	P-*value*
Novelty seeking	10.0 ± 3.3	10.1 ± 3.4	10.7 ± 3.2	2.187	0.1132
Harm avoidance	11.5 ± 4.4	11.4 ± 4.3	11.5 ± 4.7	0.090	0.9141
Reward dependence	9.5 ± 2.5	9.6 ± 2.5	10.1 ± 2.5	2.572	0.0772
Persistence	2.5 ± 1.5	2.6 ± 1.5	2.7 ± 1.5	0.700	0.4970
Self-directedness	16.0 ± 5.0	16.2 ± 4.6	15.4 ± 5.2	1.327	0.2662
Cooperativeness	17.2 ± 3.5	17.5 ± 3.3	17.4 ± 3.7	0.424	0.6548
Self-trascendence	3.7 ± 3.0	3.4 ± 2.8	3.5 ± 2.7	0.695	0.4993
Female subjects (N=*653*)	*TCI scores, mean* ± *s.d.*			*One-way ANOVA*	
rs6311	*A/A* (N=*169*)	*A/G* (N=*310*)	*G/G* (N=*167*)	*F*	P-*value*
Novelty seeking	10.0 ± 3.3	10.1 ± 3.3	10.7 ± 3.2	2.187	0.1132
Harm avoidance	11.3 ± 4.1	11.5 ± 4.2	11.6 ± 4.3	0.151	0.8603
Reward dependence	10.5 ± 2.5	11 ± 2.5	10.6 ± 2.4	2.447	0.0873
Persistence	2.5 ± 1.4	2.5 ± 1.6	2.6 ± 1.5	0.443	0.6421
Self-directedness	15.7 ± 4.6	15.8 ± 4.5	15.4 ± 4.3	0.446	0.6278
Cooperativeness	18.2 ± 3.5	18.7 ± 3.1	17.9 ± 3.1	3.976	0.0192
Self-trascendence	4.2 ± 2.9	4.5 ± 2.9	4.8 ± 3.2	1.490	0.2261
rs6313	*T/T* (N=*168*)	*C/T* (N=*312*)	*C/C* (N=*168*)	*F*	P-*value*
Novelty seeking	9.9 ± 3.7	9.7 ± 3.6	9.9 ± 3.6	0.100	0.9049
Harm avoidance	11.3 ± 4.0	11.5 ± 4.2	11.5 ± 4.3	0.131	0.8769
Reward dependence	10.5 ± 2.5	11 ± 2.4	10.6 ± 2.4	2.775	0.0631
Persistence	2.5 ± 1.4	2.5 ± 1.6	2.7 ± 1.5	0.601	0.5488
Self-directedness	15.7 ± 4.6	15.9 ± 4.5	15.4 ± 4.4	0.524	0.5924
Cooperativeness	18.2 ± 3.5	18.8 ± 3.1	17.9 ± 3.2	4.716	0.0097
Self-trascendence	4.2 ± 2.9	4.5 ± 2.9	4.8 ± 3.2	1.487	0.2269
rs643627	*A/A* (N=*164*)	*A/G* (N=*336*)	*G/G* (N=*150*)	*F*	P-*value*
Novelty seeking	10.4 ± 3.7	9.8 ± 3.6	9.0 ± 3.5	5.995	0.0026*
Harm avoidance	11.0 ± 4.1	11.3 ± 4.3	12.3 ± 3.9	4.123	0.0166
Reward dependence	10.8 ± 2.5	10.8 ± 2.4	10.6 ± 2.5	0.243	0.7842
Persistence	2.6 ± 1.6	2.5 ± 1.5	2.5 ± 1.5	0.041	0.9597
Self-directedness	15.9 ± 4.3	15.7 ± 4.4	15.6 ± 4.9	0.183	0.8326
Cooperativeness	18.5 ± 3.3	18.4 ± 3.4	18.3 ± 2.8	0.109	0.8967
Self-trascendence	4.6 ± 3.0	4.6 ± 3.1	4.2 ± 2.8	1.123	0.3258

Abbreviations: ANOVA, analysis of variance; TCI, Temperament and Character Inventory.
*$P<0.007$.

SNPs (rs6311, rs6313 and rs643627) were selected for genotyping. These SNPs cover about two-thirds of the *HTR2A*.

The distribution of genotypes was tested for Hardy–Weinberg equilibrium using the chi-square goodness-of-fit test. Associations between TCI scores and the *HTR2A* gene polymorphisms were assessed by one-way analysis of variance. With regard to the relationship between temperament and specific gene polymorphisms, different results have been obtained in male and female subjects.[14,15] Therefore, we analyzed the TCI score when the subjects were stratified by gender. Two-way analysis of variance was used to evaluate the effects of the PBI score for maternal overprotection and genotype on HA score. For the maternal overprotection score, a score equal to or lower than the median was defined as low overprotection, whereas factor scores above the median were defined as high overprotection. All *P*-values were two-tailed, and Bonferroni correction was used to control for multiple comparisons.

RESULTS

All SNPs were in Hardy–Weinberg equilibrium. The *post-hoc* analyses revealed that the statistical power for this study was 0.80 for detecting a small effect (Cohen's criteria f=0.1) in case of TCI analysis, whereas the power exceeded 0.70 for the detection of a small effect size in case of PBI analysis.

A significant association was detected between rs643627 and NS in females (P=0.0026, Table 1). This result was still positive after the Bonferroni correction (seven independent TCI dimensions). *Post-hoc* analysis revealed that the number of individuals in the AA group was significantly higher in comparison with the GG group (P=0.0006).

Two-way analysis of variance showed that significant main effects of maternal overprotection on HA in males were seen for rs6311 (P=0.0005, Figure 1), rs6313 (P=0.0004, Figure 2) and rs643627 (P=0.0003), and these results were positive after the Bonferroni correction (seven independent TCI dimensions and PBI category). There were no significant main effects of genotypes to HA in both male and female subjects. Regarding the interaction of genotype and maternal overprotection with HA, a significant interaction was observed in rs6311 (P=0.0290, Figure 1) and rs6313 (P=0.0230, Figure 2) in females only. However, these results were not positive after the Bonferroni correction (seven independent TCI dimensions plus PBI category).

DISCUSSION

Our results provided statistical evidence for the association between rs643627 and NS only in females. Comings *et al.*[16] showed that variance of NS can be better explained by SNPs related to *5-HT* genes than by SNPs related to the dopaminergic system. Our result showed the same tendency. Several recent animal and human studies have suggested that sex hormones modulate the serotonergic system.[17,18] The *HTR2A* gene might have a different effect on gender-related temperament through sex hormone mediation.

Several studies have reported that HA was assumed to be influenced by parental overprotection.[10,11] In our research, maternal overprotection was associated with significantly higher HA scores in males, which shows that, for male subjects, maternal overprotection exerts a greater influence on HA score than genotype. This is in accordance with the study of Oshino *et al.*,[11] who concluded that the effects of genetic polymorphisms on personality traits might be nullified by parental rearing in males.

Jokela *et al.*[19] reported that the TT group of rs6313 showed a high HA score in high-stress environment. It shows the same tendency as our result. In this study, in the high-overprotection group (high stress level), the HA score of the TT group was high. We could suppose that the T allele of rs6313 receives the influence of the environment directly.

Several caveats should be noted regarding the interpretation of our results. First, the parental rearing assessed in this study may be a distorted perception of recipients, colored by their adult personality. However, this possibility is low, as Parker[20] showed that the PBI score reflects the actual parenting assessed by significant others with acceptable validity. Second, we used brief diagnostic unstructured interviews to screen for the psychiatric conditions of subjects.

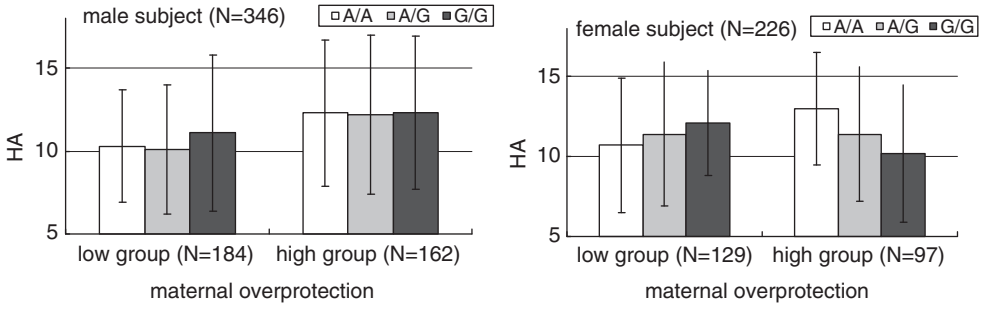

Figure 1 Harm avoidance (mean ± s.d.) by rs6311 and maternal overprotection group.

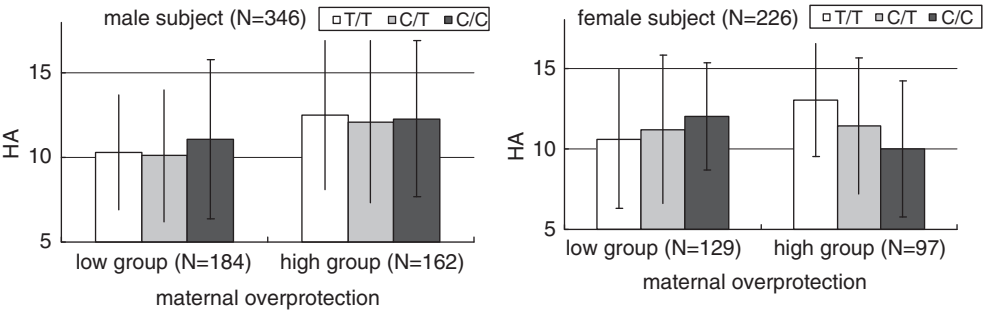

Figure 2 Harm avoidance (mean ± s.d.) by rs6313 and maternal overprotection group.

The result of this study suggests that *HTR2A* gene, parental rearing and the gene–environment interaction are factors that significantly influence the development of temperament. Further research regarding parental rearing as an environmental factor is needed for obtaining conclusive results regarding temperament development.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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