



Mu-Opioid Receptor Polymorphism Moderates Sensitivity to Parental Behaviors During Characterization of Personality Traits

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Purpose: Attachment research shows that attachment experiences with parents in childhood influence the characterization of personality traits. Meanwhile, it is known that mu-opioid receptor function is involved in human attachment. Furthermore, a few studies suggest that the A118G polymorphism of the mu-opioid receptor gene (*OPRM1*) is associated with altered mu-opioid receptor function. Thus, we examined if the *OPRM1* polymorphism moderates the sensitivity to parental behaviors and thereby contributes to the characterization of personality traits.

Materials and Methods: Participants were 725 healthy Japanese. Parenting practices of their parents were evaluated by the Parental Bonding Instrument (PBI) with the care and protection subscales. Personality was evaluated using the Temperament and Character Inventory (TCI). The *OPRM1* A118G polymorphism was detected by a PCR method.

Results: Multiple regression analyses revealed significant effects of the interaction between the *OPRM1* genotype and maternal protection on scores of the self-directedness and cooperativeness dimensions, while significant main effects of the *OPRM1* genotype on scores of the TCI were not found. Further analyses showed that there were significant negative correlations between maternal protection scores and the two dimensional scores in the A/A and A/G genotypes with higher correlation coefficients in the former, but not in the G/G genotype.

Conclusion: The present study suggests that the *OPRM1* polymorphism contributes to the characterization of personality traits by moderating the sensitivity to parental behaviors, especially maternal protection.

Keywords: *OPRM1*, attachment, personality, PBI, TCI, gene–environment interaction

Introduction

The attachment theory by Bowlby¹ suggests that to obtain felt security a child instinctively displays attachment behaviors such as crying, clinging, and following, which result in attaining proximity to a parent figure. When the parent figure reacts and supplies care, the child starts to explore the surrounding while being watched affectionately by the parent figure. Thus, to provide a secure base and to encourage a child to explore from that base are important roles of parents.¹ This attachment relationship may be observed in altered intensity and forms with significant others throughout life. A child who experienced the relationship of favorable attachment mentioned above tends to grow up to be self-reliant, secure, and co-operative. Conversely, a child who experienced lack of care and overprotection by parents

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tends to grow up to be over-dependent, insecure, and anxious, and is prone to develop depression or anxiety disorders in stressful situations. Within this framework of attachment theory, Parker et al² suggested the Parental Bonding Instrument (PBI) to evaluate parenting practices individuals received in childhood. Subsequent studies show that parental rearing evaluated by the PBI is related to psychiatric disorders such as major depression, obsessive-compulsive disorder, and eating disorders.^{3–7} With regard to other aspects, our studies suggest that anomalous parenting as assessed by the PBI is associated with some personality dimensions of the Temperament and Character Inventory (TCI) and the NEO Personality Inventory.^{8,9} These empirical studies suggest a close connection between human attachment and the characterization of personality, supporting Bowlby's¹ attachment theory with practical data.

The brain opioid theory of social attachment posits that brain opioids are deeply implicated in the elaboration of social bonding processes including infant–mother attachment in mammals.¹⁰ This theory is supported by many animal experiments, eg, exogenous opiates reduce distress vocalizations of socially isolated puppies, and mouse pups lacking the mu-opioid receptor gene (*OPRM1*) display deficits in attachment behaviors toward mothers.^{11,12} Furthermore, a human study using positron emission tomography with [¹¹C] carfentanil, a selective ligand to mu-opioid receptor, shows that low mu-opioid receptor availability is correlated with attachment avoidance characterized by reduced attachment emotions and behaviors.^{13,14} These studies suggest that mu-opioid receptor function is involved in human attachment, eg, occurrence of attachment behaviors and emotional responses to attachment experiences.

The A118G polymorphism in the exon 1 of the *OPRM1* (rs1799971) results in an Asn40Asp amino acid exchange at the putative glycosylation site in the extracellular terminus.¹⁵ It is reported that the cell culture systems expressing the G allele of this polymorphism have lower levels of forskolin-induced cAMP activation, agonist-induced receptor activation, and surface receptor expression.¹⁶ In human autopsy brain tissues, the G allele is associated with 1.5-fold lower levels of mRNA and 10-fold lower levels of protein of mu-opioid receptor compared to the A allele.¹⁷ In studies using positron emission tomography, participants with the G allele show a reduction of baseline mu-opioid receptor availability compared to those homozygous for the A allele.^{18,19} Furthermore,

Cimino et al²⁰ recently showed that the G allele is associated with an insecure attachment style in children with or without disruptive mood regulation disorder.

The discussions so far may suggest that the A118G polymorphism of the *OPRM1* is involved in human attachment and plays some roles in the characterization of personality. To date, association studies between the *OPRM1* A118G polymorphism and personality yielded negative results.^{21,22} However, these studies did not take gene–environment interaction(s) into account, and their negative results may be ascribable to this deficit. In fact, we previously reported that the interaction between the *BDNF* Val66Met genotype and parental rearing influenced formation of some personality traits, though this genotype per se did not show such effects.^{23,24}

Therefore, the purpose of this study was to test the hypothesis that the *OPRM1* A118G polymorphism moderates the sensitivity to parental behaviors during childhood and thereby contributes to the characterization of personality traits as assessed by the TCI.

Materials and Methods

Participants

Originally, 818 participants were enrolled in the study. They were recruited from medical students or staff in Yamagata University Hospital and its affiliated hospitals by KN, AS, TS, NT, and KO. Criteria of exclusion were 1) serious physical illnesses as clarified by a self-report checklist, 2) current or past history of psychiatric disorders of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, as clarified by the psychiatric screening previously described,^{4,25} and 3) parental divorce or death before the age of 16. The DSM-IV was used in this study, since the DSM-5 was not yet available in 2009 when the enrollment started. Eight participants had serious physical illnesses, 39 had psychiatric disorders, 14 had parents divorced or deceased, and 24 had missing data. In eight participants, DNA extraction or PCR amplification was failed. The remaining 725 cases were used for statistical analyses. Four hundred and twenty-three were males and 302 were females. The mean age±SD was 26.7±7.9 years. This study was conducted in accordance with the Declaration of Helsinki, and received the approval of the Ethics Committee of Yamagata University School of Medicine (approval no. 31/26.12.2002). Written informed consent was obtained from all participants.

Assessment of Parental Behaviors

Parenting practices of the participants' parents during the first 16 years were evaluated by the Japanese version of the PBI, which has high reliability and validity.²⁶ The PBI has the care subscale in which a high score shows involvement and care and a low score shows rejection and indifference, and the protection subscale in which a high score means intrusion, control, and overprotection and a low score means encouragement of autonomy and independence. Cronbach's alphas in the present study were 0.925 for the paternal care, 0.851 for the paternal protection, 0.892 for the maternal care, and 0.874 for the maternal protection.

Assessment of Personality Traits

Personality traits were evaluated using the Japanese version of the Temperament and Character Inventory (TCI),²⁷ which has high internal consistency and construct validity. The TCI is a self-report scale based on psychobiological theory of personality.⁸ This theory suggests that personality is composed of two factors, ie, temperament and character. Temperament represents automatic responses to emotional stimuli, and is moderately heritable. Character represents self-concepts about goals and values, and is moderately influenced by sociocultural learning. Temperament has four dimensions, ie, novelty seeking, harm avoidance, reward dependence, and persistence. Novelty seeking is the exploratory activity and intense excitement in response to novel stimuli, harm avoidance is the inhibition of behavior in response to aversive stimuli or no reward, reward dependence is the maintenance of behavior in response to reward and succorance, and persistence is the perseveration with behavior despite frustration and fatigue. Character has three dimensions, ie, self-directedness, cooperativeness, and self-transcendence. Self-directedness is the concept of the self as an autonomous individual, cooperativeness is the concept of the self as an integral part of humanity or society, and self-transcendence is the concept of the self as an integral part of a unified whole. In the present participants, Cronbach's alphas for the novelty seeking, harm avoidance, reward dependence, persistence, self-directedness, cooperativeness, and self-transcendence were 0.719, 0.838, 0.694, 0.524, 0.798, 0.797, and 0.782, respectively.

Analysis of Genotyping

DNA was extracted from peripheral blood using a QIAamp DNA Blood Kit (Qiagen, Tokyo, Japan). The

OPRM1 A118G polymorphism was determined by a real time PCR and cycling probe technology for SNP typing (Takara Bio Inc, Otsu, Japan). The primers and probes were 5'-gTC AgT ACC ATg gAC AgC Ag -3' (forward primer), 5'- TgA CAA TCA CAT ACA TgA CCA g -3' (reverse primer), 5' -Tgg CAA CCT -(FAM) 3', and 5' -Tgg CgA CC -(ROX) 3', respectively, where underlined letters in the probes indicate the RNA. The amplification and detection were performed along the standard protocol of the manufacturer's instruction (Takara Bio Inc, Otsu, Japan). After the completion of the assessments of the PBI and TCI, KN, TS, and YM, who were blind to these data, performed genotyping analyses at the Department of Psychiatry of Yamagata University School of Medicine.

Statistical Analyses

The effects of interactions between the *OPRM1* polymorphism and the PBI factors on the TCI dimensions were tested by forced multiple linear regression analysis,²⁸ in which dependent variables were seven TCI dimensional scores, and independent variables were the *OPRM1* genotype, four subscale scores of the PBI, products of the *OPRM1* genotype and the PBI factors, age and sex. The *OPRM1* genotypes were coded according to the number of the G allele (A/A=0, A/G=1, G/G=2), and dummy variables were used for sex (female=0, male=1). The PBI subscale scores were centered prior to analyses. In this model, all variables had variance inflation factor values of less than 2.0 and, thus, the effects of multicollinearity did not influence results of regression. When a significant interaction effect between the *OPRM1* genotype and a PBI factor was found in some TCI dimension, the correlation between scores of the PBI factor and those of the TCI dimension in each *OPRM1* genotype was tested using linear regression analysis.

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 22 (IBM Japan, Tokyo, Japan). A *P*-value less than 0.05 was considered significant. Bonferroni correction was used for multiple testing.

Results

Demographic characteristics, the PBI, and TCI scores and the *OPRM1* genotypes of the participants are shown in Table 1. The distribution of the *OPRM1* genotype was in the Hardy-Weinberg equilibrium ($\chi^2=1.581$, $P=0.209$).

In multiple regression analyses, the main effects of the *OPRM1* genotype on the TCI scores were not significant,

Table 1 Demographic Characteristics, the PBI and TCI Scores, and the *OPRM1* Genotypes of the Subjects

	Mean±SD or Number
Age, years	26.7±7.9
Males/females	423/302
PBI score	
Paternal care	24.4±7.1
Paternal protection	10.6±5.3
Maternal care	28.4±5.7
Maternal protection	11.5±5.9
TCI score	
Novelty seeking	21.7±5.1
Harm avoidance	18.7±6.0
Reward dependence	16.0±3.6
Persistence	4.3±1.8
Self-directedness	29.3±6.1
Cooperativeness	28.3±5.1
Self-transcendence	8.8±4.4
<i>OPRM1</i> genotype	
A/A	203
A/G	377
G/G	145

Abbreviations: *OPRM1*, mu-opioid receptor gene; PBI, Parental Bonding Instrument; TCI, Temperament and Character Inventory.

but effects of the interaction between the *OPRM1* genotype and maternal protection on scores of the self-directedness ($P<0.05$) and cooperativeness ($P<0.01$) dimensions were significant (Table 2). In subsequent analyses, the effects of maternal protection on the self-directedness and cooperativeness dimensions were genotype-specific, ie, there were significant ($P<0.005$) negative correlations between maternal protection scores and these dimensional scores in the A/A and A/G genotypes with higher correlation coefficients in the former, but not in the G/G genotype (Figure 1).

Discussion

As expected, the present study revealed significant effects of the interaction between the *OPRM1* polymorphism and maternal protection on self-directedness and cooperativeness, despite the lack of main effects of this polymorphism on any personality dimensions. The pattern of interaction was exactly the same in the two dimensions, ie, maternal protection had significant negative effects in the A/A and A/G genotypes with stronger degrees in the former, but not in the G/G genotype. These results suggest that the *OPRM1* polymorphism does not directly contribute to the

Table 2 Multiple Regression Analyses of the TCI Scores

	Novelty Seeking	Harm Avoidance	Reward Dependence	Persistence	Self-Directedness	Cooperativeness	Self-transcendence
Main effects							
<i>OPRM1</i>	0.022	0.007	0.038	-0.064	0.029	-0.030	0.031
Paternal care	-0.042	-0.059	0.074	-0.022	0.12	0.102	0.089
Paternal protection	-0.136	0.165*	0.173*	-0.071	-0.095	0.104	0.034
Maternal care	-0.009	-0.111	0.225**	0.119	0.114	0.143	0.065
Maternal protection	0.015	0.145	-0.141	-0.064	-0.412***	-0.263**	-0.004
Age	-0.063	0.013	0.036	-0.082*	-0.011	0.027	0.014
Sex	0.012	-0.095**	-0.150***	0.011	0.074*	-0.099**	-0.078
Interaction effects							
<i>OPRM1</i> × Paternal care	0.005	-0.047	0.056	0.004	0.031	-0.009	-0.086
<i>OPRM1</i> × Paternal protection	0.131	-0.071	-0.100	0.015	0.094	-0.169	-0.056
<i>OPRM1</i> × Maternal care	0.043	0.049	-0.098	0.002	-0.089	-0.039	-0.013
<i>OPRM1</i> × Maternal protection	-0.032	-0.056	0.135	0.044	0.160*	0.224**	0.117
Model summary							
R ²	0.104	0.304***	0.289***	0.200**	0.415***	0.293***	0.147

Notes: Figures in the Table show β except for multiple regression coefficient. * $P<0.05$, ** $P<0.01$, *** $P<0.001$.

Abbreviations: *OPRM1*, mu-opioid receptor gene; PBI, Parental Bonding Instrument; TCI, Temperament and Character Inventory.

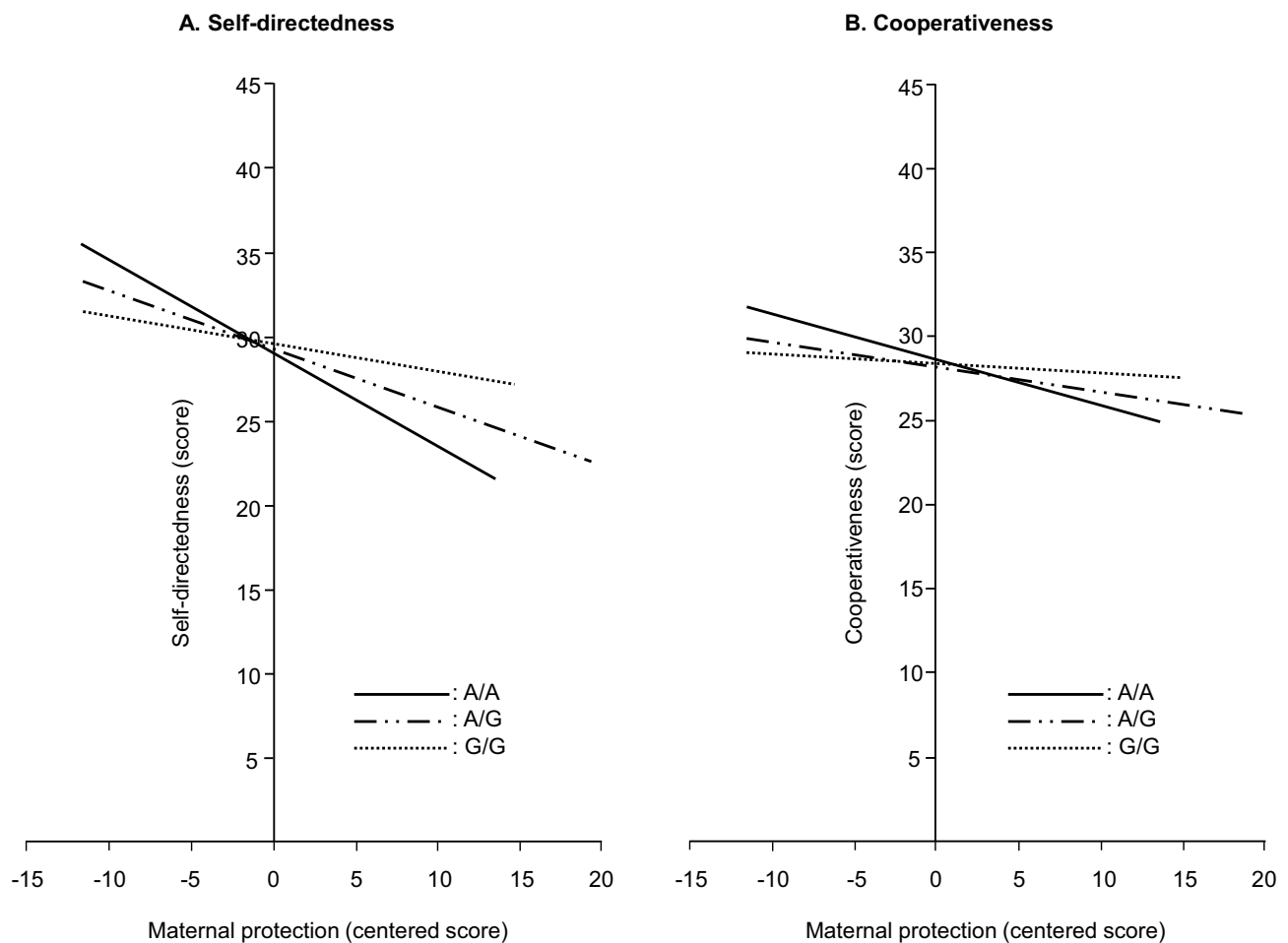


Figure 1 Effects of maternal protection on self-directedness (A) and cooperativeness (B) in the three genotypes of the mu-opioid receptor gene.

Notes: (A) The regression equations are $y = -0.557x + 29.119$ ($r = -0.494$, $P < 0.005$) in the A/A genotype, $y = -0.341x + 29.315$ ($r = -0.329$, $P < 0.005$) in the A/G genotype, and $y = -0.165x + 29.560$ ($r = -0.186$, n.s.) in the G/G genotype. (B) The regression equations are $y = -0.268x + 28.563$ ($r = -0.293$, $P < 0.005$) in the A/A genotype, $y = -0.148x + 28.095$ ($r = -0.170$, $P < 0.005$) in the A/G genotype, and $y = -0.059x + 28.300$ ($r = -0.075$, n.s.) in the G/G genotype.

characterization of personality traits, but indirectly contributes to the characterization of self-directedness and cooperativeness by moderating the sensitivity to maternal protection. As far as we know, the present study is the first to show the presence of a gene–environment interaction regarding this genetic polymorphism.

The results of this study summarized above suggest that the G allele of the *OPRM1* polymorphism is associated with lower sensitivity to maternal protection. The present result is in line with the result by Troisi et al²⁹ that the G allele is less sensitive to poor parental rearing. In relation to this, Moles et al¹² suggest that *OPRM1* knocked-out mice have lower sensitivity to maternal separation, resulting in fewer distress calls. Meanwhile, the *OPRM1* G allele is also associated with lower function of mu-opioid receptor in humans.^{17–19} Taken together, it is considered that the G allele of the *OPRM1* polymorphism

induces lower mu-opioid receptor function, which in turn induces lower sensitivity to maternal protection.

In the present study, the participants with the *OPRM1* A allele showed not only lower scores of self-directedness and cooperativeness in response to higher maternal protection but also higher scores of these dimensions in response to lower maternal protection. This result suggests that *OPRM1* is one of the plasticity genes, as suggested by Belsky et al,³⁰ and this feature may explain the lack of simple correlations between the *OPRM1* genotype and personality traits.^{21,22} On the other hand, several studies show that low scores of self-directedness and cooperativeness are predictive of the presence of personality disorders,^{31,32} which are often comorbid with various psychiatric disorders such as major depression, anxiety disorders, eating disorder, and substance abuse.³³ Thus, if individuals with the *OPRM1* A allele receive high

maternal protection during childhood, they may become more susceptible to various psychiatric disorders. Conversely, if they receive low maternal protection during childhood, they may be protected against development of these disorders.

Last and not least, it should be stressed that self-directedness and cooperativeness, which were specifically influenced by the interaction effect between the *OPRM1* genotype and maternal protection, are closely connected with human attachment. Namely, these dimensions represent the self-concept as an autonomous individual and that as an integral part of society,⁸ which are the developmental tasks accomplished through favorable attachment experiences, especially with parents.¹ Also, these dimensions are closely related to working models of the self and other, which underlie and determine adult attachment styles.³⁴ Therefore, the present study indirectly supports the view that the mu-opioid receptor plays an important role in human attachment.¹⁰ In this regard, our study is in line with that by Cimino et al²⁰ suggesting the importance of the *OPRM1* polymorphism in human attachment.

There are two possible limitations in the present study. Firstly, the assessment of parental behaviors was performed by the PBI, which relies on respondent's memory. Therefore, the parental characteristics reported by our participants might be colored by their personality to some extent, though PBI ratings correlate with the actual parental rearing assessed by significant others with acceptable validity.³⁵ Secondly, the present results obtained in Japanese may be difficult to extend to other ethnic groups, because a considerable ethnic diversity is reported in the allele frequencies of the *OPRM1* polymorphism.¹⁵

Conclusion

The *OPRM1* genetic polymorphism contributes to the characterization of self-directedness and cooperativeness by moderating the sensitivity to parental behaviors, especially maternal protection.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available because the authors are not allowed to publish the raw data of subject's genetic information by the ethics committee of the Yamagata University School of Medicine. Data are, however, available from the corresponding author upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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