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ORIGINAL ARTICLE

Exploratory research on genetic polymorphisms associated with positive empathy and trait forgivingness among the Japanese

Masahiro Matsunaga[1], Yohsuke Ohtsubo[2], Takahiko Masuda[3], Yasuki Noguchi[4], Hidenori Yamasue[5], Keiko Ishii[6]

1 Department of Health and Psychosocial Medicine, Aichi Medical University School of Medicine, Japan.
2 Graduate School of Humanities and Sociology, The University of Tokyo, Japan.
3 Department of Psychology, University of Alberta, Canada.
4 Department of Psychology, Graduate School of Humanities, Kobe University, Japan.
5 Department of Psychiatry, Hamamatsu University School of Medicine, Japan.
6 Department of Cognitive and Psychological Sciences, Graduate School of Informatics, Nagoya University, Japan.

Correspondence to: Masahiro Matsunaga
Department of Health and Psychosocial Medicine, Aichi Medical University School of Medicine, Aichi 480-1195, Japan
e-mail: matsunag@aichi-med-u.ac.jp

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Abstract

OBJECTIVES: Previous studies have indicated that good human relationships contribute significantly to subjective well-being. We recently focused on two important ways of developing good interpersonal relationships: positive empathy, which focuses on the happiness of other people, and trait forgivingness, a tendency to forgive others. We novelly conducted an exploratory genome-wide association study (GWAS) to identify candidate gene polymorphisms associated with positive empathy and trait forgivingness among the Japanese.

MATERIAL AND METHODS: We for the first time identified several genetic polymorphisms associated with positive empathy and trait forgivingness through the GWAS based on a small sample population and relatively low threshold. We subsequently validated three genetic polymorphisms from these candidate genes using a real-time polymerase chain reaction system.

RESULTS: The results demonstrated that polymorphism in the vomeronasal type-1 receptor 1 (*VN1R1*) (rs61744949), a putative human pheromone receptor, is associated with positive empathy. In addition, genetic polymorphisms in the 5-hydroxytryptamine (serotonin) receptor 7 (*HTR7*: rs77843021) and tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon (*YWHAE*: rs9908013), which are associated with dopamine and serotonin biosynthesis, are associated with trait forgivingness.

CONCLUSION: This study novelly illustrated the influence of the genetic polymorphism in *VN1R1* on positive empathy and that of genetic polymorphisms in *HTR7* and *YWHAE* on trait forgivingness. It identified a relationship between previously unreported genetic polymorphisms and the necessary abilities for developing good human relationships. This will significantly impact future research on positive psychology and social psychology.

INTRODUCTION

Subjective well-being, which is defined as people's positive evaluations of their lives, includes positive emotions, engagement, satisfaction, and meaning (Diener & Seligman, 2004). Happy feelings can be an indicator of the degree of well-being. Therefore, a person's degree of happiness is an approximate measure of their degree of welfare (Raibley, 2012). Previous studies have shown that good human relationships make people happy (Diener & Seligman, 2002; Matsunaga *et al.* 2018; Saphire-Bernstein & Taylor, 2013), indicating that the ability to develop good human relationships plays a critical role in increasing subjective well-being.

We recently focused on two important abilities for developing good interpersonal relationships: positive empathy and trait forgivingness. Empathy is defined as the ability and propensity to vicariously share in and understand the experiences of other people (Decety & Cowell, 2014). Being empathetic toward a person in need is a critical source of altruistic motivation; it facilitates affiliation and enhances in-group identification (Decety *et al.* 2012; Hu *et al.* 2020; Zaki, 2014). Recent study findings suggest that positive empathy, an empathetic response that focuses on other people's joy, plays a crucial role in improving subjective well-being. Happy feelings are contagious, i.e., happiness can be shared. In other words, people who are surrounded by happy people are likely to experience increased levels of subjective happiness (Fowler & Christakis, 2008; Matsunaga *et al.* 2017). However, this does not mean we always catch another person's happiness; indeed, people's sensitivity to the happiness of others varies (Matsunaga *et al.* 2017). Therefore, an individual's emotional state, mental health, and personal circumstances depend on the extent to which they are influenced by the emotions of others.

Trait forgivingness is a person's disposition to forgive others (Berry *et al.* 2005). The term "forgivingness" was coined by Roberts (1995), specifically in reference to the disposition to forgive others and distinguish the concept from the more commonly used term "forgiveness," which refers to positive motivational changes toward transgressors, such as reduced vindictiveness and avoidance and increased benign intention (McCullough *et al.* 1997). Although trait forgivingness is sometimes referred to as "trait forgiveness," we use the former to avoid confusion. Trait forgivingness facilitates interpersonal relationships because conflicts are unavoidable, even in committed relationships. Empirical studies have revealed that trait forgivingness is correlated with subjective well-being and mental/physical health outcomes (Worthington *et al.* 2007).

Recent studies have found that social abilities such as empathy are influenced by genetic background. A previous genetic study indicated that a single nucleotide polymorphism (SNP) in the serotonin 2A receptor gene (*HTR2A* rs6311 guanine (G) vs. adenine (A)) is associated with sharing happiness by modulating the activity of the mentalizing/theory-of-mind network. Individuals with the *HTR2A* AA genotype felt less happy than G allele carriers when their friends were in happy situations (Matsunaga *et al.* 2017; Matsunaga *et al.* 2022). A previous study also suggested that favorable genes for developing good human relationships may be beneficial to an individual's survival (Matsunaga *et al.* 2021). In addition, polymorphisms in the oxytocin receptor (*OXTR* rs53576 G vs. A) gene were found to be related to interpersonal adaptability and the score on trait forgivingness increased as the number of G alleles of *OXTR* increased from 0 to 2 (Zhao *et al.* 2019). A genome-wide association study (GWAS), a method for determining genotypes at 500,000 to 1,000,000 locations and statistically examining the relationship between SNP frequencies and diseases primarily as well as quantitative traits, recently identified previously unreported genes associated with interpersonal adaptability based on large sample populations. For example, intronic SNP (a mutation in introns in the gene region that may change the gene expression level and phenotype) in *LRRC4C*, which is implicated in excitatory synapse development, was associated with self-reported empathy (Warrier *et al.* 2018).

Omics research is considered to be significant and valuable, as it facilitates discoveries. It is essential to determine the extent to which omics research can result in unprecedented discoveries. Conversely, within the framework of recent multiple tests, the number of true positives that can be detected is important. In GWASs, the number of genetic polymorphisms ranges from hundreds of thousands to millions and frequency differences are tested for each of them. Therefore, multiplicity adjustment is essential. In GWASs, 5.0×10^{-8}, which is called the genome-wide significance level, is generally used as a strict significance level (Hoggart *et al.* 2008). However, considering GWASs as omics research, the use of a strict genome-wide significance level significantly undermines the potential for discoveries, which is the fundamental objective of omics research (Matsui, 2017). To the best of our knowledge, no GWAS has explored genetic polymorphisms associated with positive empathy and trait forgivingness. Therefore, we for the first time conducted an exploratory GWAS based on a small sample population and relatively low threshold to identify candidate gene polymorphisms associated with positive empathy and trait forgivingness among the Japanese. Subsequently, we verified whether these candidate gene polymorphisms are associated with positive empathy and trait forgivingness using a real-time polymerase chain reaction (PCR) system.

MATERIAL AND METHODS

Ethics and consent to participate

We recruited 416 healthy undergraduate students from Kobe University (198 males, 217 females, and one who

Tab. 1. Results from GWAS examining the candidate genes associated with positive empathy

SNP	Chr	Frequency of Effect allele	Frequency of Other allele	BP	Effect allele	Other allele	CHUSQ	P	OR	Protein Name
rs17160747	7	0.36	0.01613	77689491	G	A	23.23	1.43E-06	34.31	membrane associated guanylate kinase, WW and PDZ domain containing 2
rs1991906	4	0.4074	0.04688	189522233	T	C	22.8	1.80E-06	13.98	long intergenic non-protein coding RNA 1060
rs3823804	7	0.2857	0	77673804	C	T	22.31	2.32E-06	NA	membrane associated guanylate kinase, WW and PDZ domain containing 2
rs13408003	2	0.6786	0.2647	49119864	C	A	21.24	4.05E-06	5.864	follicle stimulating hormone receptor
rs61744949	19	0.1964	0.6029	57967049	G	T	20.84	4.99E-06	0.161	vomeronasal 1 receptor 1
rs6769477	3	0.5185	0.1333	22010312	T	C	19.52	9.98E-06	7	zinc finger protein 385D
rs74759436	16	0.4	0.05172	87759251	A	G	19.43	1.04E-05	12.22	kelch domain containing 4
rs5976850	23	0.2195	0.6977	127833769	G	A	19.29	1.12E-05	0.1219	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 1
rs10406026	19	0.2069	0.5758	57984096	A	C	17.45	2.94E-05	0.1922	zinc finger protein 772
rs3094303	11	0.2586	0.01471	75114071	G	A	16.8	4.16E-05	23.37	ribosomal protein S3
rs77066959	11	0	0.2759	37699228	A	G	16.79	4.18E-05	0	uncharacterized
rs3779320	7	0.3929	0.08824	77691587	T	C	16.3	5.4E-05	6.686	membrane associated guanylate kinase, WW and PDZ domain containing 2
rs4655467	1	0.6379	0.2794	214026838	T	C	16.29	5.42E-05	4.544	uncharacterized
rs78387945	2	0.3333	0	156612315	T	C	16.26	5.53E-05	NA	potassium inwardly-rectifying channel, subfamily J, member 3
rs2492608	9	0.2069	0.5588	29896094	C	T	16.2	5.71E-05	0.2059	leucine rich repeat and Ig domain containing 2
rs2502104	9	0.2069	0.5588	29931748	T	C	16.2	5.71E-05	0.2059	leucine rich repeat and Ig domain containing 2
rs12444181	16	0.3621	0.07353	83305223	C	T	15.91	6.63E-05	7.151	cadherin 13
rs10837466	11	0.05172	0.3382	40682623	C	A	15.69	7.46E-05	0.1067	leucine rich repeat containing 4C
rs117312638	3	0.2143	0	142294719	T	C	15.69	7.48E-05	NA	ATR serine/threonine kinase
rs1352384	23	0.07692	0.475	121186770	G	A	15.57	7.94E-05	0.09211	glutamate receptor, ionotropic, AMPA 3
rs4495512	9	0.1897	0.5294	29918652	C	T	15.45	8.47E-05	0.208	leucine rich repeat and Ig domain containing 2
rs56402950	7	0.2143	0	149180219	T	C	15.24	9.48E-05	NA	zinc finger protein 746

SNP = single nucleotide polymorphism, Chr = Chromosome, BP = base pair, P = P-value, CHISQ = chi-square test statistic, OR = Odds ratio

opted not to report their gender; mean age = 19.47 years, standard deviation [SD] = 1.23, range = 18–33). This study was approved by the Ethics Committees of Nagoya University (approval number: NUPSY-190415-M-01), Kobe University (approval number: 2014-10), and Aichi Medical University (approval number: 14–036). All the participants provided written informed consent in accordance with the Declaration of Helsinki.

For the GWAS, we collected as many samples as possible within our research budget. For the second validation analysis using a real-time PCR system, we conducted a statistical power analysis using G * Power, version 3.1.9.4 (Faul *et al.* 2007). We assumed that the effect size of this study would be equivalent to that observed in a previous study (Matsunaga *et al.* 2018). An a priori power analysis estimated the sample size necessary for this study as $N = 252$ (analysis of variance, fixed effects, omnibus, one-way; effect size = 0.25; alpha error = 0.05; 1-beta error = 0.95; number of groups = 3). This study used data obtained from two sub-studies of the aforementioned research project (Ishii *et al.* 2018; Matsunaga *et al.* 2017, 2018; Zheng *et al.* 2020). The first sub-study, which was conducted at Kobe University in 2015, included 213 participants. The second sub-study, which was conducted at Kobe University in 2018, included 203 participants. Therefore, the dataset analyzed in this study included 416 participants.

The participants were recruited through a psychology subject pool in each of the universities and received 4000 yen (approximately USD 40). The sampling in this study was not completely random, as it targeted students interested in participating in the experiment who volunteered to participate. Therefore, a certain degree of selection bias is possible.

Genotyping

Nail samples were collected and genomic DNA was extracted from these samples using ISOHAIR kits (Nippon Gene Co., Ltd., Tokyo, Japan) (Tanaka *et al.* 2012). First, to search for candidate gene polymorphisms associated with positive empathy and trait forgivingness, we requested the Japonica Array Genotyping Service for the GWAS (Toshiba Corporation, Tokyo, Japan). Sixty-five samples from the second sub-study (203 participants) were used in this GWAS because the selected samples had the minimum quality necessary to conduct a GWAS (A260/A280 ≥ 1.6; genomic DNA concentration ≥ 50 ng/μL). Although all but one sample did not meet the recommended sample quality control metric for the Japonica Arrays (dish quality control > 0.82 and call rate < 97%), the quality of the GWAS was not problematic, as it was an experiment conducted to identify candidate gene polymorphisms.

We selected genetic polymorphisms based on the criteria of genes for which SNP markers are commercially available and whose functions are easy to estimate. After we selected the candidate gene polymorphisms, the SNP markers for rs61744949 (vomeronasal type-1 receptor 1: *VN1R1*), rs77843021 (5-hydroxytryptamine (serotonin) receptor 7, adenylate cyclase-coupled: *HTR7*), and rs9908013 (tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon: *YWHAE*) were genotyped using TaqMan® SNP Genotyping Assays (Thermo Fisher Scientific Inc., Waltham, MA, USA), which were functionally tested by the manufacturer and available on demand. The SNP assay contained forward and reverse PCR primers as well as two allele-specific probes conjugated with either VIC or FAM fluorescent markers. Each PCR mixture comprised a DNA template, an SNP-specific genotyping assay, and a Taqman Genotype master mix (Thermo Fisher Scientific Inc.). All the PCRs and allelic discrimination reactions were performed using the StepOne Plus™ real-time PCR system (Thermo Fisher Scientific Inc.). The distribution of *VN1R1* genotypes was as follows: 72 GG, 177 GT, 154 TT, and 13 undetermined. This did not significantly deviate from the Hardy–Weinberg equilibrium, $\chi^2(1) = 2.81$, $p = 0.244$. The distribution of *HTR7* genotypes was as follows: 0 CC, 41 CT, 373 TT, and 2 undetermined. This did not significantly deviate from the Hardy–Weinberg equilibrium, $\chi^2(1) = 1.12$, $p = 0.570$. The distribution of *YWHAE* genotypes was as follows: 21 CC, 130 CT, 249 TT, and 16 undetermined. This did not significantly deviate from the Hardy–Weinberg equilibrium, $\chi^2(1) = 0.55$, $p = 0.758$.

Evaluation of positive empathy and trait forgivingness

To assess positive empathy, we used a questionnaire (Matsunaga *et al.* 2018). The participants were asked to evaluate their happiness levels on a 5-point Likert scale (1: not happy at all; 2: slightly happy; 3: moderately happy; 4: very happy; 5: extremely happy) when people around them were happy. In addition, to assess trait forgivingness, the participants were asked to evaluate their levels of forgivingness using a Japanese version of the Trait Forgivingness Scale (Berry *et al.* 2005; see Ohtsubo *et al.* [2015] for the Japanese version) comprising 10 items (e.g., I can forgive a friend for almost anything; I have always forgiven those who hurt me) measured on a 5-point scale ranging from "strongly disagree" to "strongly agree."

Statistical analyses

For the GWAS analyses, we applied the χ^2 test with a relatively low threshold ($p < 0.0001$, uncorrected) using plink v1.07 software (Shaun Purcell, Boston, Massachusetts, USA) based on a previous exploratory data analysis (Teo, 2010). Data analyses from TaqMan® SNP Genotyping Assays were conducted using SPSS version 27 (IBM, Armonk, NY, USA). Differences in psychological indices between genogroups were tested using one-way analysis of variance (ANOVA) followed by Bonferroni-corrected multiple comparisons.

Tab. 2. Results from GWAS examining the candidate genes associated with trait forgivingness

SNP	Chr	Frequency of Effect allele	Frequency of Other allele	BP	Effect allele	Other allele	CHUSQ	P	OR	Protein Name
rs2159108	5	0.08333	0.4688	145380618	C	T	22.71	1.89E-06	0.103	SH3 domain containing ring finger 2
rs166047	5	0.06667	0.4394	145395368	A	T	22.59	2.01E-06	0.09113	SH3 domain containing ring finger 2
rs11740294	5	0.06667	0.4394	145400118	A	G	22.59	2.01E-06	0.09113	SH3 domain containing ring finger 2
rs11748238	5	0.06667	0.4394	145419826	T	G	22.59	2.01E-06	0.09113	SH3 domain containing ring finger 2
rs6536296	4	0.3448	0.03226	140531714	T	G	19.55	9.78E-06	15.79	uncharacterized
rs118046582	5	0.3077	0.01613	130728747	G	T	18.95	1.34E-05	27.11	CDC42 small effector 2
rs77843021	10	0.6154	0.04167	92576565	C	T	18.31	1.88E-05	36.8	5-hydroxytryptamine (serotonin) receptor 7, adenylate cyclase-coupled
rs10437529	10	0.03333	0.3281	1647114	G	A	17.81	2.44E-05	0.07061	adenosine deaminase, RNA-specific, B2 (non-functional)
rs34822613	2	0.6724	0.2969	65085743	A	G	17.21	3.35E-05	4.861	uncharacterized
rs78031359	17	0	0.2424	7984786	C	A	16.66	4.47E-05	0	arachidonate 12-lipoxygenase, 12R type
rs9908013	17	0.4423	0.1034	1243440	C	T	16.22	5.65E-05	6.874	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon
rs117756257	1	0.01667	0.2742	155196558	A	G	16.08	6.08E-05	0.04487	glucosidase, beta, acid pseudogene 1
rs116903688	5	0.3167	0.04545	169416593	T	C	16.04	6.2E-05	9.732	dedicator of cytokinesis 2
rs13250662	8	0.1034	0.4242	64072039	T	C	15.96	6.46E-05	0.1566	YTHDF3 antisense RNA 1 (head to head)
rs73535008	8	0.3667	0.07576	14684622	G	A	15.8	7.05E-05	7.063	sarcoglycan, zeta
rs10487324	7	0.4333	0.1212	110036601	A	G	15.54	8.08E-05	5.544	IMP2 inner mitochondrial membrane peptidase-like (S. cerevisiae)
rs35142374	2	0.6724	0.3182	65085839	G	A	15.51	8.2E-05	4.398	uncharacterized
rs2613697	8	0.2833	0.03125	21072616	A	G	15.17	9.84E-05	12.26	uncharacterized

SNP = single nucleotide polymorphism, Chr = Chromosome, BP = base pair, P = P-value, CHISQ = chi-square test statistic, OR = Odds ratio

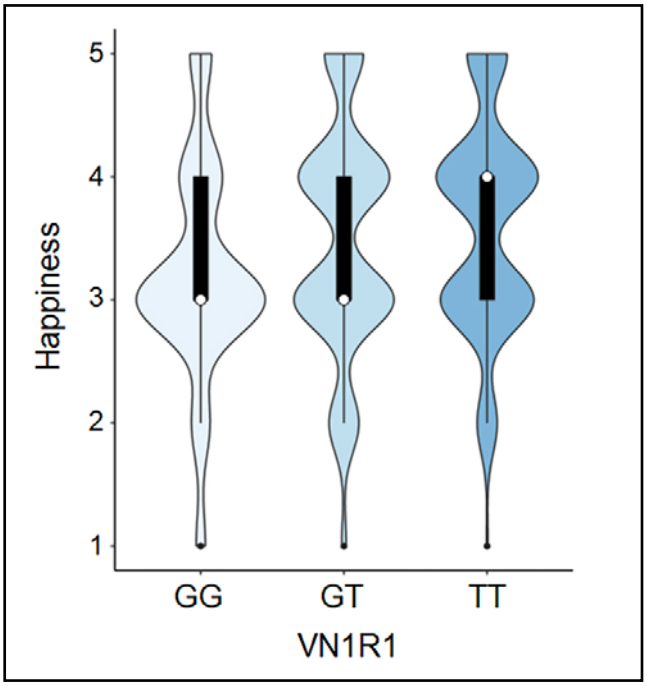

Fig. 1. The violin plot lines indicate the kernel density of the distribution (i.e., a smoothed histogram). The boxes span the first to third quartiles and the circle inside the boxes represents the median. The endpoints of the axis are labeled using the minimum and maximum values. The vertical axis shows the rating score of happiness that one feels when the people around them are happy. *VN1R1*: vomeronasal type-1 receptor 1 (rs61744949).

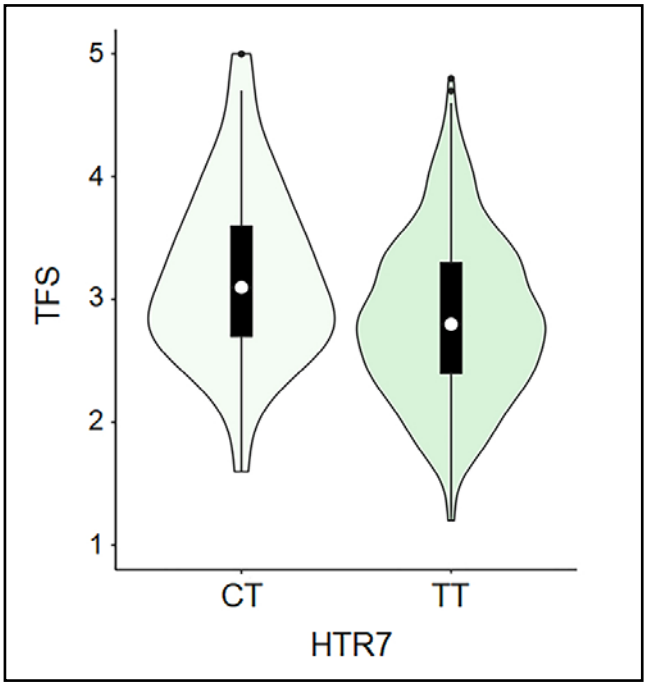

Fig. 2. The violin plot lines indicate the kernel density of the distribution (i.e., a smoothed histogram). The boxes span the first to third quartiles and the circle inside the boxes represents the median. The endpoints of the axis are labeled using the minimum and maximum values. The vertical axis shows the rating score of trait forgivingness. *HTR7*: 5-hydroxytryptamine (serotonin) receptor 7, adenylate cyclase-coupled (rs77843021). TFS: trait forgivingness.

Furthermore, to remove the influences of several confounding factors such as age and gender from the effects of the candidate gene polymorphisms on positive empathy and trait forgivingness, we used the following regression model:

$$Y = \beta_0 + \beta_1 G + \beta_2 S + \beta_3 A + \varepsilon$$

In the formula presented above, "G (genotype)" represents a matrix of variables to control for the genotype (*VN1R1*: G = 2 if the participant's genotype is TT, G = 1 if the genotype is GT, and G = 0 if the genotype is GG; *HTR7*: G = 0 if the participant's genotype is TT, G = 1 if the genotype is CT; *YWHAE*: G = 0 if the participant's genotype is TT, G = 1 if the genotype is CT, and G = 2 if the genotype is CC). "S (sex)" is a matrix of variables used to control for gender (S = 0 if the participant is female, and S = 1 if the participant is male). "A (age)" represents a matrix of variables used to control for age, whereas "ε" represents the individual-specific error.

Furthermore, the normality of the data (rating scores of happiness and trait forgivingness) was analyzed using the Shapiro–Wilk test and Spearman's rank correlation coefficients were calculated to determine the correlations between the rating scores of happiness and trait forgivingness. Differences in these psychological indices between genogroups were also analyzed using one-way ANOVA followed by Bonferroni-corrected multiple comparisons. For *HTR7*, the rating score of trait forgivingness was compared using the Student's t-test.

RESULTS

We for the first time conducted an exploratory GWAS using a small sample size (n = 65) with a relatively low threshold ($p < 0.0001$, uncorrected) to identify candidate genes. This GWAS identified several candidate genes associated with positive empathy (Table 1) and trait forgivingness (Table 2). From these candidate genes, we selected genetic polymorphisms that are easy to validate, one for positive empathy (rs61744949 (*VN1R1*) and two for trait forgivingness (rs77843021 (*HTR7*) and rs9908013 (*YWHAE*)).

We then attempted to validate the effects of the candidate gene polymorphisms on positive empathy and trait forgivingness using the entire sample of this study (n = 416) and a real-time PCR system. The rating scores of happiness among individuals with different *VN1R1* genotypes were compared and an ANOVA revealed a significant main effect of *VN1R1* [F (2, 400) = 4.701, p = 0.010, $\eta^2 p$ = 0.023, power = 0.786]. A multiple comparisons test indicated that the happiness rating score in the TT genotype group was significantly higher than that in the GG (p = 0.007) genotype group (GG = 3.222 ± 0.106, GT = 3.492 ± 0.068, TT = 3.617 ± 0.073) (Figure 1). Table 3 shows the results

of the multiple regression analysis, which tested the hypothesis that variations in *VN1R1* are associated with the happiness rating score, even after controlling for the potentially confounding variables of age and gender. This regression model was statistically significant [F (3, 399) = 5.297, p = 0.001] and confirmed that individuals with TT polymorphisms in *VN1R1* are significantly more susceptible to the happy feelings of the people around them than G carriers (p = 0.005). As shown in Table 3, the happiness rating score exhibited a sex-dependent trend. Females had a higher happiness score than males (male = 3.39 ± 0.689, female = 3.59 ± 0.565, p = 0.022). Consequently, we performed a subgroup analysis based on sex to understand the contribution of the *VN1R1* polymorphism. An ANOVA revealed a significant main effect of *VN1R1* [F (2, 189) = 4.067, p = 0.019, η^2p = 0.041, power = 0.718] in males. A multiple comparisons test indicated that the happiness rating score in the male TT genotype group was significantly higher than that in the male GG (p = 0.029) genotype group (GG = 3.140 ± 0.146, GT = 3.282 ± 0.114, TT = 3.615 ± 0.109). No significant difference was observed among females (GG = 3.345 ± 0.155, GT = 3.632 ± 0.081, TT = 3.618 ± 0.096).

Furthermore, an ANOVA revealed a significant main effect of *HTR7* [F (1, 412) = 9.683, p = 0.002, η^2p = 0.023, power = 0.874] on the rating score of trait forgivingness and a multiple comparisons test indicated that the rating score of trait forgivingness in the CT genotype of *HTR7* (3.188 ± 0.103) was significantly higher than that in the TT genotype (2.849 ± 0.034) (p = 0.002) (Figure 2). Table 4 shows the results of the multiple regression analysis. This regression model was statistically significant [F (3, 410) = 3.544, p = 0.015] and confirmed that individuals with the CT polymorphism in *HTR7* are more characteristically prone to forgivingness than those with the TT genotype (p = 0.005).

In addition, an ANOVA revealed a significant main effect of *YWHAE* [F (2, 397) = 4.513, p = 0.012, η^2p = 0.022, power = 0.769] on the rating score of trait forgivingness and a multiple comparisons test indicated that the rating score of trait forgivingness in the CC genotype group was significantly higher than that in the TT (p = 0.024) genotype group (CC = 3.200 ± 0.143, CT = 2.933 ± 0.057, TT = 2.805 ± 0.041) (Figure 3). Table 5 shows the results of the multiple regression analysis. This regression model was statistically significant [F (3, 396) = 3.286, p = 0.021] and confirmed that individuals with the CC genotype of *YWHAE* were more characteristically prone to forgiving others than T carriers (p = 0.004).

Because neither the rating scores of happiness (p < 0.001) nor those of trait forgivingness (p = 0.003) were considered to be normally distributed through the Shapiro–Wilk test, we conducted Spearman's correlation analysis between the rating scores of happiness and trait forgivingness, finding that these scores were positively correlated (r = 0.233, p < 0.001). Because there was a correlation between these two variables, we further analyzed the relationship between *VN1R1* and trait forgivingness. We also analyzed the relationship between *HTR7* and *YWHAE* and positive empathy. An ANOVA did not indicate a significant main effect of *VN1R1* on trait forgivingness [F (2, 400) = 1.830, p = 0.162] (GG = 2.751 ± 0.078, GT = 2.927 ± 0.050, TT = 2.861 ± 0.053). An ANOVA also did not indicate a significant main effect of *YWHAE* on positive empathy [F (2, 397) = 1.863, p = 0.156] (CC = 3.667 ± 0.197, CT = 3.577 ± 0.079, TT = 3.414 ± 0.057). However, there was a significant difference in the rating score of positive empathy between the CT genotype of *HTR7* (3.731 ± 0.115) and the TT genotype (3.477 ± 0.047) (t = 2.03, p = 0.047).

DISCUSSION

Previous studies have indicated that psychological well-being refers to the diverse and interconnected dimensions of physical, mental, and social well-being that extend beyond the conventional definition of health. It includes choices and activities aimed at achieving physical vitality, mental alacrity, social satisfaction, a sense of accomplishment, and personal fulfillment (Naci & Ioannidis, 2015). Happy feelings are good indicators of mental well-being and good human relationships increase happiness levels (Diener & Seligman, 2002;

Tab. 3. Results from the regression analysis examining the association between *VN1R1* and the happiness rating score

Predictor variables	*β*	t	*p*-value
VN1R1 T	**0.139**	**2.822**	**0.005**
Sex	**-0.102**	-2.079	**0.038**
Age	-0.073	-1.484	0.138
N	403		
Adjusted R^2	0.031		

All predictor variables were included in the regression analysis. Boldface indicates statistically significant variables. *β*: Standardized beta coefficient.

Tab. 4. Results from the regression analysis examining the association between *HTR7* and the trait forgivingness rating score

Predictor variables	*β*	t	*p*-value
HTR7	**0.147**	**3.007**	**0.003**
Sex	0.048	0.981	0.327
Age	0.001	0.025	0.980
N	414		
Adjusted R^2	0.018		

All predictor variables were included in the regression analysis. Boldface indicates statistically significant variables. *β*: Standardized beta coefficient.

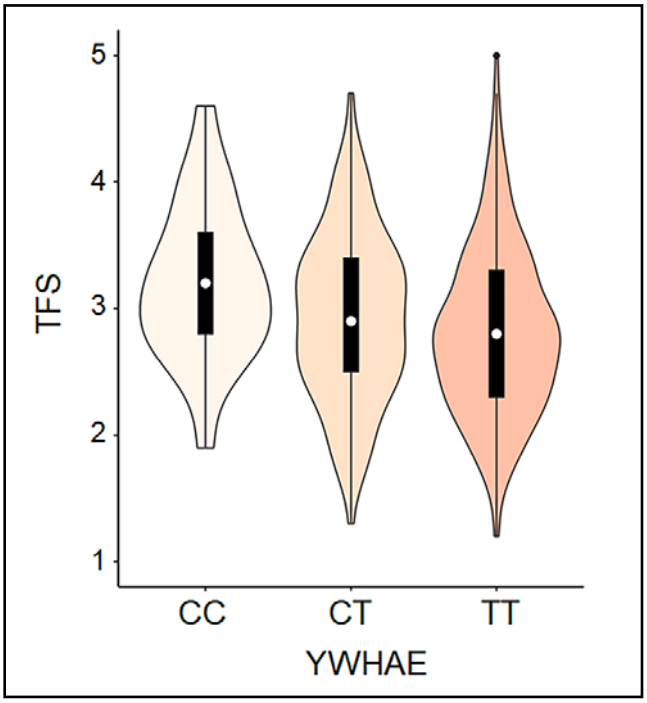

Fig. 3. The violin plot lines indicate the kernel density of the distribution (i.e., a smoothed histogram). The boxes span the first to third quartiles and the circle inside the boxes represents the median. The endpoints of the axis are labeled using the minimum and maximum values. The vertical axis shows the rating score of trait forgivingness. *YWHAE*: tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon (rs9908013). TFS: trait forgivingness.

Tab. 5. Results from the regression analysis examining the association between *YWHAE* and the trait forgivingness rating score

Predictor variables	*β*	t	*p*-value
YWHAE C	**0.145**	**2.921**	**0.004**
Sex	0.057	1.154	0.249
Age	0.007	0.146	0.884
N	400		
Adjusted R^2	0.017		

All predictor variables were included in the regression analysis. Boldface indicates statistically significant variables. *β*: Standardized beta coefficient.

Matsunaga *et al.* 2018; Saphire-Bernstein & Taylor, 2013). Therefore, we have begun paying significant attention to our ability to improve human relationships. In recent years, GWASs have been established in the fields of positive psychology and social psychology. Previous research using large-sample GWASs found that several genetic polymorphisms are associated with subjective well-being (Kim *et al.* 2022; Okbay *et al.* 2016), thereby suggesting that our genetic basis may be involved in socio-psychological items such as subjective well-being. To the best of our knowledge, no GWAS has explored genetic polymorphisms associated with positive empathy and trait forgivingness, which are crucial abilities for developing good human relationships. In this study, we conducted an exploratory GWAS based on a small sample population to discover genetic polymorphisms associated with positive empathy and trait forgivingness. Our exploratory GWAS with a relatively low threshold ($p < 0.0001$, uncorrected) indicated an association between several genetic polymorphisms and positive empathy (Table 1) as well as trait forgivingness (Table 2). We selected genetic polymorphisms with relatively easy-to-understand functions from the candidate gene polymorphisms, after which we performed a validity evaluation test using a real-time PCR system.

The results indicated that *VN1R1* genotypes (rs61744949) associated with positive empathy and individuals with TT polymorphisms in *VN1R1* are significantly more susceptible to the happiness of the people around them than G carriers (Figure 1). The human *VN1R1* is considered to be a putative pheromone receptor and is expressed in the human olfactory mucosa (Bensafi *et al.* 2004; Henningsson *et al.* 2017; Wallrabenstein *et al.* 2015). Despite there being numerous unclear aspects regarding human pheromones, previous reports have indicated that hedione (methyl dihydrojasmonate), a compound with an aroma that is similar to that of jasmine, can activate *VN1R1* (Wallrabenstein *et al.* 2015). Other studies have also indicated that the genetic polymorphism in *VN1R1* (rs28649880) influences socio-sexual behaviors such as number of sex partners (Henningsson *et al.* 2017). Although whether there is a relationship between pheromones and empathy has not been comprehensively determined, the results of this study that suggest an association between a putative pheromone receptor gene and the social emotion of positive empathy are interesting. Moreover, there may be gender differences in the effect of *VN1R1* on positive empathy. Women tend to have higher empathic ability than men (Doherty *et al.* 1995), in line with the finding of the present study that women had higher happiness scores than men. In this study, the effect of *VN1R1* on positive empathy was more pronounced in men than in women, suggesting its lower effectiveness in groups with high levels of empathy. Hedione activates the orbitofrontal cortex (OFC), which is known to be involved not only in the olfactory system (Wallrabenstein *et al.* 2015), but also in the self-inhibitory control system (Zhuang *et al.* 2021). It has also been suggested that a small OFC volume is associated with antisocial personality disorder, which includes the symptom of not being sensitive to or respectful of others (Raine *et al.* 2011). The OFC volume is smaller in men than in women, while men with antisocial personality disorder have even smaller volumes (Raine *et al.* 2011). Since prefrontal regions including the OFC are activated when people feel positive empathy (Matsunaga *et al.* 2017), the sex difference in the effect of *VN1R1* may thus be explained by OFC functions.

The results also indicated an association between genetic polymorphisms in *HTR7* (rs77843021) and trait forgivingness. The rating score of trait forgivingness in the CT genotype of *HTR7* was significantly higher than that in the TT genotype (Figure 2). The *HTR7* gene encodes the serotonin (5-HT) receptor 7 (5-HT7R), which is expressed in both the central nervous system and in peripheral tissues (Gellynck *et al.* 2013; for reviews, see Matthys *et al.* 2011). Based on the wide distribution of 5-HT7R in the animal brain (cortex, thalamus, hypothalamus, and hippocampus), previous studies have suggested that 5-HT7R is widely involved in many neuropathological processes such as anxiety, impulsivity, and depression (Volpicelli *et al.* 2014). Furthermore, the results of this study also indicated an association between genetic polymorphisms in *YWHAE* (rs9908013) and trait forgivingness. The rating score of trait forgivingness in the CC genotype group of *YWHAE* was significantly higher than that in the TT genotype group (Figure 3). Tyrosine 3-monooxygenase (tyrosine hydroxylase: TH) is an enzyme that converts tyrosine into dihydroxyphenylalanine (DOPA), the precursor of dopamine, and tryptophan 5-monooxygenase (tryptophan hydroxylase: TPH) introduces an oxygen atom into tryptophan, yielding 5-hydroxytryptophan, a metabolic intermediate in the biosynthesis of serotonin (Jacobsen *et al.* 2015). The activity of TH and TPH enzymes is regulated by the members of the 14-3-3 protein family encoded by several genes such as *YWHAE* (Jacobsen *et al.* 2015). Therefore, genetic polymorphisms in *YWHAE* might be associated with dopamine and serotonin signal transduction. Previous studies have indicated an association between genetic polymorphism in *YWHAE* (rs28365859) and schizophrenia as well as attention deficit hyperactivity disorder (ADHD), and these are associated with dopamine and serotonin dysfunctions (Jacobsen *et al.* 2015; Oades, 2008; Stahl, 2018). Using functional magnetic resonance imaging (fMRI), we recently demonstrated that the theory-of-mind network (i.e., bilateral temporoparietal junction, precuneus, and medial prefrontal cortex) of a victim is involved in their forgiveness of their transgressor (Ohtsubo *et al.* 2018). The medial prefrontal cortex, which significantly contributes the cognitive process, plays the roles of emotion regulation, motivation, and sociability (Xu, *et al.* 2019), is modulated by midbrain dopamine and serotonin systems (D'Ardenne *et al.* 2012; Sargin *et al.* 2019), thereby suggesting that genetic polymorphisms in *HTR7* and *YWHAE* might influence such brain activities by modulating 5-HT signal transduction.

In addition, our analysis showed that positive empathy and trait forgivingness were positively correlated psychological indices, but *VN1R1* was not associated with trait forgivingness, and *YWHAE* was not associated with positive empathy. Although these are psychological indices that are positively correlated with each other, there is some degree of independence between the indices, which is considered to result in the validity of conducting separate association analyses in this study. Conversely, the *HTR7* genetic polymorphism affects positive empathy. The interaction between *VN1R1* and *HTR7* on positive empathy requires further investigation.

Gene frequencies and cultural differences

According to the database, the allele frequency of *VN1R1* is G = 0.724727, T = 0.275273 among Europeans and G = 0.3457, T = 0.6543 among Asians (https://www.ncbi.nlm.nih.gov/snp/rs61744949). The gene frequencies in this study were G = 0.3982 and T = 0.6017, similar to those in the Asian database. Therefore, numerous Europeans have G and numerous Japanese have T. In this study, people with the T genotype were found to have relatively high empathy levels toward happiness. This means that more people in Japan have a higher level of positive empathy than those in Europe. Like many Asian countries, Japan is considered to be a collectivistic society (Cheng *et al.* 2013). *Wa* is a Japanese cultural concept that translates to "harmony" in English (Konishi *et al.* 2007). In recent years, cultural and social psychology fields have focused on the possibility of co-evolution of culture and genes where genetic and cultural characteristics interact to achieve adaptation to the ecological environment (Gintis, 2011). For example, in previous studies, genotypes in the serotonin transporter gene, which affects serotonin neurotransmission and is highly susceptible to emotional stimuli, have a high affinity with collectivism, and there are many people with such highly sensitive serotonin transporter genes in collectivistic countries (Chiao & Blizinsky, 2010). Therefore, the results showing that there are numerous people with polymorphisms associated with high levels of positive empathy in Japan provides useful information for considering the co-evolutionary theory of culture and genes. Several papers on the co-evolution of culture and genes have been published (e.g., Matsunaga *et al.* 2018) and we plan to study *VN1R1* from this perspective in future research. In addition, the allele frequency of *HTR7* is reported to be T = 0.99976 and C = 0.00024 among Europeans and T = 0.992 and C = 0.008 among Asians (https://www.ncbi.nlm.nih.gov/snp/rs77843021). The allele frequency of *YWHAE* has also been calculated to be T = 0.67950 and C = 0.32050 among Europeans and T = 0.693 and C = 0.307 among Asians (https://www.ncbi.nlm.nih.gov/snp/rs9908013). The gene frequencies of these polymorphisms in European and Japanese populations in the database did not differ significantly.

Limitations and directions for future research

This study has several limitations. First, a typical GWAS constitutes a very large sample size and provides high-quality analysis. Although a certain degree of reliability can be secured by combining validity analysis

using a real-time PCR system, the present GWAS had a small sample population. Further studies based on larger sample populations and high-quality analyses are needed in the future. Second, this GWAS indicated that several candidate gene polymorphisms are associated with positive empathy and trait forgivingness. However, we validated only three genetic polymorphisms using a real-time PCR system because we picked up genetic polymorphisms based on the criteria of genes for which SNP markers are commercially available and whose functions are easy to estimate. Other candidate polymorphisms may also be significantly associated with positive empathy and trait forgivingness if validation analysis using a real-time PCR system is performed by creating specific SNP markers that are not commercially available. However, this requires further investigation.

CONCLUSION

This study novelly shows that the genetic polymorphism in *VN1R1* (rs61744949) influences positive empathy. It is also the first to show that genetic polymorphisms in *HTR7* (rs77843021) and *YWHAE* (rs9908013) influence trait forgivingness. Although the present study has limitations such as a limited sample size, a low threshold for the GWAS, and an absence of functional analysis of the genes, the discovery of related genetic polymorphisms is expected to result in advancements in the fields of positive psychology and social psychology.

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