Culture, distress, and oxytocin receptor polymorphism (OXTR) interact to influence emotional support seeking

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Research has demonstrated that certain genotypes are expressed in different forms, depending on input from the social environment. To examine sensitivity to cultural norms regarding emotional support seeking as a type of social environment, we explored the behavioral expression of oxytocin receptor polymorphism (OXTR) rs53576, a gene previously related to socio-emotional sensitivity. Seeking emotional support in times of distress is normative in American culture but not in Korean culture. Consequently, we predicted a three-way interaction of culture, distress, and OXTR genotype on emotional support seeking. Korean and American participants (n = 274) completed assessments of psychological distress and emotional support seeking and were genotyped for OXTR. We found the predicted three-way interaction: among distressed American participants, those with the GG/AG genotypes reported seeking more emotional social support, compared with those with the AA genotype, whereas Korean participants did not differ significantly by genotype; under conditions of low distress, OXTR groups did not differ significantly in either cultural group. These findings suggest that OXTR rs53576 is sensitive to input from the social environment, specifically cultural norms regarding emotional social support seeking. These findings also indicate that psychological distress and culture are important moderators that shape behavioral outcomes associated with OXTR genotypes.

genetics | social support | psychological distress | stress coping | gene-by-culture interaction

The behavioral expression of certain genotypes is sensitive to input from the social environment (1). Specifically, studies have demonstrated that certain genotypes are expressed in different forms depending upon the harshness/beneficence of social conditions. This interaction between genes and environment has been observed with the serotonin transporter gene (2, 3), the monoamine oxidase A gene (4), the dopamine receptor gene seven-repeat polymorphism (5), and the glucocorticoid receptor gene (6), among others (7). For example, in the case of the serotonin transporter gene, individuals who are homozygous for the allele associated with lower transcriptional efficiency of the promoter (s/s) are at a greater risk for depressive symptomatology in unsupportive social environments, but those with the same genotype show lower depressive symptomatology in supportive social environments, compared with those with s/l or l/l genotypes (3, reviewed in ref. 8). Persons with the genotype for low levels of the enzyme metabolizing the neurotransmitters serotonin, epinephrine and norepinephrine [monoamine oxidase A (MAOA)] may be more likely to develop antisocial behavior as adults if maltreated as children than persons with the high MAOA activity genotype (4).

Guided by this perspective, the present investigation explored the possibility that an oxytocin receptor gene (OXTR rs53576) may be sensitive to social input in the form of culture-specific relational norms. OXTR rs53576 is a polymorphic site in the oxytocin receptor gene, which is localized in a single copy to chromosome 3 of the human genome (9). Recent studies have identified a connection between OXTR and social behavior phenotypes in humans. Individuals with the G allele of OXTR rs53576, relative to those with the A allele, exhibit more sensitive parenting behavior (10), report being less lonely (11), show more empathy (12), and have lower rates of autism (13). In addition to findings regarding OXTR, research links social and emotional sensitivity to oxytocin as a neuropeptide. For example, intranasal administration of oxytocin leads to increased ability to infer the affective mental state of others (14) and greater interpersonal trust (15).

We examined whether culture-specific norms regarding relationships represent a source of social input that affects phenotypic expression of OXTR. We focused on norms surrounding the behavior of seeking emotional support—turning to one's social network for emotional solace—in times of stress. Emotional support has been found to ameliorate both psychological and biological stress reactivity (16), and the effects of lacking support on health and mortality are on par with well-established risk factors such as lipid levels and smoking (17). As such, it is an important behavioral response to stress. Emotional support seeking is a common response to stress that is influenced by both genetic factors (18) and culture (19–21).

Culture is a system of beliefs, institutions, and practices that govern norms and patterns of behaviors (22), including emotional support seeking. The norms regarding the seeking of emotional support differ markedly between Asian and American cultures, however. Across many different types of stressors, such as academic, health and social stressors, Asians are less likely to seek emotional support for dealing with their stressful events compared with European Americans (19–21). This cultural difference emerges with both open-ended assessments and standard coping inventories (20). The effectiveness of support seeking also varies cross-culturally, as it can have a negative impact on the psychological and biological stress responses of Asians responding to laboratory stressors (23). This cultural difference occurs because Asians are more concerned about the potential negative relational implications of support seeking than are European Americans (20, 21). Furthermore, studies (20) have found that U.S.-born Asians with greater exposure to the U.S. culture seek emotional support more than Asian immigrants and Asian nationals with less exposure to the U.S. culture, and the difference between the U.S.-born Asians and European Americans is minimal, supporting the argument that this difference is rooted in culture (ref. 19 discusses these generational patterns). We examined whether Koreans and Americans differed in the link between OXTR rs53576 and emotional support seeking for managing distress.

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In the present study, Koreans' and Americans' current psychological distress in response to a recent stressor and their seeking of emotional support were assessed, and they were genotyped for *OXTR*. (The American group included a small group of U.S.-born Korean Americans as comparisons who are genetically similar to Koreans but who were raised in American culture.) Consistent with prior research (19–21), we predicted that Americans would report using emotional support more than Koreans to manage distress. We further predicted that, under conditions of high distress, Americans with the GG/AG genotype [note that, consistent with approaches in other studies to deal with skewed genotypic distribution (10, 24), we combine the heterozygous genotype with the rarest homozygous genotype], who are more sensitive to relational norms, would seek emotional support more than Americans with the AA genotype, because emotional support seeking is a normative coping response in the United States. In contrast, Koreans with the GG/AG genotype would not increase support seeking any more than those with the AA genotype, because emotional support seeking is a nonnormative coping response. We did not expect these differences to emerge in the absence of distress. Thus, we predicted a three-way interaction among culture, psychological distress, and *OXTR* genotype on seeking emotional support.

Results

An ANOVA was conducted to examine whether there were cultural and genetic differences in the level of psychological distress, a composite measure of the Perceived Stress Scale (25) and the Brief Symptoms Inventory (26). There were no significant main effects for culture or genotype and no interaction on this measure (*P* values range between 0.12 and 0.97). Because the distribution of emotional support scores skewed left, the variable was transformed by squaring it before analysis. (Reported means and SDs are not transformed for ease of interpretation.)

A series of hierarchical linear regression analyses were conducted to test the gene–culture interaction hypothesis that culture would moderate the relationship among *OXTR*, psychological distress and emotional support seeking. At Step 1, the contrast-coded culture variable (−1 for Americans and 1 for Koreans), the contrast-coded *OXTR* variable (−1 for AA, and 1 for GG/AG), and the level of psychological distress (mean centered) were entered as predictors. At Step 1, there was the predicted cultural difference in reported emotional support seeking [β = 0.31, $t(270) = -5.16$, $P < 0.001$], as Koreans reported seeking less emotional support than did Americans. There were no other significant main effects. At Step 2, the two-way interactions were entered. There were no significant two-way interactions. At Step 3, the three-way interaction of culture, *OXTR*, and psychological distress was entered. As predicted, there was a significant three-way interaction among culture, *OXTR* and psychological distress [β = −0.23, $t(266) = -3.53$, $P < 0.001$, $\Delta R^2 = 0.04$ (the three-way interaction remains significant if the analysis excludes Korean Americans at $P = 0.003$)]. When OXTR is examined as three genotypes (−1 for AA, 0 for AG, and 1 for GG), the three-way interaction effect remains significant [β = −0.15, $t(266) = -2.49$, $P = 0.01$, $\Delta R^2 = 0.02$].

To examine the gene–culture interaction among participants with high and low psychological distress, participants were divided into two groups using a median split. An ANOVA with two factors (culture and genotype) was conducted separately for those with high and low psychological distress. In the high psychological distress group, there was a significant main effect of culture, $F(1, 132) = 4.78$, $P = 0.03$, $\eta^2 = 0.03$, showing that Americans (mean = 4.10, SD = 1.48) reported more emotional support seeking than Koreans (mean = 3.25, SD = 1.43), but no main effect of OXTR, $F(1, 132) = 0.58$, $P = 0.45$, $\eta^2 = 0.004$. The main effect of culture was qualified by the predicted significant interaction between culture and genotype, $F(1, 132) = 6.33$, $P = 0.01$, $\eta^2 = 0.04$, as

Fig. 1 shows. Planned pairwise comparisons show that Americans with the GG/AG genotype (mean = 4.24, SD = 1.46) reported seeking emotional support more than those with the AA genotype [mean = 3.44, SD = 1.47, $P = 0.04$, Cohen's $d = 0.55$. Analysis with three genotypes (AA, AG, and GG) revealed that among high distress Americans, the AG genotype significantly differed in emotional support seeking from the AA ($P = 0.01$) but not from the GG ($P = 0.11$). AG and GG genotypes do not significantly differ from each other in any other comparisons (high-distress Koreans and low-distress Americans and Koreans).] Koreans did not significantly differ by genotypes (mean = 3.01, SD = 1.45 for GG/GA, and mean = 3.55, SD = 1.38 for AA, $P = 0.15$, Cohen's $d = 0.38$), although individuals with the GG/AG genotype were somewhat less likely to seek emotional support than those with the AA genotype. The cultural difference in emotional support seeking was driven primarily by persons with the GG/AG genotype. Additional pairwise comparisons revealed that among those with the GG/AG genotype, Americans reported more emotional support seeking than Koreans ($P < 0.001$, Cohen's $d = 0.85$), whereas there was no cultural difference among those with the AA genotype ($P = 0.85$, Cohen's $d = 0.08$).

In the low psychological distress group, there was also a significant main effect of culture [$F(1, 134) = 16.11$, $P < 0.001$, $\eta^2 = 0.11$], showing that Americans (mean = 3.78, SD = 1.52) reported more emotional support seeking than Koreans (mean = 3.05, SD = 1.23), but no significant main effect of OXTR [$F(1, 132) = 0.01$, $P = 0.93$, $\eta^2 < 0.001$]. The interaction was marginally significant [$F(1, 134) = 3.24$, $P = 0.07$, $\eta^2 = 0.02$] (Fig. 1). However, the pairwise comparisons show that American individuals with the AA genotype (mean = 4.22, SD = 1.16) did not significantly differ in their emotional support seeking from individuals with the GG/GA genotype (mean = 3.65, SD = 1.60), $P = 0.21$, Cohen's $d = 0.41$. Among Koreans, individuals with the AA genotype
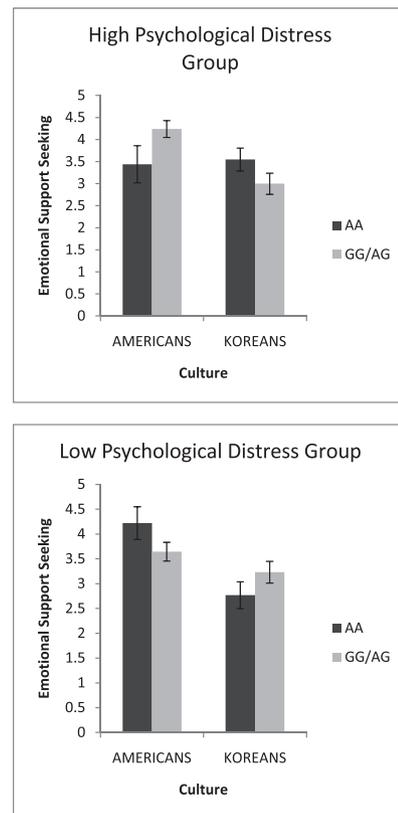

Fig. 1. Gene–culture interaction and emotional support seeking, separated by the level of psychological distress (nontransformed means and SEs).

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(mean = 2.77, SD = 1.17) did not significantly differ from those with the GG/GA genotype (mean = 3.23, SD = 1.25), $P = 0.20$, Cohen's $d = 0.38$. Additional pairwise comparisons revealed that among both genotype groups, Americans reported more emotional support seeking than Koreans [$P = 0.001$, Cohen's $d = 1.24$ for AA genotype, and, $P = 0.048$, Cohen's $d = 0.40$ for GG/AG genotypes].

Supplemental Analyses of Korean Americans. Koreans and European Americans differ not only in terms of culture, but also in the makeup of genes other than the two genes examined in the present study, which leaves gene–gene interactions as an alternative explanation for the present results regarding *OXTR* and culture. Thus, supplemental analyses were conducted to compare Korean Americans who were born and raised in the United States with European Americans and Koreans. Korean Americans would, by and large, share genetic makeup with Koreans but would be more culturally "Americanized." If culture moderates the relationship of *OXTR* to emotional support seeking, the Americanized Korean Americans' pattern should resemble the pattern of European Americans more than the pattern of Koreans.

Two separate analyses were conducted, one comparing Korean Americans with Koreans and the other comparing Korean Americans with European Americans in the same hierarchical linear regression analyses testing the gene–culture interaction on emotional support seeking. At Step 1, the contrast-coded culture variable (−1 for European Americans and 1 for Korean Americans in one analysis and −1 for Korean Americans and 1 for Koreans in another), the contrast coded *OXTR* variable (−1 for AA, and 1 for GG/AG) and the level of psychological distress (mean centered) were entered as predictors. At Step 2, the two-way interactions were entered, and there were no significant two-way interactions. At Step 3, the three-way interaction of culture, *OXTR*, and psychological distress was entered. In the comparison of Korean Americans and European Americans, there was no significant effect involving culture [$\beta = -0.14, t(136) = -1.49, P = 0.14$ for the main effect of culture, and $\beta = 0.02, t(132) = 0.17, P = 0.87, \Delta R^2 < 0.001$ for the three way interaction]. In the comparison of Korean Americans and Koreans, however, there was a significant main effect of culture [$\beta = 0.16, t(162) = 2.15, P = 0.03$], such that Korean Americans sought more support than Koreans, and a significant three-way interaction [$\beta = 0.29, t(158) = 2.96, P = 0.004, \Delta R^2 = 0.05$], reflecting the same pattern as that reported in the primary analyses. Taken together, this analysis shows that Korean Americans' pattern is indeed much more similar to culturally similar European Americans than to genetically similar Koreans.

Discussion

In recent decades, scientific appreciation of the ways in which phenotypic expression of genotypes is affected by environmental input has grown. In particular, it has become clear that several genotypes show sensitivity to input from the social environment, altering and even reversing their phenotypic expression, depending upon social conditions. The present study examined whether cultural norms can also moderate behavioral expression associated with a specific gene.

The G allele of *OXTR* rs53576 has been linked to socio-emotional sensitivity in previous studies (10–12), and we examined whether it is sensitive to culture-specific relational norms associated with seeking emotional support in response to stress. There is a robust cultural difference in social norms regarding emotional support seeking, such that American norms favor it but Korean norms discourage it, a difference that was also supported by the results of the present study; that is, Americans reported seeking more emotional support than Koreans.

Building on these findings, we predicted a three-way interaction such that, under conditions of distress, American G carriers would show more enhanced emotional support seeking than Americans

homozygous for the A allele, whereas Koreans would not differ by genotype. No such differences were expected among people experiencing low distress. Consistent with predictions, among participants experiencing high distress, there was a significant interaction between genotype and culture, such that carriers of the G allele showed enhanced sensitivity to cultural norms under conditions of distress. Emotional support seeking was higher among Americans with the *OXTR* G allele compared with Americans homozygous for the A allele, whereas the reverse but nonsignificant pattern was found in Koreans, resulting in a greater cultural difference among G carriers than people homozygous for the A allele. The present findings add *OXTR* to a growing list of genes the phenotypic expression of which is substantially modified and even reversed by input from the social environment (1, 3, 8).

The three-way interaction obtained in the present study indicates that distress and cultural norms regarding whether it is appropriate to share distress with others influenced the behavioral outcome of GG and AG genotypes of *OXTR*. Most of the previous research examining moderation of genotypic expression by input from the social environment has focused on the harshness or beneficence of the social environment (1–8). The results of the present study thus add cultural norms as a form of social input that can affect behavioral expression. That is, culture may affect the decision to seek or not to seek support, in conjunction with the psychological propensities influenced by a particular gene.

The expected cultural difference in emotional support seeking was found among individuals with the GG/AG genotype, regardless of their level of distress, but the same difference was found among individuals with the AA genotype only when their distress level was low. Given these results, it may be that those individuals with the AA genotype are able to respond concordantly with the cultural expectation when their distress level is low, but when their distress level is high, they may be less able to behave in a culturally concordant manner, hence displaying lower sensitivity to culture-specific relational norms.

A notable aspect of *OXTR* is the pattern of ethnic differences in its allelic distribution, specifically a larger proportion of the A allele among Koreans than European Americans. Because psychological and behavioral differences often have at least some genetic basis (27, 28), and there are ethnic differences in the distribution of genotypes of many polymorphisms (29), researchers have considered how the interaction of culture and genes may explain cultural differences among ethnic groups. One possibility, termed "culture–gene coevolution," proposes that cultural tendencies are adaptive and evolve and influence the social and physical environments under which genetic selection operates (30, 31). The current study shows a greater proportion of OXTR G allele among Americans than Koreans. To be sure, OXTR is only one of perhaps many genes that could underlie complex social behaviors such as emotional support seeking. Nevertheless, one interesting possibility is that the OXTR distribution difference might be linked to the difference in cultural values placed on emotional support seeking. That is, as there are more individuals with the socially affiliative genotype in America, American culture might foster seeking support from close others as a stress coping strategy, compared with Korean culture, in which there are fewer individuals with the socially affiliative genotype.

Adding to this idea regarding a long-term culture-level adaptation, the present findings provide an example of how genes and culture may interact in shaping behavioral patterns at a more individual and proximal level. Culture is not only constrained by genetics, but also influences the behavioral outcomes of genes (32, 33), and consequently, can result in diverse psychological and behavioral expressions of genotypes. Because the functional effect of the rs57576 polymorphism at the molecular level is presently unknown, whether and how it is related to oxytocin signaling pathways is also unknown. There is a possibility that culture, as a social input, may have an impact at the molecular level (34) as

well as at the behavioral level, as shown in the present research. The current findings should encourage researchers to investigate the pathways linking the molecular and behavioral levels to further understand this culture-specific genetic effect.

In the present paper, we focused on a particular polymorphism, *OXTR*, and the behavior of social support seeking, but our findings underscore the importance of examining the interaction of genetic and cultural influences with respect to other human behaviors as well, especially behaviors that have documented cross-cultural differences (an example of interaction between serotonin receptor gene and culture in cognitive style is discussed in ref. 33). The present findings provide further evidence to the old adage that people are products of both nurture and nature, and our approach provides a potential framework for understanding how these influences interact.

Materials and Methods

Participants were 134 Koreans (63 female and 71 male; 54 community members and 80 college students; mean age = 25.06 y) and 140 Americans (108 European Americans and 32 Korean Americans; 79 females and 61 males; 44 community members and 96 college students; mean age = 24.54 y). (Sex, age, and student/community status did not significantly differ between two cultural groups. We conducted all reported analyses also controlling for these variables, and in all cases, they did not change the significance levels.) The Korean participants were recruited in Korea, and their ethnicity was confirmed by their indication of Korea as the country of birth as well as by their name at the recruitment. Participants were recruited in the United States based on their self-categorized ethnicity. Participants were allowed to choose only one ethnic category among six ethnic groups (e.g., Asian American, European American, African American, Latino American, Native American, Native Pacific Islander), but an "Other" category was provided for those who did not clearly fit into these categories or for those with mixed ethnicities. Asian Americans were asked to further specify their ethnicity. Only those who indicated that they are European American or Korean American and that they were born and raised in the United States were recruited to participate in the study. Student participants were recruited through class announcements, and community participants were recruited among campus employees and from adult classes in both countries. Participants received either course credit or payment ($10 or 10,000₩ for students and $20 or 20,000₩ for community members) for their participation.

Procedure and Measures. Participants completed questionnaires assessing their level of psychological distress and their tendency to seek social support. A bilingual assistant translated the scales developed in English into Korean, and another independent bilingual assistant translated the Korean scales back to English to ensure the accuracy of the translation for Korean participants. After completion of the questionnaires and demographics, participants provided saliva samples for genetic analyses.
Psychological distress. As measures of current psychological distress, participants completed the Perceived Stress Scale (PSS) (25) and the Brief Symptoms Inventory (BSI) (26). The PSS is a 10-item scale that assessed the level of stress experienced over the last month on a scale of 0 (never) to 4 (very often) (α = 0.77 among Koreans and α = 0.85 among Americans; e.g., In the last month, how often have you felt nervous and "stressed"?). The BSI included a list of 53 psychological symptoms (e.g., feeling so restless you couldn't sit still or feeling

easily annoyed or irritated) for which participants rated their experiences in the last 7 d on scale of 0 (not at all) to 4 (extremely) (α = 0.97 among Koreans and α = 0.96 among Americans). Responses to these two scales (intercorrelation $r = 0.65$, $P < 0.001$ for Americans and $r = 0.57$, $P < 0.001$ for Koreans) were standardized and averaged to yield an index of psychological distress.
Emotional support seeking. To prompt participants to think about specific stressful experiences and how they coped with them, participants were asked to describe their biggest stressor of the last 3 mo. The participants then reported how they coped with the stressor that they just described, by completing a standardized coping inventory (35) used in our prior research (20, 21). Emotional social support seeking was measured by four emotional coping items (α = 0.83 among Koreans and α = 0.90 among Americans) ("I tried to get emotional support from friends or relatives." "I discussed my feelings with someone." "I talked to someone about how I felt." "I got comfort and understanding from someone."). Participants reported how much they used each strategy on a scale from 0 (not at all) to 6 (very much).

Genotyping. After the completion of questionnaire measures, participants provided saliva or cheek swab samples collected with the OraSure oral specimen collection device (OraSure Technologies for cheek swab samples) or Oragene collection device, for saliva samples (Genotek). The Oragene samples were kept at room temperature, and the OraSure samples were stored at −20 °C for 3–4 mo until processed. DNA was extracted using the Puregene DNA purification kit (Gentra Systems). Concentrations were determined on a spectraphotometer and equalized across samples by diluting the high-concentration samples with water.

The genotype of the *OXTR* rs53576 polymorphism was then assessed using a commercially available TaqMan SNP genotyping assay. The SNP assay contains forward and reverse PCR primers as well as two allele-specific probes conjugated with either VIC or FAM fluorescent marker. Each PCR mixture consisted of DNA templates, the SNP-specific genotyping assay, and Taqman Genotype master mix (ABI). PCR amplification was carried out on an ABI 7500 real-time PCR System following the PCR conditions recommended by the manufacturer of the SNP probe. After the PCR reactions, the allelic discrimination program (ABI) generated a genotype plot in which samples were separated into four clusters, representing the GG, GA, AA, and undetermined genotypes for *OXTR*. All samples were run in duplicate, which, in all cases, were confirmed to be consistent.

There was a higher proportion of A allele of *OXTR* among Koreans (57 AA, 55 AG, and 22 GG) than among Americans [29 AA, 54 AG, and 57 GG, $\chi^2(2, n = 274) = 24.51$, $P < 0.001$]. Americans included European Americans (13 AA, 41 AG, and 54 GG) and Korean Americans (16 AA, 13 AG, and 3 GG). European Americans' distribution significantly differed from that of Koreans [$\chi^2(2, n = 242) = 40.85$, $P < 0.001$], but Korean Americans' distribution did not [$\chi^2(2, n = 166) = 1.18$, $P = 0.56$]. Korean Americans' distribution significantly differed from European Americans [$\chi^2(2, n = 140) = 27.23$, $P < 0.001$], showing that, at least in terms of *OXTR* genotype distribution, Korean Americans were more similar to Koreans than to European Americans. These genotypes did not deviate from Hardy–Weinberg equilibrium in any cultural group [$\chi^2(2, n = 134) = 1.90$, $P = 0.17$ for Koreans; $\chi^2(2, n = 32) = 0.02$, $P = 0.88$ for Korean Americans; and $\chi^2(2, n = 108) = 1.38$, $P = 0.24$ for European Americans]. These distributions are comparable to the OXTR genotypic distributions from previous studies with ethnically similar samples (11, 13).

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