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Using multiple genes in a gene-culture interaction on expressive tendencies

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by

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ABSTRACT

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Building on gene–environment interaction (G × E) research, this study investigates how a genetic susceptibility index interacts with culture to influence expressive tendencies in a gene–culture interaction. Previous studies have identified specific genetic variants associated with greater susceptibility to environmental influences. Taking culture as a form of environment, individuals with more susceptible variants are expected to exhibit behavior more in line with cultural norms. We assessed susceptibility using a genetic susceptibility index, which was composed of multiple polymorphisms previously identified in gene—culture interaction studies of susceptibility genotypes. American and Korean participants completed assessments of expressive behavior, including value of expression, emotional suppression, and cognitive reappraisal tendencies, and were genotyped for *OXTR, 5HTR1A, SERT,* and *DRD4*. Increased expressive values and behaviors are normative in an American cultural context, but not in an East Asian cultural context like Korea. Comparing between Americans and Koreans, we found the predicted interaction on expression: Individuals with higher genetic susceptibility to environmental influence were more likely to exhibit expressive tendencies in accordance with cultural norms. Specifically, among Americans,

increased genetic susceptibility was associated with greater value of expression and lower emotional suppression, while Koreans showed the opposite pattern. For cognitive reappraisal, which does not differ between the cultures, we found no interactive effect between genetic susceptibility and culture. Both cultural groups showed an association between increased genetic susceptibility and use of cognitive reappraisal. These findings suggest cultural factors moderate the influence of genetic susceptibility across multiple genes on the manifestation of expressive tendencies.

A growing body of research has shown the effect of interactions between genes and the environment on psychological outcomes (e.g., Bakermans-Kranenburg & van Ijzendoorn, 2011; Caspi et al., 2002, 2003; Eisenberg, Campbell, Gray, & Sorenson, 2008; Taylor et al., 2006). Rather than treating genetic and environmental influences as separate, the gene–environment (G × E) interaction framework proposes that environmental conditions may moderate the manifestation of a particular underlying genotype (Caspi et al., 2002, 2003).

Building on this framework, researchers have proposed that the socio-cultural context also be considered a form of environment, which can similarly interact with biological predispositions to influence psychological outcomes (Kim et al., 2010a; Kim et al., 2010b). This approach has broadened gene–environment interaction studies, which typically conceptualize the "environment" as personal life experiences that differ in terms of quality, for example degree of life stressors (Belsky et al., 2007; Kim-Cohen & Gold, 2009). According to this gene–culture (G × C) framework, the extent to which individuals are influenced by cultural norms may differ depending on their underlying genetic predispositions. Individuals carrying the variants of genes associated with susceptibility may be predisposed to be more receptive to environmental input. Thus, such individuals are expected to exhibit behavior more in accordance with the norms of their surrounding cultural context.

Much of the past research in behavioral genetics has relied on the single target gene approach. However, recently concerns have been raised about using the candidate gene approach to examine proposed gene–environment interaction effects (Duncan et al., 2011). In particular, studies with small sample sizes may be underpowered, suggesting that many positive gene–environment findings represent Type I errors. By summing across multiple

loci, a composite index of genetic risks may increase effect size and improve power (Belsky et al., 2013).

The present research takes a multi-gene approach to investigate patterns of gene–culture interaction in shaping social psychological tendencies, focusing on comparisons between the United States and Korea. We propose that a set of genes may contribute to increased environmental susceptibility. Using a polygenetic model, we predicted that individuals at higher genetic susceptibility based on multiple polymorphic sites would be more receptive to social input in the form of cultural norms, and thus, would exhibit greater adherence to cultural norms.

Gene–Culture Interaction Framework

Existing research on gene–environment interaction has shown that depending on genetic variation, individuals can differ in their susceptibility to environmental inputs (Caspi et al., 2002, 2003). According to the gene–environment (G × E) framework, an individual may be genetically predisposed to a particular outcome, but that outcome may only manifest phenotypically given certain pressures from the environment. In other words, environmental conditions moderate the influence of genetic variants (and vice versa). For example, carrying the short (s) of the 5-HTTLPR polymorphism of the serotonin transporter (*SLC6A4*) gene increases the likelihood of exhibiting depressive symptoms, especially for those individuals exposed to early life stress (Caspi et al., 2003). Similarly, maternal insensitivity was positively associated with externalizing behaviors only among children with the 7-repeat *DRD4* allele (Bakermans-Kranenburg & van IJzendoorn, 2006), showing that carrying the 7-repeat *DRD4* allele increases susceptibility to environmental inputs. Gene–environment interactions have been found with additional genes from a variety of neurotransmitter

systems, including the dopamine D4 receptor (*DRD4*) (Bakermans-Kranenburg & van IJzendoorn, 2011; Sasaki et al., 2013), the oxytocin receptor genes (*OXTR*) (Chen et al., 2011), and the gene encoding monoamine oxidase A (*MAOA*) (Caspi et al., 2002; Foley et al., 2004; Kim-Cohen et al., 2006).

Building upon the gene–environment interaction framework, the gene–culture (G × C) interaction framework expands the definition of environment to include the sociocultural context, which can similarly interact with underlying genetic variation to influence psychological outcomes. Culture refers to a mutually shared system of beliefs, values, and institutions, which together define particular norms and practices about how to act properly and thereby influence the development of psychological tendencies (Markus & Kitayama, 1991; Kitayama, 2002).

Such cultural norms may shape how underlying genetic tendencies are manifested in behaviors. In particular, gene–culture interactions studies have highlighted genes conceptualized as 'plasticity' genes (Belsky et al., 2007). Variation of such genes may be associated with susceptibility to environmental input, in the form of input from the cultural context on how socially sensitive individuals should act, resulting in underlying genotypes being differentially manifested in phenotypes across cultural contexts. Individuals genetically predisposed to be socially sensitive are expected to exhibit behaviors more in accordance with the surrounding cultural norms and expectations.

A number of papers provide empirical evidence for the gene–culture interaction framework. Specifically variation at the four polymorphic sites included in our genetic susceptibility index has been shown to moderate the effects of cultural influence on behaviors and psychological tendencies. The *OXTR* rs53576 polymorphic region has been

shown to moderate cultural differences in both emotion support-seeking (Kim et al., 2010a) and emotional suppression (Kim et al., 2011). Similarly variation in the serotonin 1A receptor gene (*5HTR1A*) polymorphism rs6295 moderated a cultural difference in holistic attention (Kim et al., 2010b). In addition, culture moderated the influence of serotonin transporter polymorphism (5-HTTLPR) on sensitivity to disappearance of facial expression (Ishii et al., in press). A recent study provided evidence that the Exon 3 variable number tandem repeat (VNTR) polymorphism of the D4 receptor gene (*DRD4*) moderates cultural divergence on the overarching independence-interdependence social orientation (Kitayama et al., under review). These findings suggest that these are genes that may predispose people to susceptibility to environmental input.

Beyond the evidence from genetic association, oxytocin, serotonin, and dopamine as neurotransmitters have been implicated in a variety of affiliative social behaviors from cooperation and trust to emotion regulation and decision-making (Bartz et al., 2011; Knutson et al., 1998; Love, 2013). Across these neurotransmitter systems, similar associations and overlapping behavioral effects have been reported. Dopamine (Holden & Liu, 2005), serotonin (Anderson et al., 1990; McBride et al., 1998; McBride, 1989; Novotny et al., 2000; McDougle et al., 1996), and oxytocin (Modahl et al., 1993, 1998) have all been linked to autism spectrum disorders, which are marked by impairment in social, emotional, and communication skills. In additional, experimental manipulations that alter the activity of oxytocin, dopamine, and serotonin have separately demonstrated the role of these neurotransmitter systems in social decision-making processes (Mikolajczak et al., 2010; Declerk et al., 2010; Wood et al., 2006; Sevy et al., 2006). Therefore the existing association and experimental evidence suggests similar roles of these genes in social processes. Given

the evidence linking these neurotransmitter systems and the evidence from G × C and G × E studies, we investigated the effects of *OXTR*, *5HTR1A*, *SERT*, and *DRD4* polymorphisms as an overall index of genetic susceptibility to environmental input in relation to expressive tendencies.

Susceptibility Genes: OXTR, 5HTR1A, SERT, DRD4

OXTR encodes for the oxytocin receptor, a protein that binds the hormone and neurotransmitter oxytocin, and is localized to human chromosome 3 (Gimpl & Fahrenolz, 2001; Simmons, Clancy, Quan, & Knoll, 1995). One variant of *OXTR*, *OXTR* rs53576, is a single-nucleotide polymorphic site of the oxytocin receptor gene, located in intron 3 of the coding region (Gimpel & Farenholz, 2001). The A-allele of *OXTR* rs53576 has been associated with autism (Wu et al., 2005); the G-allele has been linked to increased prosocial temperament (Tost et al., 2010). Although its molecular mechanisms are unknown, *OXTR* rs53576 has been associated with differences in amygdala activation and in hypothalamic structure (Tost et al., 2010). In terms of behavior, individuals homozygous for G allele of *OXTR* rs53576 show more sensitive parenting behavior (Bakermans-Kranenburg & van IJzendoorn, 2008), more responsiveness to infant crying (Riem, Pieper, Out, Bakermans-Kranenburg, & van IJzendoorn, 2011), and greater empathic accuracy (Rodrigues, Saslow, Garcia, John, & Keltner, 2009).

5HTR1A and *SERT* are both involved in serotonin signaling. *5HTR1A* encodes for the serotonin HT_{1A} receptor, which is widely expressed in the central nervous system including in the cerebral cortex, hippocampus, septum, and amygdala (Ito, Halldin, & Farde, 1999; Glennon, Dukat, & Westkaemper, 2000; de Almedia & Mengod, 2008). We examined the role of *5HTR1A* rs6295 [aka, C(-1019)G] polymorphism, which is located in the promoter

region of the *5HTR1A* gene and is known to influence serotonin signaling. The G-allele of the *5HTR1A* rs6295 prevents binding of repressor proteins, which leads to increase gene expression and hence reduced serotonin levels (Lemonde et al., 2003; Huang et al., 2004). Relevant to social cognition, serotonin has been implicated in a variety of cognitive processes, including attention (Schmitt et al., 2000; Ahveninen et al., 2002; Ramaekers et al., 1995) and cognitive flexibility (Clarke et al., 2004).

SERT encodes for the serotonin transporter protein, which transports serotonin from the synaptic cleft to the presynaptic neuron for reuse. We examined the role of a polymorphic region within the serotonin transporter gene (*SLC6A4)*, known as 5-HTTLPR, comprising a short (S) allele and a long (L) allele version. This polymorphism is located within the promoter region of the serotonin transporter gene and is known to result in differential 5-HTT expression and function (Lesch et al., 1996; Hariri, 2009). The S-allele of 5-HTTLPR is linked to decreased 5-HTT mRNA expression resulting in higher serotonin concentrations in the synapse compared to the L-allele (Lesch et al., 1996). Evidence from behavioral genetics has implicated the S-allele of the serotonin transporter gene in increased negative emotion tendencies, including anxiety (Sen et al., 2004; Munafo et al., 2005), harm avoidance (Munafo et al., 2005), and fear conditioning (Lonsdorf et al., 2009).

DRD4 encodes for the dopamine D_4 receptor and contains a 48-base pair variable number tandem repeat (VNTR) in exon III, which ranges from 2- to 11-repeats (van Tol, 1992). The various D4 repeat sequences have differential influences on gene expression, with the 7-repeat version reducing gene expression, compared to the 2- and 4-repeat version (Schoots & Van Tol, 2003). Behaviorally certain variants of the *DRD4* VNTR polymorphism have been linked to risk-taking and antisocial behaviors, including increased novelty or

sensation seeking (Ebstein et al., 1996), gambling (Perez de Castro et al., 1997), risk taking (Kuhnen and Chiao, 2009), decreased altruism (Bachner-Melman et al., 2005), and reduced sensitivity to reciprocal fairness (Zhong et al., 2010).

Further the target genes of interest and related neurotransmitter systems are anatomically and functionally related within the hypothalamic region of the brain. In the hypothalamic paraventricular nuclei (PVN) and supraoptic nuclei (SON), oxytocin is synthesized and released with projections to the posterior pituitary, the limbic systems, and different autonomic centers. Dopamine D4 receptors and serotonin 1A receptors are expressed in the hypothalamic PVN and SON regions and appear to modulate oxytocin neuronal activation. Specifically stimulation of dopamine D4 receptors (Succu et al., 2007) and serotonin 1A receptors (Jorgensen, 2003) increases oxytocin release. Although the activity of the serotonin transporter has not been empirically linked to oxytocin activity, since the transporter protein acts by removing serotonin from the synaptic cleft, it should theoretically lower the availability of serotonin, thus reducing oxytocin activity. Taken together, the evidence suggests that the candidate genes are related behaviorally, as well as functionally within the brain.

The Present Work

The present study aims to test the G × C model using the genetic susceptibility index based on the four polymorphisms from the four genes (*OXTR*, *5HTR1A*, *SERT*, and *DRD4*) implicated in environmental susceptibility. More specifically, we examined the interaction between the genetic susceptibility index and culture (i.e. American and Korean participants) in shaping the tendencies of self-expression. Based on prior research (e.g., Butler et al., 2007; Kim & Sherman, 2007; Lee et al., 2009; Matsumoto et al., 2008), we expected that Koreans

would value expression less and exhibit less emotional expression, compared to Americans. Moreover, as described earlier, studies have found G × C interaction on different types of expressive behaviors (e.g., emotion expression/suppression) using the single target gene approach. Thus, we predicted a gene–culture interaction on expressive tendencies using our multi-gene susceptibility index. Specifically we predicted that among Americans, increased genetic susceptibility would be associated with higher value of expression and greater emotion expression, while Koreans would show the opposite pattern. Further we examined the relationship between genetic susceptibility and cognitive reappraisal, an emotion regulation strategy, which has not been shown to differ between cultures (Gross & John, 2003; Matsumoto et al., 2008). Given that cognitive reappraisal tendencies do not differ by culture, we did not predict a gen-culture interaction on cognitive reappraisal. Instead, we predicted a direct relationship, whereby increased genetic susceptibility would be associated with increased cognitive reappraisal tendencies for both Koreans and American participants.

METHODS

Participants

Participants included 99 Koreans (41 males and 58 females; mean age = 22.42) and 152 Americans (60 males and 92 females, mean age = 19.31), including 45 Asian Americans and 107 European Americans. Asian American and European American participants were recruited in the United States based on their self-categorized ethnicity from the option of six ethnic groups (including: Asian American, European American, African American, Latino American, Native American, and Native Pacific Islander). For participants who identified their ethnicity as Asian American, we asked them to specific their country of origin. Only participants who answered that their family was from East Asian countries (i.e., Korean,

Japan, and China) were included as East Asian Americans in the analyses. Korean participants were recruited in Korea, and selected on the basis of country of birth and name at recruitment. Participants were recruited through the psychology department participant pool and class announcements. For participation, participants received either course credit or monetary compensation ($10 or 10,000₩ respectively).

Procedure and Materials

As part of a larger collection of questionnaires, participants completed the following measures on a computer: the Value of Expression Questionnaire, VEQ (Kim & Sherman, 2007) and the Emotion Regulation Questionnaire, ERQ (Gross & John, 2003). The VEQ was designed to assess the extent to which participants value expression and includes a total of 11 items: 6 items assessing the importance of expression in behavior (e.g., "I express my feelings publicly, regardless of what others say") and 5 items assessing the importance of beliefs related to expression (e.g., "The freedom of speech is the most important right"). Participants responded on a 1 (strongly disagree) to 8 (strongly agree) scale. The ERQ assesses individual differences in two emotion regulation strategies: emotion suppression and cognitive reappraisal. The questionnaire includes a total of 10 items: four items measuring suppression (e.g., "I control my emotions by not expressing them") and six items measuring cognitive reappraisal ("I control my emotions by changing the way I think about the situation I am in"), assessed on a 1 (not at all) to 7 (very much) scale. After completing the questionnaires, participants answered demographic questions, including age, gender, ethnicity, place of birth, and language spoken at home, and provided saliva samples for genotyping. All the measures described were originally developed in English. A bilingual research assistant translated the scales from English into Korean and a second bilingual

research assistant back-translated the scales to confirm the accuracy of the original translation.

Genotyping

Saliva samples were collected using an Oragene Saliva kit OG-500. DNA was extracted following the manufacturer recommendation (DNA Genotek, Ontario, Canada). DNA was quantified using A260/A280 ratio.

The *OXTR* and *5HTR1A* polymorphisms were genotyped using similar procedures. The *OXTR* rs53576 polymorphism was genotyped using a 50-nuclease assay to discriminate between the two alleles (Taqman SNP Genotyping Assay *OXTR* -C-3290335_10, Applied Biosystems Inc., Foster City, CA). The *5HTR1A* rs6295 [aka, C(-1019)G] polymorphism was genotyped using a 5′ nuclease assay to discriminate between the two alleles (Taqman SNP Genotyping Assay C__11904666_10, Applied Biosystems Inc.). Polymerase chain reactions were performed using 5-mL reaction volumes in 384-well plates with 5 ng of DNA. The standard protocol provided with the kit was followed. End point reads of fluorescence levels were obtained with an ABI 7900HT Sequence Detection System.

The genotypes of the *5-HTTLPR* rs25531 polymorphism were identified using following protocol. The forward primer was labeled with 6FAM-5'-GGC GTTGCC GCT CTG AAT GC-3', the reverse primer was unlabelled 5'-GAG GGA CTGAGC TGG ACA ACC AC-3', which yielded 484-bp (short) and 527-bp (long) fragments. Polymerase chain reaction (PCR) was performed in a total volume of 25 µL, containing 50 ng of DNA; 1µl of each primer (10µM stock); 1.5µl of (25mM)MgCl2; 2% DMSO (v/v); 2.5 U Amplitaq Gold DNA polymerase (Applied Biosystems, Foster City, California); 2ul of Deaza dNTP (2mM each dATP, dCTP, dTTP, 1mMdGTP, 1mM deaza dGTP). Cycling conditions consisted of

1) an initial 12 min denaturation at 94°C; (2) 8 cycles with denaturation for 30 sec at 94°C, varied annealing temperatures consisting of 30 sec at 66°C (2 cycles), then 65°C (3 cycles), then 64°C (3 cycles), followed by hybridization for 1 min at 72°C; (3) 35 cycles with an annealing temperature of 63°C and the same denaturation and hybridization parameters; and (4) a final extension for 20 min at 72°C. The PCR products were electrophoresed on an ABI 3730 DNA analyzer (Applied Biosystems) with a LIZ1200 size standard (AppliedBiosystems). Data collection and analysis used Genemapper software (Applied Biosystems)

DRD4 genotypes were identified using the labeled forward primer VIC-50-AGG ACC CTC ATG GCC TTG-30 and the unlabelled reverse primer 50-GCG ACT ACG TGG TCT ACT CG-30 (Lichter et al., 1993). Polymerase chain reaction (PCR) was performed in a total volume of 10ml containing 25ng of DNA, 0.5ml of each primer (10mM stock), 0.1ml Takara LA Taq, 5ml 2x GC Buffer II (Takara Bio Inc., USA) and 1.6 ml dNTP. PCR cycling conditions consisted of an initial 1 min denaturation at 95°C, followed by 30 cycles of 94°C for 30 s, 62°C for 30 s, 72°C for 2min and finally 72°C for 5min. PCR products were electrophoresed on an ABI 3730 DNA analyzer (Applied Biosystems) with a LIZ1200 size standard (Applied Biosystems). Data collection and analysis used Genemapper software (Applied Biosystems).

Genetic Susceptibility Index

We created a single index of genetic susceptibility to environmental input by averaging across variation of candidate polymorphisms of the four genes. To compute the genetic susceptibility index, we employed an additive model (Lewis, 2002; Minelli, 2005), which assumes a monotonic increase in association with environment susceptibility as one

moves from zero to one and one to two copies of the relevant allele, and then averaged across the genes.

Because no evidence exists to determine the exact contributions of the individual polymorphisms to environmental susceptibility, we used an unweighted count of alleles to construct the index. In other words, we assumed each gene contributed equally to environmental susceptibility. For *SERT*, *5HTR1A*, and *OXTR*, the theoretically most environmentally susceptible homozygote was assigned a value of 2, the theoretically least susceptible homozygote was assigned a value of 0. Heterozygotes were assigned a value of 1. For *SERT*, the *s/s* variant was assigned 2; *s/l* was assigned 1; *l/l* was assigned 0. For *OXTR*, the G/G genotype was assigned 2; A/G was assigned 1; A/A was assigned 0. For *5HTR1A*, the G/G genotype was assigned 2; C/G was assigned 1; C/C was assigned 0. For *DRD4*[1], participants were divided into individuals having two 2- or 7-repeat alleles (so: 2/2, 2/7, or 7/7 variants) (valued as 2), those having at least one 2- or 7-repeat allele (valued as 1), and those having no 2- or 7-repeat allele (valued as 0). We then averaged across the values for each of the four genetic variants. Therefore, the highest possible value on our index of genetic susceptibility is 2; and the lowest possible value is 0. For the interactive effects of isolated genes in a culture x gene ANOVA performed for each gene on each expression-related outcome, see Table 1.

[1] Previous research has shown that the distribution of DRD4 variants differs across ethnic groups (Chang et al., 1996). Across populations, the 2-, 4-, and 7-repeat alleles are most common (Wang et al., 2004). Between Caucasian and East Asian populations, the 4-repeat allele is most common and is considered the non-susceptibility variant. However, the DRD4 variant considered to be the susceptibility variant differs across populations. In Caucasian populations, individuals carrying the 7-repeat allele exhibit the greatest antisocial tendencies (Ebstein et al., 1996), while such tendencies are highest among 2-repeat allele carriers in East Asian populations (Zhong et al., 2010) or the 2- and 7-repeat alleles combined (Reist et al., 2007). Further evidence suggests that the 2- and 7-repeat alleles share similar properties (Reist et al., 2007), especially in decreased efficiency activating the downstream effector when dopamine binds to them compared to the 4-repeat allele (Asghari et al., 1996; Wang et al., 2004). Thus, we grouped the 2- and 7-repeat alleles tougher as susceptibility variants and treated all other alleles (i.e., 3-, 4-, 5-, 6-, 8-, 9-, 10-, and 11-repeats) as non-susceptibility variants across our American and Korean participants.

RESULTS

Distributions of *SERT, 5HTR1A, OXTR, DRD4, and Susceptibility Index*

For both serotonin-related genes, namely *SERT* and *5HTR1A*, the theoretically more environmentally susceptible alleles were more common among Koreans than among Asian Americans and European Americans. The distributions for *5HTR1A* are consistent with distributions from previous studies (Chiao & Blizinsky, 2010). For *OXTR*, the more susceptible alleles were less common among Koreans as compared to Asian Americans and European Americans, with findings comparable to distributions from previous studies using similar samples (Kim et al. 2010b). For DRD4, among Koreans, European Americans, and Asian Americans, the most common variant was the 4/4 variant, and among European Americans and the least common variants were the 2/2 and the 7/7 forms, distributions consistent with past research using similar ethnic groups (Chang et al., 1996; Chen et al., 1999). The distribution of participants with the susceptibility variants (i.e., 2- or 7-repeat alleles) and those with the non-susceptibility variants (i.e., 3-, 4-, 5-, 6-, 8- 9-, 10-, and 11-repeats) did not differ between the two groups, $\chi^2(2, N = 274) = 4.700$, $p = .095$. For complete allelic distributions of the individual genes, see Table 2.

To examine the distribution of the computed genetic susceptibility index, we conducted a one-way ANOVA comparing Koreans to Asian Americans to European Americans. There was no significant difference between the cultural groups, $F(2, 256) = 2.245$, $p = .108$. Further, comparing between Americans (both European Americans and Asian Americans) and Koreans, there was no difference between the two distributions according to the two-sample Kolmogorov-Smirnov test ($D = 0.1188$, $p = 0.3638$).

Gene–culture Interaction on Value of Expression and Emotion Suppression

To examine the gene–culture interaction with respect to expressive behavior, including the value of expression and emotion suppression, we conducted a series of moderated regression analyses to test the hypothesis that the relationship between a composite index of genetic tendency to environment susceptibility and outcomes related to expression would be moderated by culture. For each analysis, the composite genetic susceptibility index and culture variable were entered on Step 1 and the interaction term was entered on Step 2. The three cultures were grouped to compare Asian Americans and European Americans together with Koreans.

Value of Expression At step 1, there was no significant main effect of culture (b = -.153, $t(194)$ = -1.226, p = .222) and no significant main effect of genetic susceptibility (b = -.224, $t(194)$ = -.976, p = .330). Together these two predictors explained approximately 1.4% of the variance in scores on the value of expression behavior subscale, which was not statistically significant, R^2 = .014, $F(2, 194)$ = 1.422, p = .244. At step 2, the interaction term explained an additional 1.6% of the variance in the value of expression behavior scores, which was marginally significant, $F(1, 193)$ = 3.235, p = .074. To explore this interaction, we plotted the simple slope of value of expression scores on genetic environmental susceptibility for Koreans and for Americans (including both Asian Americans and European Americans). As predicted, we found a significant negative relationship between genetic susceptibility and value of expression for Koreans [simple b = -.582, $t(193)$ = -1.921, p = .056]. Korean participants at higher genetic susceptibility were less likely to report expressive behaviors and expression-related beliefs. For Asian Americans and European Americans, the relationship between genetic susceptibility and value of expression was not significant [simple b = .248, $t(193)$ = .713, p = .477]. (See Figure 1.)

Emotion Suppression In Step 1, there was a significant main effect of culture (b = .339, $t(253) = 2.390$, p = .018) but there was no significant main effect of genetic susceptibility (b = -.144, $t(253) = -.624$, p = .533). Together these two predictors explained approximately 2.3% of the variance in scores on emotion suppression, which was statistically significant, $F(2, 253) = 2.926$, p = .055. At step 2, the interaction term explained an additional 2.6% of the variance in emotion suppression scores, which was significant, change in R^2 = .026, $F(1, 252) = 6.912$, p = .009. To explore this interaction, we plotted the simple slope of emotion suppression scores on genetic susceptibility for Asian Americans and European Americans, and separately for Koreans. As predicted, we found a negative relationship between genetic susceptibility and emotion suppression for Asian Americans and European Americans [simple b = -.599, $t(252) = -2.090$, p = .038], such that more susceptible Asian Americans and European Americans reported less emotion suppression, compared to less susceptible participants. For Koreans, the predicted positive relationship between genetic susceptibility and emotion suppression was marginally significant [simple b = .649, $t(252)$ = 1.715, p = .088] in the predicted direction. (See Figure 2.)

In summary, for Asian Americans and European Americans, greater genetic susceptibility was associated with increased expressive tendencies, including greater reported value of expressive behaviors and lower emotion suppression scores. These tendencies are consistent with exposure to an American cultural context in which expression is highly emphasized. In contrast, for Korean living in a cultural context that places less importance on expression, increased genetic susceptibility to environmental input was associated with decreased expressive tendencies, including valuing expression less and reporting greater emotion suppression tendencies. In other words, a genetic predisposition for susceptibility to

environmental influence appears to be associated with greater adherence to the surrounding cultural norms.

Relationship between genetic susceptibility and cognitive reappraisal

To examine the link between genetic susceptibility and cognitive reappraisal, we conducted a moderated regression analysis to test whether the relationship between the composite genetic susceptibility index and cognitive reappraisal tendencies would be moderated by culture. The genetic susceptibility index and culture were entered on Step 1 and the interaction term was entered on Step 2. As before, the three cultures were grouped to compare Asian Americans and European Americans together with Koreans separately.

In Step 1, there was a marginally significant main effect of culture (b = -.203, t(253) = -1.713, p = .088) and a significant main effect of genetic susceptibility (b = .581, t(253) = 3.015, p = .003). Together these two predictors explained approximately 4.2% of the variance in scores on emotion suppression, which was statistically significant, R^2 = .042, F(2, 253) = 5.531, p = .004. In Step 2, the interaction term explained an additional .4% of the variance in emotion suppression scores, which was not significant as predicted, change in R^2 = .004, F(1, 252) = 1.114, p = .292. (See Figure 3.)

Supplemental Analyses of East Asian Americans

In addition to the main analyses comparing Americans (both Asian Americans and European Americans) to Koreans, we also separated participants into Asians (including East Asian Americans and Koreans) and European Americans to examine the role of biological genetic makeup. Compared to European Americans, East Asian Americans should be biologically more similar in terms of genetic makeup to Koreans but should be more culturally similar to Americans based on acculturation. If cultural exposure moderates the

association between our genetic susceptibility index and culturally variant psychological outcomes, then the interactive pattern should not be significant when grouping Asians and European Americans.

Two separate moderated regression analyses were run to examine the gene–culture interaction with respect to expressive tendencies, including the value of expression and emotion suppression. The genetic susceptibility index and expression-related dependent variables (namely value of expression and emotion suppression) were entered in Step 1 and the interaction term was entered in Step 2. Here the culture variable was dummy-coded to compare Asian Americans and Koreans with European Americans. In the comparison between Asians and European Americans with respect to value of expression, there was a main effect of culture (b = -.371, t(193) = -2.881, p = .004) but there was no main effect of genetic susceptibility (b = -.176, t(193) = -.779, p = .437). There was no interactive effect, change in R^2 = .009, F(1, 193) = 1.879, p = .172. Similarly, for emotion suppression, there was a significant main effect of culture (b = .362, t(252) = 2.586, p = .010) and no main effect of genetic susceptibility (b = -.152, t(252) = -.659, p = .510). There was no interactive effect, change in R^2 = .006, F(1, 252) = 1.571, p = .211. Together these analyses support the grouping of East Asian Americans with European Americans. While Asian Americans may be more similar to Koreans at the genetic level, the pattern of Asian Americans is more similar to European Americans, based on cultural exposure.

DISCUSSION

The present study provides initial evidence that culture and the combined contributions of multiple genes can influence expression-related tendencies. We found the predicted interactive effect between cultural context and a genetic susceptibility index

composed of *OXTR*, *5HTR1A*, *SERT*, *D4DR* polymorphisms on expressive values and behaviors. Specifically, the genetic susceptibility index was associated with whether individuals exhibited expressive-tendencies consistent with the surrounding cultural norms. For Americans living in a cultural context that emphasizes expression, those individuals at higher genetic susceptibility valued expression more and suppressed emotion less, compared to individuals at lower genetic susceptibility to environmental input. Among Koreans, the pattern was reversed, such that those at higher genetic susceptibility valued expression less and suppressed emotion more, compared to those at lower genetic susceptibility. Further, we found an association between genetic susceptibility and cognitive reappraisal, an emotion regulation strategy, which does not differ between American and East Asian cultures. As expected given the lack of reported cultural differences in cognitive reappraisal tendencies, we did not find an interactive effect between genetic susceptibility and culture on cognitive reappraisal. Instead, for both Americans and Koreans, genetic susceptibility was associated with increased use of cognitive reappraisal coping strategies, underscoring the proposed role of genetic susceptibility in environmental sensitivity. Increased genetic susceptibility was linked to greater cultural divergence only for those expression-related outcomes known to differ between cultures.

Previous research has related individual polymorphisms in the genes included in the genetic susceptibility index to altered predisposition to sensitivity to environmental inputs in the form of sociocultural norms (Kitayama et al., under review; Ishii et al., in press; Kim et al., 2010a; Kim et al., 2010b). However, to our knowledge, the present study is among the first to examine the influence of multiple genetic susceptibility variants in relation to the manifestation of culturally divergent psychological tendencies. This approach may help

overcome the small effect size associated with the minor contribution of any single allele (Ioannidis et al., 2006). For example, a meta-analysis of non-human lymphocyte antigen genetic association study suggested that the typical effect size of individual genetic variants for complex diseases are odds ratios of 1.2 – 1.6 (Ioannidis et al., 2006). To consider the contributions of multiple loci to complex traits determined by multiple genes, summing across variants to yield a composite index can potentially increase effect size and improve statistical power (Belsky, 2013).

Our approach of using multiple genetic variants can be likened to designing a scale measure using multiple items in order to increase reliability. Scales, which include multiple-items, tend to be more reliable, compared to single-item scales. According to the Spearman-Brown prediction formula, item responses include both random measurement error and true score variance (Spearman, 1910; Brown, 1910). To increase the reliability of the overall score, one can increase the number of items that assess roughly the same underlying psychological construct. Aggregating across multiple items effectively cancels out meaningless errors. We propose that the genetic variants included in our genetic susceptibility index link to similar underlying biological and psychological functions, namely altering susceptibility to environmental inputs. By combining multiple genes, we effectively assess the same underlying phenomenon to increase reliability of the overall measure.

There are several limitations to this study. The findings are based on a relatively small sample size. Even combining the contributions of multiple loci may not sufficiently increase the effect size to overcome the modest sample size. In addition, we used a simple additive model to account for the contributions of multiple genetic variants. Additive models alone cannot account for more complicated interactive genetic phenomenon, like epistasis

and dominance. In the study of genetic contributions to complex traits, researchers have asserted that genes do not generally act in a simple additive model, but rather through complex interacting networks (Colhoun, 2003). Future work could more fully account for the complexity of biological and social factors involved, including the possibility of gene-gene interactions. Integrative gene network approaches, which highlight key elements and biological processes relevant to traits, may uncover potential regulatory relationships between genes providing evidence of the interactive dynamics of genes (e.g., Lee et al., 2012).

In the present study, the selection of genetic variants was limited to those polymorphisms already identified in previous gene–culture interaction studies as relevant to environment susceptibility. Functional evidence for the role of the polymorphism in modulating neurotransmitter activity may be lacking. To link variation at a small site to larger biological processes, it is important for future work to consider the functional basis of the alteration. Further, the selection of genes could be better informed by neuroanatomical structure and function. For example, correlations between mRNA expression levels of neurotransmitter receptors in the brain may point to potential functional relationships among receptors (Janusonis, 2014). Genes may also encode for protein components of the same neurotransmitter system, suggesting a method of combining the influence of genes in a more sophisticated manner. In the present study, we considered the contributions of polymorphisms of both the *5HTR1A* and *SERT* gene, two genes involved in serotonin signaling activity. The same system also includes genes that encode for the protein that synthesizes serotonin and the protein that degrades serotonin. A system-informed approach

could take into account variation of each of these genes, which might combine and interact to influence biological and psychological outcomes.

The gene–culture interaction framework has now been studied with several polymorphic sites and psychological outcomes (Kitayama et al., under review; Ishii et al., in press; Kim et al., 2010a; Kim et al., 2010b). Our findings suggest that future gene–culture interaction studies may benefit from a focus on multiple genes that relate to environmental susceptibility rather than examining variation of individual genes.

Table 1. The main effects and culture x gene interaction effects in culture × individual gene ANOVA's performed for each gene on each behavioral outcome.

		Main Effect of Gene		**Gene × Culture**	
DV	**Gene**	*F*	*p*	*F*	*p*
Value of expression	*OXTR*	(2, 203) = .086	.921	(2, 203) = 7.865	.001
	DRD4	(2, 202) = .071	.934	(2, 202) = .341	.712
	5HTR1A	(2, 198) = .930	.518	(2, 198) = .121	.886
	SERT	(2, 209) = 1.689	.372	(2, 209) = .405	.667
Emotion Suppression	*OXTR*	(2, 268) = .116	.896	(2, 268) = 5.110	.007
	DRD4	(2, 264) = 5.006	.167	(2, 264) = .204	.815
	5HTR1A	(2, 261) = 3.937	.203	(2, 261) = .633	.532
	SERT	(2, 275) = .086	.921	(2, 275) = .379	.685
Cognitive Reappraisal	OXTR	(2, 268) = 32.608	.030*	(2, 268) = .049	.952
	DRD4	(2, 264) = .344	.744	(2, 264) = 1.247	.289
	HTR1A	(2, 261) =1.128	.470	(2, 261) = 6.668	.001*
	SERT	(2, 275) = .342	.745	(2, 275) = 1.715	.182

Table 2. Distributions of *OXTR, 5HTR1A, SERT, and DRD4* polymorphism variants.

Gene	Culture	Genotype			Test of differences between cultures	Hardy–Weinberg Equilibrium
OXTR		**AA**	**AG**	**GG**		
	Koreans	50	40	9		$X(2, N = 99) = .06, p > .05$
	AA/EA	42	79	57		$X(2, N = 178) = 2.00, p > .05$
					$X(2, N = 284) = 45.718, p < .001$	
5HTR1A		**CC**	**CG**	**GG**		
	Koreans	5	38	55		$X(2, N = 98) = .23, p > .05$
	AA/EA	30	76	66		$X(2, N = 172) = .99, p > .05$
					$X(2, N = 270) = 12.155, p = .002$	
SERT		**L/L**	**S/L**	**S/S**		
	Koreans	4	33	.63		$X(2, N = 90) = .16, p > .05$
	AA/EA	49	89	.25		$X(2, N = 184) = .019, p > .05$
					$X(2, N = 284) = 45.718, p < .001$	
DRD4		**no 2- or 7-repeat**	**one 2 or 7-**	**two 2- or 7's**		
	Koreans	71	23	3		$X(2, N = 91) = .01, p > .05$
	AA/EA	107	59	11		$X(2, N = 92) = .36, p > .05$
					$X(2, N = 274) = 4.700, p = .095$	

Figure 1. The interaction between culture and genetic susceptibility on value of expression.

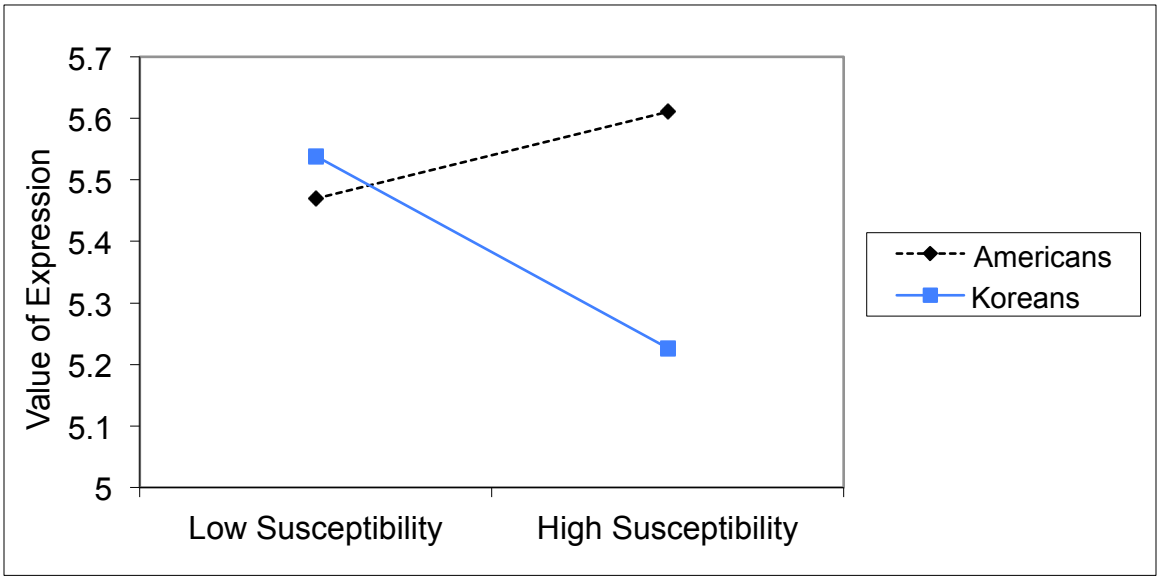


Figure 2. The interaction between culture and genetic susceptibility on emotion suppression.

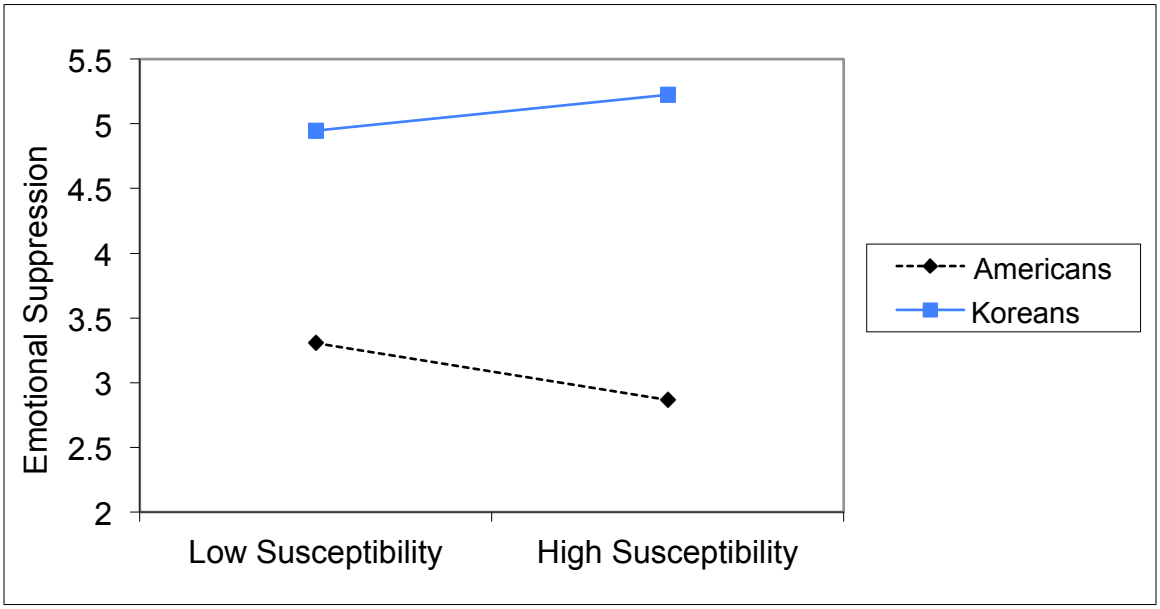
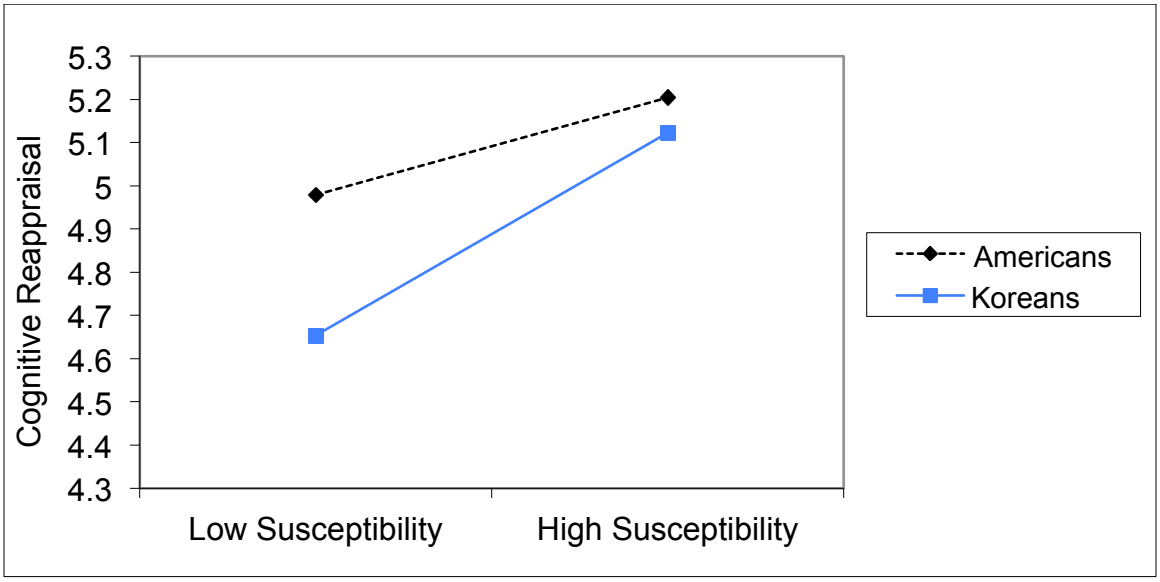


Figure 3. The relationship between genetic susceptibility and cognitive reappraisal.



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