The Serotonin Transporter Polymorphism (5-HTTLPR):

Allelic Variation and Links with Depressive Symptoms

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ABSTRACT

We use data from a nationally-representative sample of older adults in Taiwan to explore variation in the serotonin transporter polymorphism (5-HTTLPR) and to examine interactions among sex, stressful experience, and 5-HTTLPR genotype on depressive symptoms. The Taiwan sample comprises a much higher frequency of the S/S genotype and a lower frequency of the L/L genotype than Western samples, but the distribution is comparable to those in East Asian populations. Nearly 9% carry an allele (XL) that has rarely been reported in the literature. Our findings are consistent with research demonstrating that the effects of the 5-HTTLPR polymorphism are moderated by exposure to stressful experience. We find a positive relationship between depressive symptoms and both lifetime exposure to trauma and major life events in the previous year for persons with the S/S or S/L genotypes, but not for those with the L/L genotype or at least one XL allele. We find no evidence that these gene-environment interactions vary by sex. Our findings raise questions about why East Asian populations exhibit relatively low rates of depression despite a high frequency of the unfavorable S allele.

INTRODUCTION

Serotonin (5-HT), a key central nervous system neurotransmitter, is involved in regulating a broad range of psychological traits, behaviors, and physical functions, including mood, sleep, appetite and sexual activity. The serotonin transporter protein (5-HTT), which terminates the action of serotonin by facilitating its reuptake from the synapse to the pre-synaptic neuron, appears to be part of the pathway leading to various psychiatric disorders and has been a target of widely used pharmacological treatments. It is thus not surprising that the gene associated with serotonin transport (SLC6A4) has been the focus of extensive research. More than a decade ago, a polymorphism in the promoter region of the gene encoding 5-HTT, referred to as 5-HTTLPR, was identified by Heils et al. (1996): a 44bp deletion/insertion generated two alleles of 5-HTTLPR, with the 14-repeat short variant having less transcriptional activity and lower serotonin uptake than the 16-repeat long variant. Researchers speculated that the differential transcriptional activity caused by this polymorphism would influence complex traits and diseases, including affective disorders (Collier et al. 1996; Heils et al. 1996).

Subsequent studies suggest a nuanced relationship between the 5-HTTLPR polymorphism and psychiatric disorders. First, although the vast majority of studies have considered the 5-HTTLPR polymorphism to be functionally bi-allelic, researchers have identified alleles beyond the short (S) and long (L) variants found by Heils and colleagues. Gelernter et al. (1997) identified two uncommon alleles that are longer than the L variant: 1) an extra-long allele, which they designated XL, was found in both an African American and a Japanese sample; and 2) a single instance of an allele of length between the L and XL alleles, which they labeled VL, was also observed in the Japanese sample. In the same year, Delbruck and colleagues (1997) identified a “novel allelic variant” of 5-HTTLPR (which they designated as XL) among persons of African origin but not among Caucasians or East Asians. One study in Japan reported two XL variants, one with 18 and one with 20 repeats (Narita et al. 2001), whereas another identified alleles with 19 and 20 repeats

in a Japanese sample (Kunugi et al. 1997). With more detailed genotyping of 5-HTTLPR among Japanese and Caucasian subjects, Nakamura et al. (2000) identified four different S alleles and six different L alleles as well a few other alleles (15-, 19-, 20- and 22-repeats) found only in the Japanese sample. Thus, a dichotomous classification of 5-HTTLPR is likely to obscure potential differences in allele effects.

A second set of discoveries suggests that the effects of 5-HTTLPR on psychiatric disorders may be moderated by environmental factors. Much of this research has focused on how stressful life events affect the relationship between 5-HTTLPR and depression or depressive symptoms. In a well-cited study, Caspi and colleagues (2003) failed to find any direct association between 5-HTTLPR and depression but found that, among those exposed to stressful events, presence of the short allele was related to depressive symptoms in a graded fashion: levels of depressive symptoms were lowest among persons with L/L genotype, intermediate among S/L, and highest among those with S/S genotype. Several studies have found a similar gene-environment interaction (Brummett et al. 2008; Eley et al. 2004; Sjöberg et al. 2006; Wilhelm et al. 2006), but others have reported that the most notable distinction was between individuals homozygous for S and those with at least one L allele (Cervilla et al. 2006; Jacobs et al. 2006; Kaufman et al. 2004; Kendler et al. 2005; Kim et al. 2007; Taylor et al. 2006). Still, some studies have found no GxE interaction (Chipman et al. 2007; Gillespie et al. 2005; Kilpatrick et al. 2007; Scheid et al. 2007; Surtees et al. 2006).

A third source of complexity arises from studies hypothesizing that demographic characteristics – particularly sex, race and ethnicity – are likely to moderate the effect of 5-HTTLPR and its interaction with adverse life events on depression (Brummett et al. 2008; Sjöberg et al. 2006). Under stressful circumstances, susceptibility to depression among individuals carrying the S allele was stronger among women than men in several studies (Brummett et al. 2008; Eley et al. 2004; Sjöberg et al. 2006). Yet, two other studies reported no sex difference in the gene-environment interaction (Cervilla et al. 2006; Taylor et al. 2006). Although researchers have demonstrated that

the distribution of 5-HTTLPR genotype varies substantially across racial and ethnic groups (Brummett et al. 2008; Delbruck et al. 1997; Gelernter et al. 1997; Gelernter et al. 1999; Hu et al. 2006; Nakamura et al. 2000; Taylor et al. 2006), we are aware of only two studies that explicitly tested an interaction term among race, stressors, and 5-HTTLPR in a model of depression. These studies found no difference in the gene-environment interaction between blacks and whites (2008) or between Asians and non-Asians (Taylor et al. 2006).

In this study, we use data from a large national sample of Taiwanese participants to examine these issues. By comparing the 5-HTTLPR genotype distribution in our study with those from samples of different racial and ethnic groups, we underscore the large variation across populations. We identify a much higher frequency of XL alleles in our sample than in most previous studies, challenging earlier research that contends that the XL allele is rare. Finally, we examine the interaction between stressful experience and 5-HTTLPR genotype on depressive symptoms and explore whether this GxE interaction varies by sex. The estimates provide insight into the phenotype associated with the XL allele.

METHODS

Data

The data come from the second wave (2006) of the Social Environment and Biomarkers of Aging Study (SEBAS). SEBAS comprises a nationally representative sample of persons aged 53 and older (in 2006) in Taiwan with oversampling of persons 77 years and older and urban residents. Written informed consent was obtained for participation in both the in-home interview and hospital visit; all protocols were approved by human subjects committees in Taiwan, Georgetown University, and Princeton University. In-home interviews were completed with 1,284 respondents, including 757 participants aged 60 and over who participated in the medical examination component of the 2000 SEBAS (89.5% response rate) as well as 527 respondents from a younger cohort aged 53 to 60 (80.2% response rate).

Among those interviewed, 80.7% (n=1,036) also participated in the medical exam component of the 2006 study; 0.2% (n=3) died before the exam, 2.5% (n=32) were not eligible for the exam because of a health condition, and 16.6% (n=213) declined to participate. Both the youngest (aged 53-59) and the oldest (80+) respondents were less likely to participate in the medical exam than those aged 60-79. Participation was also lower among less educated respondents and those with ADL limitations compared with their respective counterparts. Participants did not differ significantly from non-participants in terms of self-reported health status.

On a scheduled day several weeks after an in-home interview, participants collected a 12-hour overnight urine sample (7pm to 7am), fasted overnight, and visited a nearby hospital the following morning where medical personnel drew a blood specimen and took blood pressure and anthropometric measurements. Compliance in the collection of these samples was extremely high. The resulting specimens were analyzed at Union Clinical Laboratories (UCL) in Taipei. Additional details about the SEBAS study are provided in Glei et al. (2006) and Chang et al. (2007).

Measures

Depressive symptoms are measured by a 10-item subset of the 20-item Center for Epidemiologic Studies Depression scale (CES-D) using standard coding based on the number and severity of symptoms. The score ranges from 0 to 30, with higher values indicating more frequent depressive symptoms (Cronbach's alpha = 0.83). The CES-D has demonstrated reliability in older populations (Hertzog et al. 1990) and a shortened form of the instrument was validated among elderly Chinese (Boey 1999; Cheng and Chan 2005). Because a large percentage of the population experienced at least one of the traumas or at least one of the recent major life events described below, we defined our measures of stressful experience in terms of at least two events. One dichotomous variable indicates whether the respondent ever experienced two or more types of trauma (out of seven) that involved threat of serious injury or death (e.g., natural disaster, human-made disaster, serious accident, physical abuse). Another dichotomous variable indicates

whether, in the past 12 months, the respondent experienced two or more of the following five major life events: death of spouse; death of another close family member; death of a close friend; major deterioration in the health of a family member; and loss or damage to personal property.

To determine 5-HTTLPR genotype, DNA was extracted from venous blood using the technique described in Gustincich et al. (1991) and then amplified with polymerase chain reaction (PCR). The forward primer used was 5'-GGC GTT GCC GCT CTG AAT GCC A-3', while the reverse primer was 5'-GAG GGA CTG AGC TGG ACA ACC AC-3'. PCR was performed in a total volume of 10.4μL containing 2.0 μL dNTP mix(2.5mM), 2.0 μL Taq buffer, 0.4 μL of the Taq polymerase Enzyme(5 Units), 12.0 μL DEPC H2O, 2.0 μL of the primer mix and 2.0 μL of the genomic DNA (approximately 150 ng). Cycling conditions consisted of 1) a 10 min denaturation at 95°C, 2) 45 cycles of 30 sec denaturation at 95°C, 2) 30 sec annealing at 65°C, 3) 60 sec extension at 75°C , and 4) a final cycle of 75°C for 5 min. The PCR products were separated by electrophoresis in a 2% agarose gel prepared with ethidium bromide. Three allele variants of the gene polymorphism were identified based on the PCR fragment sizes: short (S; 486bp, 14 repeats), long (L; 529bp, 16 repeats), or extra-long (XL; 612 or 654bp, 20 or 22 repeats). Subjects were classified into five genotypes: S/S, S/L, L/L, S/XL, and L/XL (no respondents were homozygous for the XL allele). The genotype frequencies are in Hardy-Weinberg equilibrium (χ^2=2.59, df=3, *p~0.46*).

Analytic Strategy

Genotype information for 5-HTTLPR is available for 1019 of the 1036 medical exam participants. The sample used for model estimation is slightly smaller (*n*=984) because of the exclusion of 34 additional participants who are missing data for the CES-D and one participant missing data on traumatic events.

We model depressive symptoms using linear regression with a random effect for township of residence to adjust for the clustered sampling design. All models include the main effects for 5-HTTLPR and controls for age, sex and respondent's education (measured as the number of

years of schooling). Because there are very few persons with L/XL genotype (*n*=24) – none of whom had experienced at least two major life events – we combine the L/XL and S/XL groups in the regression models. In the first model, we test the interaction between trauma and 5-HTTLPR. To ease interpretation, we parameterize the interaction terms to show the effect of trauma for each of four genotype groups (which is equivalent to the sum of the main effect for trauma and interaction effects between trauma and genotype). Based on the same type of formulation, the second model examines the interaction between major life events and 5-HTTLPR. The third model includes the interactions with both trauma and major life events. We calculate predicted CES-D scores by 5-HTTLPR genotype and stressful experience using the coefficients from the third model and assigning values for age, percent female, and education equal to the sample mean. Subsequently, we re-estimate these three models, this time including two- and three-way interactions among stressful exposure (trauma and/or life events), 5-HTTLPR, and sex.

RESULTS

In Table 1, we compare the 5-HTTLPR genotype and allele distributions for our Taiwan sample with samples from a diverse set of populations. These studies emerged from a PubMed search for distributions of the 5-HTTLPR polymorphism, restricted to studies that specified racial or ethnic groups of participants (and provided separate estimates if participants represented more than one group). For studies that reported distributions for control and patient samples, we present results for the former. In contrast to the Taiwan study, which is based on a national sample, the studies in Table 1 comprise a varied set of sampling strategies, including convenience samples, samples of patients or persons with a particular health condition, and community samples. In addition, the sample sizes vary from fewer than 100 participants in several studies to more than 1000 participants in the Taiwan sample as well as two Caucasian samples in New Zealand and Australia.

The comparisons reveal striking differences in the distributions of 5-HTTLPR by race and ethnic group. Almost half of the SEBAS respondents (45%) are classified as homozygous for the S allele, a prevalence of S/S that is lower than those observed in the other East Asian studies (49-74%) and similar to Native American samples (42%), but much higher than in Caucasian samples from various countries (12-24%) and African Americans (7-17%). Conversely, the proportion with the L/L genotype in the SEBAS sample (8%) is substantially lower than in Caucasians (29-43%) and African Americans (45-56%), but is generally comparable with Native American (10-14%) and other East Asian samples (1-13%).

A second notable feature of Table 1 is that the majority of studies – including all studies based on Caucasian samples – find only the S and L alleles. The few studies that found alleles longer than L (generally labeled as XL but occasionally differentiated into VL and XL) are from East Asian (Chinese or Japanese), African or African-American populations. Four of the six Japanese samples shown in Table 1 found individuals carrying an extra-long allele. Nevertheless, the relatively high frequency of the XL allele in SEBAS (almost 9% of the Taiwan population carries one XL allele) is greater than in other East Asian samples we have identified in the literature; only two studies report a higher frequency, and these are based on very small samples of Africans (Delbruck et al. 1997) and African-Americans (Gelernter et al. 1997).

Table 2 provides a description of the sample used in the statistical models. On average, respondents are 66 years old and have seven years of schooling. Just below 10 percent experienced two or more traumatic events in their lifetime, and a slightly higher proportion experienced at least two major life events during the past year. The average score on the 30 point CES-D scale is 4.7, with an observed range between 0 and 27. The CES-D scores vary substantially by genotype: the lowest value is 2.9 for L/XL, the next lowest is 4.1 for L/L, and the highest values occur for the three groups carrying at least one S allele (4.7 for S/S, 4.9 for S/L, and 5.6 for S/XL). Although this pattern is generally consistent with the presumed differences in

transcriptional efficiency of the alleles, the difference in the CES-D score across genotypes is not statistically significant.

Table 3 presents estimated coefficients from linear regression models of the CES-D score. Consistent with the previous literature, the coefficients suggest that women are more likely to report depressive symptoms than men (Grigoriadis and Robinson 2007) and that educational attainment is inversely associated with depressive symptoms in later life (Ladin 2008). Findings in the literature regarding age are more complex: although most studies suggest prevalence of major depression declines with age, patterns for depressive symptoms are inconsistent (Blazer et al. 1991; Blazer and Hybels 2005). Among older persons, most studies find increasing depressive symptoms with age (Beekman et al. 1999), as we do in the present analysis, although this age pattern often reverses direction in the presence of controls for physical illness and other confounding factors (Blazer et al. 1991).

The results provide support for the hypothesized gene-environment interaction. Among persons who experienced one or no stressful event (represented by the coefficients for 5-HTTLPR genotype), there is no genotypic variation in depressive symptoms. However, differences emerge among those exposed to at least two stressors. In Model 1, we find a positive association between exposure to two or more types of trauma and CES-D scores among individuals with the S/S (p<0.01) and S/L (p<0.01) genotypes, but not among persons with the L/L genotype or those carrying an XL allele. Similarly, Model 2 suggests that having experienced two or more major life events is associated with higher CES-D scores only among those with the S/S (p<0.05) and S/L genotypes (p<0.01). When both measures of stressors are included in Model 3, we observe little change in the coefficients. Wald tests indicate that the interactions between trauma and 5-HTTLPR are jointly significant in Model 1 (p~0.027) and of borderline significance in Model 3 (p~0.054), but the interaction terms involving recent major life events are not statistically significant in either Model 2 or 3. We estimated additional models (not shown) similar to Models 1 and 3 but distinguishing S/XL from L/XL genotype with respect to the main effects and interactions with

trauma (but not life events because of zero cell sizes). The coefficients for the interaction of at least two traumatic events with S/XL genotype are close to the corresponding coefficients for L/XL genotype, with little change in the remaining coefficients.

The patterns described above are depicted in Figure 1, which presents predicted CES-D scores, derived from the estimates for Model 3, for three mutually exclusive groups: those experiencing fewer than two traumatic and fewer than two major life events; those experiencing at least two major life events (but fewer than two traumas); those experiencing at least two traumatic events (but fewer than two major life events). We do not present results for the fourth group – those experiencing two or more major life events and traumas – because only 2 percent of the sample actually falls into this category. Larger differences by genotype are apparent for lifetime traumatic events than recent life events, a pattern that suggests that the moderating impact of stressful experience may increase with the magnitude of the stressor. The values indicate that, for traumatic events, the differences in CES-D score between persons with S/S or S/L genotype and those with L/L or an XL allele are on the order of one standard deviation in the score (5.5 points).

In the models including interaction terms with sex (not shown), the set of two- or three-way interactions with sex are not jointly significant. We recognize that these findings may be driven by limited statistical power. For example, one of the cells in the three-way tabulation of 5-HTTLPR by trauma by sex is empty (the corresponding term was dropped from the model), and several additional cells for the 3-way tabulations with trauma and life events contain fewer than five respondents.

DISCUSSION

This study provides the most comprehensive review to date of ethnic variation in the 5-HTTLPR polymorphism. Although differences in the frequencies of the S and L alleles between select groups had been identified in earlier work, some studies have erroneously assumed that the 5-HTTLPR polymorphism is bi-allelic. Our review demonstrates that extra-long alleles occur in

several samples of persons of African origin and East Asians, but they have not been found in any Caucasian group.

Still, we know relatively little about the XL allele. In light of the non-randomness and geographic restriction of most of the samples in Table 1, it is impossible to ascertain the prevalence of XL alleles in any large-scale population but Taiwan. Our data, derived from a nationally representative sample, suggest that, at least in Taiwan, the XL allele is not rare. Almost nine percent of the Taiwan population (95% C.I. 7.1-10.6%) carries an XL allele.

Recent studies demonstrate that 5-HTTLPR is more highly polymorphic than previously believed and that a reassessment of 5-HTTLPR as functionally *tri-allelic* is premature for at least two reasons. First, despite our reference to *an* XL allele, several studies, including our own, find that XL comprises variants with different numbers of repeats, at minimum 18, 19, 20 and 22 repeats (we identified both 20 and 22 repeats in the Taiwan sample).[1] Second, SNP and other variations have been identified within the S and L alleles. Nakamura et al. (2000) found several novel variants consisting of different combinations of the 14- and 16-repeats. Hu et al. (2006) failed to detect most of Nakamura's novel variants in an ethnically diverse sample of participants, but their work demonstrated a large difference in transcriptional efficiency resulting from a single base substitution in an L allele, with one of the L variants having a similar degree of 5-HTT expression as the S allele. Such findings raise the question of whether these variants are at least as important functionally as differences in the tandem repeat structure.

Using an analytic strategy similar to those in other papers, but with a focus on older adults, we examined the effects of interactions between 5-HTTLPR genotype and stressful experience on depressive symptoms. Consistent with a hypothesized gene-environment interaction, our results indicate that the relationship between 5-HTTLPR and depressive symptoms is conditioned by exposure to stressors. However, whereas previous studies reported either a graded effect (i.e., susceptibility to depression increases with the number of S alleles) or a distinction between

[1] In addition, a 15-repeat allele of 5-HTTLPR was identified by Nakamura and colleagues (2000).

persons homozygous for the S allele and those carrying at least one L allele, our models suggest that the main distinction is between persons carrying at least one S allele and other genotypes. Unlike some previous studies (Brummett et al. 2008; Eley et al. 2004; Sjöberg et al. 2006), we found no evidence that the gene-environment interaction varies by sex. Still, we are cautious to draw firm conclusions from these estimates in light of Munafò and colleagues' contention (2009) that most published studies are underpowered to examine these interactions[2] and that variation in the pattern of the interaction across studies weakens researchers' claims to have replicated Caspi's original study.

Our study raises an important question that has received relatively little attention in the literature. Is the high prevalence of the S allele in East Asian populations accompanied by high rates of depression or depressive symptoms in these populations? Because of enormous variation in how depression is measured across studies, and the selection biases inherent in relying on clinical data, this question is difficult to address. Nevertheless, two reviews based on comparable community-based studies provide a first glimpse of an answer. In a review of depression in later life (ages 55+), Beekman et al. (1999) found that across 28 studies in 13 countries the prevalence for major and minor depression combined was lowest in a study in Japan; the next lowest rates were found by a study in the Netherlands, a second study in Japan, and one in Singapore. In an examination of major depression, Weissman and colleagues (1996) found that Taiwan had the lowest rate (1.5%) among the 10 countries in their analysis; Korea – the only other Asian population in the study – had the second lowest rate (2.9%). Thus, the limited data available suggest generally *lower* rates of depression in East Asian populations despite their presumed unfavorable allele distribution for 5-HTTLPR.

These paradoxical findings are consistent with several hypotheses. One contention is that because Chinese (as well as Japanese) are more likely than other groups to perceive psychiatric

[2] Only 3 of the 15 studies examined by Munafò and colleagues (2009) have a sample size as large as that of the Taiwan study.

disorders as socially stigmatized and to fear potential "loss of face", they are reluctant to acknowledge symptoms of mental illness (Compton et al. 1991; Georg Hsu et al. 2008; Griffiths et al. 2006; Lin 1983; Shen et al. 2006; Weissman et al. 1996). A second explanation suggests that Chinese have a greater tendency toward somatization of symptoms than do Westerners, in part because they may not view psychiatric symptoms as signs of illness (Kleinman 2004; Parker et al. 2001; Xu 1987). A third and related argument is that the stoicism associated with Chinese culture encourages individuals to tolerate emotional difficulties rather than to seek help or perhaps to even acknowledge the challenges (Parker et al. 2001; Xu 1987). Yet another culture-related hypothesis is that the strong family and social networks in East Asian societies buffer individuals from the potentially negative impacts of stressful events (Chen et al. 1993; Parker et al. 2001; Taylor et al. 2006; Xu 1987). A final explanation is that the phenotypes associated with the 5-HTTLPR polymorphism may vary across ethnic groups, perhaps rendering the S allele less deleterious in Chinese and other East Asian populations. Unfortunately, despite repeated findings of significant differences in allele frequencies across groups, very few researchers have examined racial or ethnic differences in the interaction between stressful experience and 5-HTTLPR genotype.

One of the objectives of our study has been to assess phenotypic variation associated with the XL allele. Given that the L allele is believed to result in more efficient serotonin function than the S allele, are individuals who possess the XL allele especially resilient to depression? We are not aware of any other study that has addressed this question. Our analysis suggests that persons carrying an XL allele are similar to those homozygous for the L allele – neither group shows an increased risk of depressive symptoms in the presence of traumatic or life events, in contrast to persons carrying the S allele. However, the sampling variability of these estimates coupled with our inability to distinguish S/XL genotypes from L/XL genotypes in some of the statistical models, or to analyze variants of the S, L and XL alleles, prevents us from reaching a firmer conclusion.

This study has several advantages over related analyses, most notably the use of a national sample to obtain information on the 5-HTTLPR polymorphism and identification of a relatively large

number of individuals carrying the XL allele (N=89). Nevertheless, we face limited statistical power to examine some of the interactions of interest or to consider each of the observed genotypes. Our analysis raises several important issues that require further research. One question, which we are beginning to explore, is how the transcriptional efficiency of the XL allele compares with that of the S and L alleles. Additional laboratory research is needed to identify the functional importance of other alleles of the 5-HTTLPR polymorphism. Finally, community-based studies based on relatively large and diverse samples, with detailed genotyping of 5-HTTLPR variants, are necessary to identify more precisely the nature of the gene-environment interaction as well as potential variability by sex and especially ethnicity. It seems virtually certain that the links between 5-HTTLPR and depression are more complex than previously thought.

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Table 1. Distribution by 5-HTTLPR Genotype in Selected Studies

			Genotypes (%)					Alleles (%)		
Study	**Sample**	**Ages**	S/S	S/L	L/L	S/XL	L/XL	S	L	VL & XL[†]
Current	Nationally-representative (*n*=1019), Taiwan	53+	45	37	8	6	2	67	28	4
Caucasians										
Bellivier et al. (1998)	Blood donors at the Pitié-Salpétrière Hospital* (*n*=99), France	35+	12	59	29	NR	NR	41	59	NR
Brummett et al. (2008)	Convenience sample including caregivers and controls (*n*=203), North Carolina, U.S.	mean=58.3, SD=14.7	24	44	32	NR	NR	46	54	NR
Caspi et al. (2003)	Representative birth cohort (*n*=1037), New Zealand	From birth	17	51	31	NR	NR	43	57	NR
Chipman et al. (2007)	Community-based (*n*=2095), Canberra and Queanbeyan, Australia	20-24	21	46	33	NR	NR	44	56	NR
Delbruck et al. (1997)	North American Caucasians of Western European descent (*n*=62) from Philadelphia	NR	NR	NR	NR	NR	NR	44	56	NR
Delbruck et al. (1997)	Western European Caucasians from Berlin, Germany (n=216)	NR	NR	NR	NR	NR	NR	39	61	NR
Delbruck et al. (1997)	Western European Caucasians from Alsace, France (*n*=73)	NR	NR	NR	NR	NR	NR	46	54	NR
Gelernter et al. (1997)	Unrelated adults living in Connecticut (*n*=104)	NR	NR	NR	NR	NR	NR	40	60	NR
Hu et al. (2006)	Persons with (*n*=177) and without (*n*=120) psychiatric disorders, group 1, U.S.	NR	16	41	43	NR	NR	37	63	NR
Hu et al. (2006)	Persons with (*n*=154) and without (*n*=132) psychiatric disorders, group 2, U.S.	NR	12	45	42	NR	NR	35	65	NR
Hu et al. (2006)	Persons with (*n*=480) and without (*n*=291) psychiatric disorders, Finland	NR	15	52	34	NR	NR	40	60	NR
Jacobs et al. (2006)	Female twins (n=356 pairs), Belgium	18-46	22	47	31	NR	NR	46	55	NR
Nakamura et al. (2000)	Unrelated Caucasians from genomic DNAs of CEPH families (*n*=76)	NR	20	49	31	0	0	45	55	0
Otte et al. (2007)	Patients with coronary disease (*n*=557), San Francisco and Palo Alto, U.S.	mean=68, SD=11	17	52	31	NR	NR	43	57	NR

Study	Sample	Ages	Genotypes (%)					Alleles (%)		
			S/S	S/L	L/L	S/XL	L/XL	S	L	VL & XL[†]
Caucasians (cont.)										
Rees et al. (1997)	Unrelated blood donors* (*n*=118), South Wales, U.K.	mean=44, SD=11	20	50	30	NR	NR	45	55	NR
Scheid et al. (2007)	Pregnant women (*n*=568) recruited from prenatal clinics in five Michigan communities	81% aged 20-34	17	52	31	NR	NR	43	57	NR
Williams et al. (2003)	Volunteers (*n*=70) in good physical and medical health	NR	20	40	40	NR	NR	40	60	NR
Africans										
Delbruck et al. (1997)	Samples from Congo (*n*=32)	NR	NR	NR	NR	NR	NR	9	84	6
Delbruck et al. (1997)	Samples from Gabon (*n*=12)	NR	NR	NR	NR	NR	NR	21	79	0
African-Americans										
Brummett et al. (2008)	Convenience sample including caregivers and controls (*n*=203), North Carolina, U.S.	mean=58.3, SD=14.7	17	39	45	NR	NR	36	64	NR
Delbruck et al. (1997)	African Americans (*n*=186) from Philadelphia		NR	NR	NR	NR	NR	29	69	2
Gelernter et al. (1997)	Unrelated adults living in Connecticut (*n*=51)	NR	NR	NR	NR	NR	NR	25	70	6
Hu et al. (2006)	Persons with drug addictions (*n*=414) and with no psychiatric diagnosis (*n*=210), U.S.	NR	7	37	56	NR	NR	26	75	NR
Williams et al. (2003)	Volunteers (*n*=85) in good physical and medical health	NR	11	35	54	NR	NR	28	72	NR
Chinese										
Li et al. (2007)	Healthy volunteers who had a normal check-up* (*n*=96), Guangzhou, China	18+	57	35	7	NR	NR	75	25	NR
Shen et al. (2004)	Healthy blood donors* (*n*=628), Shanghai, China	mean=33.3, SD=10.1	49	39	6	4	2	71	26	3
You et al. (2005)	Healthy blood donors and hospital staff* (*n*=90), Hunan Province, China	mean=30.2, SD=11.1	49	44	7	NR	NR	71	29	NR

Study	Sample	Ages	Genotypes (%)					Alleles (%)		
			S/S	S/L	L/L	S/XL	L/XL	S	L	VL & XL[†]
Japanese										
Delbruck et al. (1997)	(*n*=14)	NR	NR	NR	NR	NR	NR	71	29	0
Gelernter et al. (1997)	Samples (*n*=48) collected in Japan	NR	NR	NR	NR	NR	NR	80	17	3
Kunugi et al. (1997)	Healthy volunteers from students and hospital staff* (*n*=212), Japan	mean=32, SD=13	62	30	5	2	0	79	20	1
Nakamura et al. (2000)	Selected from population of unrelated Japanese in Ehima (*n*=131), Japan	NR	63‡	31	1	3	2	81‡	17	2
Narita et al. (2001)	Healthy infants* (*n*=115), Dokkyo University Koshigaya Hospital, Japan	< 6 months	74	23	2	1	0	86	13	0.4
Ohara et al. (1998)	Healthy volunteers from medical staff and students* (*n*=92), Hamamatsu, Japan	mean=35.2, SD=14.5	59	35	7	NR	NR	76	24	NR
Korean										
Han et al. (2004)	Unrelated males (*n*=158) no history of psychiatric disorders from psychiatric department staff at two hospitals and medical students, South Korea	NR	61	34	5	NR	NR	78	22	NR
Kim et al. (2007)	Community-based (*n*=732), Kwangju, South Korea	65+	53	34	13	NR	NR	70	30	NR
Native American										
Hu et al. (2006)	Community-based sample of Plains Native Americans with (*n*=335) and without (*n*=121) psychiatric diagnoses	NR	42	48	10	NR	NR	66	34	NR
Hu et al. (2006)	Community-based sample of Southwest Native Americans with (*n*=359) and without (*n*=205) psychiatric diagnoses	NR	42	44	14	NR	NR	64	36	NR

NR = Not reported
CEPH = Center d'Etude du Polymorphisme Humain
[†] We group VL and XL alleles because some researchers do not distinguish among alleles longer than the L allele.
* The study reported the distributions for both patient and control samples; we present results only for the latter.
‡ Includes two people (1.5% of the sample) with a 15-repeat allele.

Table 2. Descriptive Statistics for the Analysis Sample (*N*=984)

	Mean (SD) or Percent
Age (53-97)	65.9 (9.9)
Female (%)	45.2%
Respondent's education (0-17)	7.0 (4.8)
5-HTTLPR genotype (% distribution)	
S/S	45.6%
S/L	37.3%
L/L	8.4%
S/XL	6.2%
L/XL	2.4%
Experienced 2+ types of trauma (out of 7) during lifetime (%)	9.5%
Experienced 2+ major life events (out of 5) in past 12 months (%)	11.4%
Center for Epidemiologic Studies Depression scale (CES-D) (0-27)	4.7 (5.5)
CES-D score by 5-HTTLPR genotype	
S/S	4.7 (5.3)
S/L	4.9 (5.7)
L/L	4.1 (5.7)
S/XL	5.6 (6.0)
L/XL	2.9 (3.5)

Note: For continuous variables, the observed range is given in parentheses.

Table 3. Estimated Coefficients from Linear Regression Models[a] Predicting CES-D in 2006 (*N*=984)

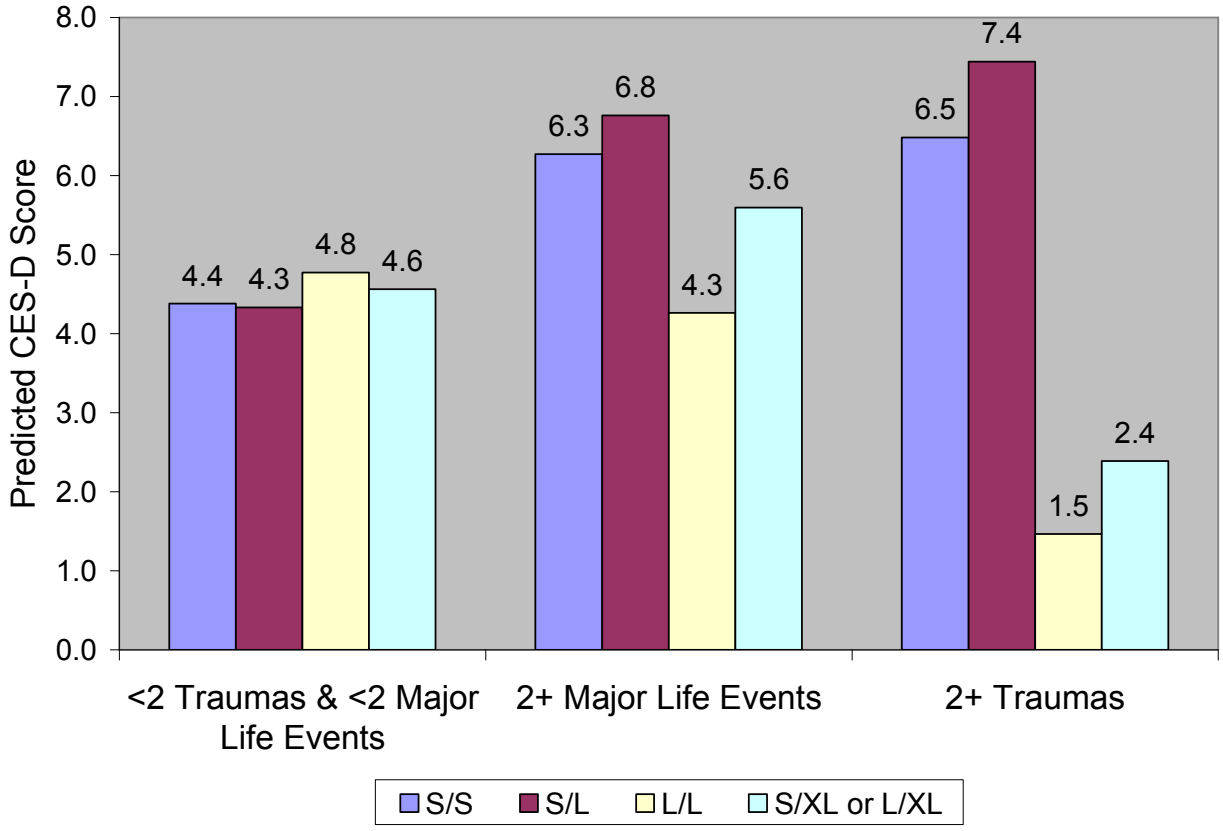
	(1)	(2)	(3)
Age	0.081**	0.081**	0.081**
Female	1.233**	1.187**	1.265**
Respondent's education	-0.154**	-0.170**	-0.158**
5-HTTLPR genotype			
S/S (ref group)			
S/L	-0.015	-0.015	-0.043
L/L	0.104	0.096	0.396
S/XL or L/XL	0.066	-0.150	0.185
GxE Interaction: 2+ Traumas (lifetime)[b]			
S/S	2.163**	--	2.105**
S/L	3.559**	--	3.105**
L/L	-3.384	--	-3.308
S/XL or L/XL	-2.285	--	-2.175
GxE Interaction: 2+ Major Life Events (past yr)[b]			
S/S	--	1.906*	1.892*
S/L	--	2.981**	2.426**
L/L	--	-0.758	-0.510
S/XL or L/XL	--	1.157	1.033
Constant	-0.236	-0.110	-0.440

* $p<0.05$; ** $p<0.01$; *** $p<0.001$, 2-sided tests.

[a] Models include a random effect for township of residence to adjust for the clustered sampling design.

[b] The interactions effects are parameterized to show the effect of the stressor for each of four genotype groups (rather than a main effect of trauma and interactions with genotype). For example, for GxE interactions with trauma, the coefficient for S/S is equivalent to the main effect for trauma and the coefficient for S/L is equivalent to the sum of the main effect for trauma and the interaction between S/L and trauma. The coefficients for 5-HTTLPR genotype pertain to the following groups in the three models respectively: (1) persons who experienced fewer than two traumatic events; (2) persons who experienced fewer than two major life events; and (3) persons who experienced fewer than two traumatic events and fewer than two major life events.

Figure 1. Predicted CES-D Score by Stressors and 5-HTTLPR Genotype



Note: Results based on Model 3 from Table 3. Predicted scores are calculated assuming age, percent female, and education correspond to the mean for the entire sample.