Research Article

Association Between Polymorphisms in the Dopamine Transporter Gene and Depression

Evidence for a Gene-Environment Interaction in a Sample of Juvenile Detainees

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ABSTRACT—*Previous research has generated examples of how genetic and environmental factors can interact to create risk for psychopathology. Using a gene-by-environment (G × E) interaction design, we tested whether three polymorphisms in the dopamine transporter gene (*DAT1*, also referred to as* SLC6A3*, located at 5p15.33) interacted with maternal parenting style to predict first-onset episodes of depression. Participants were male adolescents (*N = 176*) recruited from a juvenile detention center in northern Russia. As hypothesized, one of the polymorphisms (rs40184) moderated the effect of perceived maternal rejection on the onset of major depressive disorder, as well as on suicidal ideation. Further, this G × E interaction was specific to depression; it did not predict clinically significant anxiety. These results highlight the need for further research investigating the moderating effects of dopaminergic genes on depression.*

Depression is one of the most common forms of psychopathology. It is recurrent, debilitating, and even lethal (e.g., suicide). According to projections, by 2020 depression will be the second leading cause of disability worldwide (Murray & Lopez, 1997). It also creates a substantial financial burden. The total economic cost of depression is estimated at more than $83 billion a year in the United States (Greenberg et al., 2003). Clearly, it is critical to identify the factors that contribute to risk and resilience for depression.

According to diathesis-stress theories of depression, genetic liability (diathesis) interacts with negative life experiences (stress) to cause depressive symptoms and disorders (e.g., Monroe & Simons, 1991). Traditionally, most studies testing these theories have focused on only one component of the diathesis-stress model: either environment or genetics, but not their interaction. Such an approach allows researchers to identify particular risk factors for depression, but it does not enable a complete test of the diathesis-stress hypothesis. Thus, it is encouraging that researchers have recently begun using designs that enable them to test gene-by-environment (G × E) interactions. Studies using the G × E design have the potential to "stimulate progress in basic neuroscience, in future gene hunting, in intervention research, and in public understanding of genetics" (Moffitt, Caspi, & Rutter, 2006, p. 17). The goal of the research reported here was to contribute to this small but important body of G × E studies.

The few G × E studies examining depression have focused almost exclusively on the genes implicated in serotonin func-

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tioning, which makes sense given the success of selective serotonin reuptake inhibitors (SSRIs) in treating depression. The evidence, although not unequivocal, suggests that a functional polymorphism in the promoter region of the serotonin transporter gene (*SLC6A4*, also known as *SERT* or *HTT*) moderates the influence of stressful life events on depression (see Moffitt et al., 2006, for a review). However, recent research also points to other candidate genes for depression. For example, motivational theories of depression (e.g., Davidson, Pizzagalli, & Nitschke, 2002) suggest that genes associated with dopamine functioning may also play an important role in risk for depression.

Many researchers propose that there are at least two fundamental motivational systems that are critical in regulating behavior. One regulates approach behavior aimed at obtaining rewards and attaining goals; it is typically referred to as the approach system[1] (Davidson, 1994). The other system regulates withdrawal and inhibition of behavior in response to threat and punishment; accordingly, it is referred to as the withdrawal system.[2] Within this motivational perspective, depression has been associated most consistently with deficits in the approach system (see Shankman & Klein, 2003, for a review). Dopamine is a neurotransmitter that is critically involved in approach behavior (Schultz, 1997). Thus, if depression is related to deficits in the approach system, dopamine is likely to be involved. This hypothesis is consistent with recent findings linking dopaminergic activity and depression (Dunlop & Nemeroff, 2007). For example, research shows that long-term treatment with antidepressants leads to changes in both serotonergic and dopaminergic activity (e.g., Bonhomme & Esposito, 1998). Similarly, dopaminergic agents have been used successfully to augment antidepressant medications in treatment-resistant patients (Nierenberg, Dougherty, & Rosenbaum, 1998). The connection between depression and dopamine is also supported by the high rates of depression secondary to Parkinson's disease, which is thought to be caused by deficits in dopaminergic functioning.

Although prior research suggests an association between dopamine and depression, the few studies directly investigating the relation between dopaminergic candidate genes and depression have yielded mostly negative results. For example, Frisch et al. (1999) examined polymorphisms in three dopaminergic candidate genes (*DRD4*, *DAT1*, and *COMT*) and did not find group differences between depressed and nondepressed individuals. Similarly, Kirov, Jones, McCandless, Craddock, and Owen (1999) did not find evidence supporting the role of six dopaminergic candidate genes (*DβH*, *DAT1*, *COMT*, *DRD2*, *DRD3*, and *DRD5*) in bipolar disorder. To our knowledge, only one study has found a relation between a dopaminergic candidate gene and depression (Ohara, Nagai, Suzaki, & Ohara, 1998). In this study, a polymorphism in the *COMT* gene was associated with depressive disorder in a group of Japanese patients. However, with this one exception, the link between dopaminergic candidate genes and depression has not generally been supported.

One explanation for this lack of support is that previous studies have examined only the main effect of genotype on depression. If the diathesis-stress model is correct, then genotype should contribute to the development of depression only in combination with stressful environmental conditions. Thus, it is necessary to examine the interaction of genotype and environment before making any definitive conclusions about the relation between dopaminergic genes and depression. To this end, in the study reported here, we used a G × E design to test the moderating effects of three polymorphisms in the dopamine transporter gene (*DAT1*, also referred to as *SLC6A3*, located at 5p15.33), which is considered to play a primary role in the reuptake of dopamine into presynaptic neurons, and is thus one of the major regulators of dopamine level in the brain.

With regard to the environmental factors associated with depressive symptoms, previous research (for a review, see Garber & Flynn, 1998) converges on the idea that early exposure to negative interpersonal contexts confers risk for future depression. Specifically, a number of researchers (e.g., Bowlby, 1988) have argued that the quality of children's relationships with their parents is an important determinant of their interpersonal styles, level of self-worth, coping strategies, and risk for future depression. For example, Garber and Flynn (2001) reported that level of maternal acceptance predicted children's self-worth 1 year later, even after controlling for prior level of self-worth and mothers' history of depression. Similarly, Gibb et al. (2001) found that childhood emotional maltreatment was related to episodes of major depression in college students. These links might be especially important for understanding the emergence of depression in such high-risk populations as delinquent youths, who tend to have higher prevalence rates of emotional maltreatment than the general population (e.g., Ruchkin, Eisemann, & Hagglof, 1998). In light of these findings, we propose that parenting style, specifically, the degree of maternal rejection, is a strong candidate for the stress component of the diathesis-stress interaction that heightens risk for depression.

In summary, the present study used a G × E design to investigate risk for depression. It is among the first studies to directly examine the moderating effects of a dopaminergic candidate gene in the development of clinically significant depression. Specifically, we hypothesized that variations in the dopamine transporter genotype would interact with parenting style (i.e., maternal rejection) to predict major depressive disorder in a group of adolescents. Adolescents are a particularly good population for testing diathesis-stress models of depression because rates of depression rise dramatically during this life period (Hankin et al., 1998).

[1]This system has also been called the behavioral approach system (Gray, 1994), the behavioral activation system (Fowles, 1980), and the behavioral facilitation system (Depue & Iacono, 1989).

[2]The withdrawal system has also been called the behavioral inhibition system (Gray, 1994).

METHOD

Participants

Participants ($N = 176$) were a subset of a larger sample used in previous studies (e.g., Ruchkin, Koposov, af Klintenberg, Oreland, & Grigorenko, 2005; Ruchkin, Schwab-Stone, Vermeiren, Koposov, & Steiner, 2002). They were recruited over a period of 6 months from a group of male adolescent inmates (mean age = 16.2 years, $SD = 0.8$ years) who had been court-ordered to the only juvenile detention facility in the Arkhangelsk region of northern Russia. This region is ethnically homogeneous: Approximately 98% of the population is of Russian ancestry. At the time of the study, the mean sentence length at the facility was 4.3 years, and all participants had been incarcerated for at least 6 months.

This sample was particularly appropriate for the present study because delinquent male adolescents tend to have a high prevalence of depression, as well as a history of harsh parenting (i.e., maternal rejection). Specifically, prevalence rates for depressive disorder range between 11% and 33% among delinquent male youths, and up to 50% may have less severe affective symptoms (see Vermeiren, 2003, for a review). Recent research suggests that in investigating potential causal factors, targeting high-risk groups may be a more efficient strategy than simply targeting general populations (Shaffer, Garland, Gould, Fisher, & Trautman, 1988).

Materials

Beck Depression Inventory

The Beck Depression Inventory (BDI; Beck, Steer, & Garbin, 1988) was administered to assess depressive symptoms. Total scores on the BDI range from 0 to 63, with higher scores reflecting greater levels of depressive symptomatology. The BDI has high internal consistency, test-retest reliability, and validity in both psychiatric and normal samples (Beck et al., 1988). Cronbach's alpha for the scale was .89 in the present sample.

Maternal Rejection

To assess maternal rejection, we used the EMBU (the Swedish acronym for Own Memories of Parental Rearing; Perris, Jacobsson, Lindstrom, von Knorring, & Perris, 1980), a questionnaire that measures aspects of parental rearing (rejection, warmth, and overprotection). We used the short version of the EMBU (Arrindell et al., 1999), comprising 23 items that the respondent answers on 4-point Likert scales. The maternal-rejection subscale of the EMBU assesses physical punishment, hostility, lack of respect for the child's point of view, and unjustified criticism in front of other individuals. Cronbach's alpha for the maternal-rejection subscale was .77 in the present sample. Participants' scores tended to be normally distributed. However, because outliers can affect the results of interaction analyses, participants who scored more than 3 standard deviations from the mean were excluded from analyses ($n = 3$).

Schedule for Affective Disorders and Schizophrenia for School-Age Children

The Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) is a widely used and extensively validated semistructured psychiatric interview. We used it to identify current and past diagnoses, according to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM–IV; American Psychiatric Association, 1994), in the sample. This instrument consists of introductory and screening interviews and five diagnostic supplements that assess affective disorders, psychotic disorders, anxiety disorders, behavioral disorders, and substance-abuse, eating, and tic disorders. We based psychiatric diagnoses on the information provided by the adolescents only. Interrater reliability for this measure is high, with interrater agreement for scoring screen questions and diagnoses ranging from 94% to 100% (Kaufman et al., 1997).

Procedure

All participants were given a detailed description of the study and informed of the voluntary and confidential nature of their involvement. The appropriate ethics committees in Russia, Sweden, and the United States approved the study. As explained earlier, psychopathology was assessed with the K-SADS-PL (Kaufman et al., 1997). The interview was conducted by two psychiatrists who received standard K-SADS training from the author of the instrument and were blind to the self-report data collected. Maternal parenting style and depressive symptoms were assessed using the EMBU and BDI, respectively. These self-report questionnaires were administered during small-group sessions (5–8 participants), with each participant seated at a separate table. In addition, two nurses obtained blood samples from participants' arm veins. DNA was extracted from samples collected via 5-ml vacutainer tubes containing ethylenediaminetetraacetic acid (EDTA). The samples were delivered to one of the author's laboratories (Oreland's), where DNA was extracted. An aliquot of DNA was sent to another author's laboratory (Grigorenko's), where it was subsequently amplified with Repli-G technologies (Qiagan, Valencia, CA) and genotyped using the ABI TaqMan platform (Applied Biosystems, Foster City, CA).

The *DAT1* gene includes 15 exons covering 60 kb on the short arm of chromosome 5 (p15.33). More than 100 studies have investigated possible associations among variants of this gene and a range of psychiatric disorders. The overwhelming majority of these studies have focused on only one particular polymorphism in the gene. However, recent analyses that included a larger selection of polymorphisms recovered a heterogeneous pattern of functional variation and linkage disequilibrium within the gene. Thus, it is important to consider more than one variant at a time in order to recover replicable associations. For this project, we identified three single-nucleotide polymorphisms

TABLE 1

Genotype Counts for Three Polymorphisms of the Dopamine Transporter Gene

rs40184		rs6347		rs2652511	
Genotype	*n*	Genotype	*n*	Genotype	*n*
CC	45	CC	18	AA	35
CT	94	CT	58	AG	82
TT	35	TT	93	GG	50

(SNPs) within the *DAT1* gene: rs40184 (intron 14), rs6347 (exon 9), and rs2652511 (the promoter). These SNPs were selected because they (a) cover the gene, (b) are approximately equally spaced through the gene, (c) reside in different haploblocks (1, 2, and 5, respectively), and (d) have minor-allele frequencies of at least .3 among Whites of European ancestry (.47, .28, and .46, for rs40184, rs6347, and rs2652511, respectively). Genotype counts for the three *DAT1* SNPs in the present sample are listed in Table 1.

RESULTS

We tested whether genetic risk had a moderating effect on the association between the environmental risk and current clinical diagnosis of depression. The potential genetic risk factors were the three SNPs within the *DAT1* gene (rs40184, rs6347, and rs2652511). The environmental risk factor was maternal rejection, which was operationalized as score on the maternal-rejection subscale of the EMBU ($M = 10.73$, $SD = 2.79$). Participants were considered to have a current episode of clinically significant depression if they met DSM–IV diagnostic criteria for major depressive disorder ($n = 7$), dysthymic disorder ($n = 13$), or both ($n = 17$). Two other participants had a history of clinically significant depression.[3]

We used logistic regression to predict the log of the odds of having clinically significant depression (0 = not depressed, 1 = currently depressed). Predictor variables were entered into the regression equation in two steps. In the first step, the main effects of *DAT1* polymorphism and maternal rejection were entered. In the second step, the interaction of *DAT1* polymorphism and maternal rejection was entered. Individual variables within a given step were not interpreted unless the set as a whole was significant, in order to reduce Type I errors. The *DAT1* polymorphisms were treated categorically, using two dummy variables to represent the three possible allele types (homozygous for minor allele, heterozygous, and homozygous for major allele). Participants who were homozygous for the minor allele were used as the reference group. Score on the maternal-rejection scale was centered and treated as a continuous predictor. The interaction of *DAT1* polymorphism and maternal rejection was represented by the two product terms (i.e., each of the dummy variables multiplied by the centered maternal-rejection scores).

The likelihood ratio test was used to test for the predicted G × E interaction. This test compares the −2 log likelihood of a given model (M_1) with the −2 log likelihood of a reduced model (M_0) that drops the predictor variable (or variables) of interest. The difference between the two −2 log likelihoods, $G^2\,(M_0|M_1)$, approximates a chi-square distribution with degrees of freedom equal to the difference between the number of parameters in the two models.

DAT1 Polymorphisms

Neither the rs6347 nor the rs2652511 polymorphism interacted with maternal rejection to predict clinically significant depression, $G^2(2) = 3.63, p = .16$, and $G^2(2) = 2.49, p = .29$, respectively.

Results for the rs40184 polymorphism were consistent with our hypothesis. There was a significant interaction between rs40184 genotype and maternal rejection, $G^2(2) = 11.49$, $p = .003$. The interaction was significant for both of the dummy variables used to represent the three rs40184 alleles (see Table 2). Maternal rejection increased the likelihood of depression significantly more for adolescents who had the TT genotype than for those who had either the CC (Wald = 7.11, $p = .008$) or the CT (Wald = 7.71, $p = .005$) genotype. Figure 1 illustrates the pattern of this G × E interaction in the sample. In this figure, we plotted the proportion of adolescents who met the criteria for clinically significant depression as a function of rs40184 allele and maternal rejection (high vs. low, as determined by a median split). As the graph shows, adolescents who reported maternal rejection and also had the TT genotype for the rs40184 polymorphism were the most likely to have a current episode of clinically significant depression.

Validity Analyses

Following the recommendations of Moffitt et al. (2006), we conducted a set of secondary analyses to validate these initial

TABLE 2

Logistic Regression Analysis of rs40184 Genotype and Maternal Rejection as Predictors of Clinically Significant Depression

Step and predictor	*b*	*SE*	Wald	Model χ^2
Step 1				4.23
CC vs. TT	−0.43	0.52	0.704	
CT vs. TT	−0.95	0.47	4.07	
Rejection	0.02	0.07	0.08	
Step 2				15.71*
(CC vs. TT) × Rejection	−0.60	0.22	7.11*	
(CT vs. TT) × Rejection	−0.54	0.20	7.71*	

Note. The model predicts the log of the odds of having depression. The predictor variables are two dummy variables representing the three rs40184 genotypes, maternal rejection, and two variables representing the gene-by-environment interaction. $N = 176$.
*$p < .01$.

[3]Our results remained the same when we excluded the data from these 2 participants from the analyses.

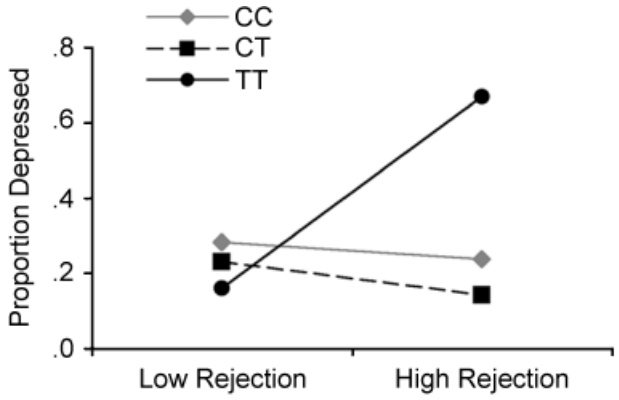

Fig. 1. Incidence of current clinically significant depression as a function of *DAT1* genotype (rs40184: CC vs. CT vs. TT genotype) and maternal rejection (high vs. low).

positive results. More specifically, Moffitt et al. suggested testing whether a G × E interaction can also predict measures that share construct validity with the disorder of interest (i.e., testing convergent validity). Thus, we examined whether the interaction of rs40184 genotype and maternal rejection would also predict individual differences in suicidal ideation and depressive symptoms. In addition, we tested whether the G × E interaction would predict an outcome other than depression (i.e., we tested discriminant validity). If the G × E interaction we obtained represents specific vulnerability to depression, it should not predict other psychiatric disorders, such as anxiety. Thus, we examined whether the G × E interaction would predict clinically significant anxiety disorders.

To establish convergent validity for our results, we tested whether the interaction of *DAT1* rs40184 polymorphism and perceived maternal rejection would predict suicidal ideation and depressive symptoms. Suicidal ideation, as assessed by the affective-disorders module of the K-SADS-PL interview and the BDI,[4] was operationalized as follows: 0 = no thoughts of suicide; 1 = suicidal thoughts, but no attempts; and 2 = both suicidal ideation and attempts. Level of depressive symptoms was operationalized as score on the BDI, a commonly used measure of depressive symptoms. We tested the G × E interaction using linear regression procedures similar to the logistic regression procedures described earlier. As in the previous analysis, the predictor variables included the appropriate terms for testing the main effects of rs40184 polymorphism and maternal rejection, as well as their interaction. As hypothesized, we found that the main effects of maternal rejection and genetic risk were not significant, but the interaction of rs40184 polymorphism and maternal rejection predicted suicidal ideation (model: $\Delta R^2 = .06$, $F = 4.43$, $p = .01$) and predicted depressive symptoms at the level of a statistical trend (model: $\Delta R^2 = .03$, $F = 2.54$, $p = .08$). The nature of the interactions was the same as that found for clinically significant depression; adolescents who had both high levels of maternal rejection and the TT genotype for the rs40184 polymorphism reported the highest levels of suicidal ideation and depressive symptoms.

To establish discriminant validity for our initial results, we tested whether the *DAT1* rs40184 polymorphism interacted with perceived maternal rejection to predict a disorder other than depression. Specifically, we examined whether the G × E interaction predicted a different Axis I disorder that is sometimes comorbid with depression—anxiety (see Alloy, Kelly, Mineka, & Clements, 1990, for a review). We used the logistic regression procedure described earlier, with current DSM–IV diagnosis of an anxiety disorder (panic disorder, phobic disorder, generalized anxiety disorder, or obsessive-compulsive disorder) as the dependent variable (0 = no anxiety disorder, 1 = current anxiety disorder). Eight of the 37 participants who met the diagnostic criteria for depression also satisfied the criteria for an anxiety disorder. As hypothesized, we found that neither the main effects nor the interaction of rs40184 polymorphism and perceived maternal rejection had a significant effect on the clinical diagnosis of an anxiety disorder, $G^2(2) = 1.27$, $p = .53$.

DISCUSSION

This study contributes to a small but growing body of G × E research. Consistent with the diathesis-stress model of depression, our results show that a polymorphism in the dopamine transporter gene (*DAT1*) moderated the effect of perceived maternal rejection on the clinical diagnosis of major depression, suicidal ideation, and depressive symptoms (at the level of a trend). These results support motivational theories of depression (e.g., Davidson, 1994), which hypothesize that depression is caused by or related to deficits in the dopamine-driven approach system. Our findings also provide the first support for the role of the *DAT1* gene in the development of depression.

On a more general level, our findings highlight the advantage of using the G × E design to study psychopathology. If we had followed prior research and examined only the main effect of *DAT1* rs40184 genotype (or environment), we would have obtained negative results. However, according to Holmbeck (1997), "the strongest moderation effects occur when there are no main effects present (i.e., when both independent variables are not associated with the dependent measure)," and such a finding would "indicate that a pure moderated effect had emerged" (p. 605). Such theorizing suggests that the *DAT1* genotype and maternal rejection contribute to the diagnosis of depression only in combination. Thus, prior studies may have failed to find an association between a measured dopaminergic candidate gene and depression because they examined only the main effect of genotype. It is also important to highlight that the present study examined multiple polymorphisms within the

[4]Because youth may report suicidal ideation in self-report format more readily than in interviews (Kaplan et al., 1994), the suicide item on the BDI was also used to identify participants with suicidal ideation.

DAT1 gene. This strategy extends previous methodologies, which have examined only a single polymorphism within a gene.

Assuming that the results reported here are replicated, they suggest that there may be a subtype of depression that is related to a deficit in the dopamine-driven approach system. Thus, it could be valuable for future interventions for depression to target the approach system specifically. One strategy would be to use psychosocial interventions to engage the approach system, which would in turn increase dopaminergic activity (see Roffman, Marci, Glick, Dougherty, & Rauch, 2005, for a discussion of the effects of psychosocial interventions on the brain). For example, strategies from cognitive-behavioral therapy could be used to help patients focus on identifying and pursuing new goals and rewards. In a recent study that is consistent with this theorizing, Dimidjian et al. (2006) found that a behavioral-activation intervention was at least as effective as antidepressant medication in reducing depressive symptoms and had lower rates of attrition.

The present study had a number of strengths. First, the G × E design made possible a full test of the diathesis-stress model of depression by focusing on the interaction of genetic diathesis and environmental liability. Another strength was the use of a structured diagnostic interview (K-SADS-PL), rather than self-report questionnaires, to assess depression. This procedure enabled us to make conclusions about clinically significant forms of depression and not just mild depressive symptomatology. Finally, we were able to establish convergent validity for our findings by showing that the G × E interaction also predicted suicidality and depressive symptoms (at the level of a trend). According to Moffitt et al. (2006), replicating a G × E interaction using multiple outcome measures provides assurance that the results are valid and did not occur by chance. Moreover, the fact that the significant interaction in our study did not predict a diagnostic outcome that has no relation to the hypothesis (i.e., anxiety disorders) suggests that the results were not due to a scaling artifact.

Despite these strengths, this study was not without flaws. First, it is unclear whether the findings will generalize to other samples. Our sample was unique because it consisted entirely of incarcerated males. However, working with this particular sample had two advantages. First, the sample was ethnically homogeneous, with only one ethnic background represented; this suggests that the sample is genetically homogeneous as well. Second, this was a highly vulnerable sample, with expected high rates of maternal rejection, harsh parenting, and other problems in parenting.

Another limitation was the use of a self-report measure of maternal rejection. The EMBU assessed perceived rejection, and thus it is unclear if participants who scored high on this measure were actually rejected by their mothers. However, it is important to note that high scores on this scale were not simply the result of increased levels of depression (i.e., depression status and score on the maternal-rejection scale were not significantly correlated). Nevertheless, more detailed information about the maternal rejection, as well as the parenting style in general, that participants experienced would be desirable.

It is also unclear why the other two *DAT1* polymorphisms that we studied did not show patterns of results similar to that of rs40184. It is interesting that the polymorphism (rs40184 SNP) that did contribute to depression onset is an intronic polymorphism; it is unclear whether this polymorphism has direct functional significance. However, it is important to note that many studies in the literature link polymorphisms of unknown function with specific psychiatric disorders (e.g., Cook et al., 1995). If rs40184 is not a functional site itself, it may still act as a marker for a nearby functional site or interact with a second functional polymorphic site.[5]

In conclusion, the present study builds on recent advances in research on G × E interactions and provides some of the first support for the role of a dopamine-related gene in the onset of depression. Although exciting, these findings need to be replicated. We look forward to further G × E studies that examine the *DAT1* gene, as well as other dopaminergic candidate genes.

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[5]The rs40184 SNP is located within the 3′ end of the *DAT1* gene and exhibits extensive linkage disequilibrium with the variable-number tandem-repeat polymorphism in the 3′-untranslated region (3′ UTR VNTR). It should also be noted that one of the other SNPs we used in this analysis, rs2652511, is located within the 5′-untranslated region, and has been associated with schizophrenia (Stöber et al., 2006); the third SNP, rs6347, was reported to be in linkage disequilibrium with a different multiallelic polymorphism associated with cocaine abuse (Guindalini et al., 2006).

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