Childhood Adversity, Monoamine Oxidase A Genotype, and Risk for Conduct Disorder

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Background: Very little is known about how different sets of risk factors interact to influence risk for psychiatric disorder.

Objective: To replicate a recent report of a genotype-environment interaction that predicts risk for antisocial behavior in boys.

Design: Characterizing risk for conduct disorder in boys in association with monoamine oxidase A genotype and exposure to familial adversity, defined by interparental violence, parental neglect, and inconsistent discipline.

Setting: A community-based sample of twin boys.

Participants: Five hundred fourteen male twins aged 8 to 17 years.

Main Outcome Measure: Conduct disorder.

Results: There was a main effect of adversity but not of monoamine oxidase A on risk for conduct disorder. Low monoamine oxidase A activity increased risk for conduct disorder only in the presence of an adverse childhood environment. Neither a passive nor an evocative genotype-environment correlation accounted for the interaction.

Conclusion: This study replicates a recent report of a genotype-environment interaction that predicts individual variation in risk for antisocial behavior in boys.

Arch Gen Psychiatry. 2004;61:738-744

There is a long history of research on risk factors for conduct disorder,1-3 in part because of the deleterious effects of aggressive, antisocial, and criminal acts on individuals and society at large. Evidence for aggregate genetic effects has been reported by many twin, family, and adoption studies, based on the pattern of resemblance between different classes of relatives, but reliable evidence for specific genetic effects is limited. Recently, an interaction between a functional polymorphism in the promoter of the monoamine oxidase A (MAO-A) gene and childhood maltreatment was reported to be associated with a significantly increased risk for antisocial behavior in boys from the Dunedin Multidisciplinary Health and Development Study.4 There was an independent effect of maltreatment but no independent effect of low MAO-A activity on risk for antisocial behavior. Low MAO-A activity was therefore a detectable risk factor only in the presence of an adverse childhood environment, and the effect was not trivial. Individuals with both the low-activity MAO-A genotype and maltreatment accounted for 12% of the birth cohort but 44% of the cohort’s violent convictions. A genotype-environment interaction may therefore account for a significant portion of individual variation in risk for antisocial behavior. This finding is a rare example of a measured gene and a measured environment jointly affecting human behavior. Such effects have been documented in experimental organisms5 and described in theoretical treatises,6 but they have rarely been explored and replicated in studies of human behavior.

In this study, we tested for the presence of an interaction between low MAO-A activity and exposure to childhood adversity that increases risk for conduct disorder in a community-based sample of boys from the Virginia Twin Study for Adolescent Behavioral Development (VTSABD).7 We did not survey maltreatment as defined by Caspi et al6 (maternal rejection, repeated loss of a primary caregiver, harsh discipline, physical abuse, sexual abuse),
but instead we defined adversity by exposure to 3 known risk factors for conduct disorder: interparental violence, parental neglect, and inconsistent discipline.3,8,9 We hypothesized that the findings of Caspi and colleagues indicate a robust effect on risk for conduct disorder of low MAO-A activity contingent on exposure to a variety of childhood adversities.

Subjects comprised 514 white male twins from the community-based, longitudinal Virginia Twin Study for Adolescent Behavioral Development. The recruitment and assessment of the 1412 twin families from which this subsample derives have been described in detail elsewhere.10,11 Male twins were included in the present study if data were available on their history of conduct disorder, exposure to childhood adversity, and MAO-A genotype. The VTSABD assessed subjects on up to 4 occasions, depending on their age (<18 years) and their willingness to participate in continued assessments. Recent history (past 3 months) of conduct disorder was surveyed at times 1, 2, 3, and 4, and a history of exposure to environmental adversities and DNA were collected at times 3 and 4. Eligible male subjects were aged 8 to 17 years (mean±SD, 12.23±2.81 years) at entry into the study.

Twins and their parents were personally interviewed at home by trained field workers. Twins were randomly assigned to different interviewers, and each co-twin was interviewed simultaneously in separate areas of the family home. Interviewers held a master’s degree in social work or an equivalent professional degree, or they had extensive experience in psychiatric interviewing. Interviewer training consisted of 3 weeks of residential instruction, and all field interviews were audiotaaped and reviewed by senior monitors. Regular meetings were conducted to avoid drift in use of the interview or other aspects of the protocol. A residential meeting was held annually to ensure that the assessment protocol was being implemented in a standardized manner.10 Informed consent was obtained in writing from parents, and assent was obtained from the child prior to the personal interview.

**ASSESSMENT OF CONDUCT DISORDER**

The past 3 months’ history of conduct disorder was assessed following the DSM-III-R criteria using the Child and Adolescent Psychiatric Assessment (CAPA)—Child and Parent Version.12 Conduct disorder was diagnosed using a symptom or rule; that is, a symptom was rated as present if endorsed by any informant. We used child, maternal, and paternal CAPA data.

**ASSESSMENT OF CHILDHOOD ADVERSITY**

The VTSABD did not survey the variables that were used to construct the maltreatment index used by Caspi et al. An adversity index was therefore constructed with 3 known correlates of conduct disorder: parental neglect, exposure to interparental violence, and inconsistent parental discipline. All 3 adversities were assessed at wave 3 of the VTSABD with the same assessment method (personal interview) and time frame of survey (ever). Three items rated by parents were used to define parental neglect: (1) Did anyone ever say you weren’t looking after the children properly? (2) Has anyone ever thought that 1 of the children became ill because the child wasn’t looked after properly or because the home wasn’t clean enough? (3) Was there ever a time when 1 of the children was very ill, but, at the time, you didn’t think the child needed to see a doctor, or was there ever a time when a doctor said you should have brought the child in earlier?

Two items rated by child subjects were used to define exposure to interparental violence: (4) Have your parents ever pushed or shoved each other during an argument? (5) When your parents fight, do they (or have they) ever hit each other? Two items rated by child subjects were used to define inconsistent parental discipline: Some parents can be strict one day, and the next day it seems as though they don’t care whether you broke a rule or not. Is it like that with either of your parents? This was rated for (6) mother and (7) father.

**ASSESSMENT OF MATERNAL SYMPTOMS OF ANTISOCIAL PERSONALITY**

A maternal history of 7 antisocial personality symptoms were surveyed by personal interview with mothers. These symptoms were (1) inability to sustain consistent work behavior; (2) failure to conform to laws or social norms; (3) irritable, aggressive, or involved in fighting or assaults; (4) failure to honor financial obligations; (5) impulsivity, moving from place to place; (6) recklessness regarding own or others’ safety; and (7) no relationship that lasted at least 1 year and was monogamous.

**DNA EXTRACTION AND GENOTYPING**

Cytology brushes were used to obtain a sample of buccal cells from the twins for DNA analysis. DNA was isolated using the In-s-taGene Matrix kit (Bio-Rad Laboratories, Hercules, Calif) protocol for cell lysis product absorption. Each sample was diluted to a working concentration of 5 to 20 ng/µL. We used primer sequences described previously.13 MAO APT1 (5’-ACACCTGAC-CGTGGAGAAG-3’), 5’-labeled with the FAM fluorophore and MAO APB1 (5’-GAACGACGCCTCATTCCGGA-3’). We amplified polymerase chain reaction products in 96-well microtitre plates in 20-µL volume containing 50 to 200 ng of genomic DNA, 1X GeneAmp PCR Gold buffer (Applied Biosystems, Foster City, Calif), 1.5 mM magnesium chloride, 10 pmol each forward and reverse primer, 0.3 mM each 2’-deoxynucleoside 5’-triphosphate, and 1.5 U HotMaster Taq DNA Polymerase (Eppendorf, Hamburg, Germany). Cycling reactions were performed on a PTC-225 DNA engine (MJ Research Inc, Waltham, Mass) with 3 minutes initial denaturation at 93°C, followed by 35 cycles of 93°C for 3 minutes, 62°C for 1 minute, 72°C for 1.5 minutes, with a final extension at 72°C for 8 minutes. We analyzed products using an 8% 96x10 capillary sequencer (SpectruMedix, State College, Pa) with ROX-labeled GS-500 (Applied Biosystems) as size standard, and we determined allele sizes using Genospectrum v2.6 DNA fragment analysis software (SpectruMedix).

**DATA ANALYSIS**

Male twins who were included in the current study (N=514) were compared with male twins who were not included because they had become too old for the study or were otherwise lost to follow-up at time 3/4 (N=823). We made this comparison to assess the representativeness of the subsample of the current study. Variation in the prevalence of conduct disorder at time 1 by participation status was evaluated using a 2-tailed chi-square test. Variation in the level of maternal antisocial personality symptoms, age at time 1, and ordinably scaled census tract variables were evaluated using a 2-tailed Wilcoxon rank sum test. Logistic regression was used to estimate risk for the clinical diagnosis of conduct disorder in association with MAO-A activity, exposure to childhood adversity, and the interaction between MAO-A activity and childhood adversity. Modeling conduct disorder symptom counts within a linear regression framework may be more powerful statistically, but the results
obtained with logistic regression are likely to be more robust. An interaction identified by linear regression may reflect heteroscedasticity, that is, an unequal mean-variance relationship over the range of scale scores and an artifact of the scale of measurement. We therefore sought to avoid misinterpretation of scalar effects by modeling the clinical diagnosis of conduct disorder. Logistic regression was performed in PROC GENMOD (SAS version 6.12; SAS Institute Inc., Cary, NC) to adjust for the correlation between co-twins.18 One-tailed probability levels are reported for the interaction term estimated in the regression model because this is a replication study and the direction of effects can be specified. A 2-tailed Fisher exact test was used to compare the prevalence of conduct disorder among subjects with low vs high MAO activity in association with no, probable, or definite exposure to childhood adversity.

RESULTS

REPRESENTATIVENESS OF THE SAMPLE
Male twins who participated in the current study were, as expected, younger at entry into the study (mean±SD age, 10.4±1.6 years) than nonparticipants (mean±SD age, 13.04±2.51 years, P<.001), and participants had a lower prevalence of conduct disorder at time 1 (3.89%) than nonparticipants (8.45%, P < .001). Mothers of participants had fewer antisocial personality symptoms (mean±SD, 0.67±0.87) at time 1 than mothers of nonparticipants (mean±SD, 0.95±1, P<.001). Participants did not differ significantly from nonparticipants on the following census-based indicators of regional socioeconomic status: median family income (P = .31), rural vs urban residence (P = .69), or proportion of college-educated adults (P = .55). Participants were more likely, however, to reside in areas with lower levels of male unemployment (3.03%) than nonparticipants (3.75%, P = .02). Participants and their mothers were therefore less symptomatic at entry into the study than twins who became too old for the study or were otherwise lost to follow-up. Our subsample is therefore not representative of the total sample at time 1, but any bias would likely serve to attenuate rather than overstate the magnitude of effects observed in this study.

PREVALENCE OF CONDUCT DISORDER, MAO-A GENOTYPES, AND EXPOSURE TO CHILDHOOD ADVERSITY
Among participating male twins, the prevalence of conduct disorder across time 1-4 was 11.48%. The prevalence of any low-activity MAO-A allele was 29.38%. Broken down by the number of repeats at the MAO-A promoter polymorphism (and by activity type), the frequency of each allele was 2 repeat, 0.39% (low); 3 repeat, 28.79% (low); 3.5 repeat, 2.33% (high); 4 repeat, 68.29% (high); and 5 repeat, 0.19% (low). The prevalence of exposure to any interparental violence was 2.53%; any parental neglect, 12.65%; and inconsistent maternal or paternal discipline, 17.32%.

As expected, all 3 adversities were significantly associated with conduct disorder (univariate odds ratio [OR]: interparental violence, OR, 3.6, P=.04; parental neglect, OR, 2.46, P = .008; inconsistent parental discipline, OR, 2.15, P = .01), even after controlling for their intercorrelations within a multiple regression framework (multivariate OR: interparental violence, OR, 3.38, P = .05; parental neglect, OR, 2.55, P = .006; inconsistent discipline, OR, 2.05, P = .03). Parental neglect, interparental violence, and inconsistent discipline were therefore largely independent correlates of risk for conduct disorder.

Childhood adversity was coded as a categorical variable to replicate the study by Caspi et al.4 In that study, the presence of any 1 adversity was coded as probable exposure, and the presence of any 2 adversities was coded as definite exposure. The prevalence of probable adversity (25.49%, 131/514) or definite adversity (2 adversities, 3.5%, 18/514) in the VTSABD was somewhat lower than the prevalence of probable maltreatment (28%) or definite maltreatment (8%) in the Dunedin sample. This likely reflects the much larger number of items (n = 21) used to assess maltreatment in the Dunedin study than the number of items (n = 7) used to assess adversity in the VTSABD. Given the low prevalence of the definite exposure category, adversity was also coded as an ordinal variable by counting the positive responses to the 7 items used to assess parental neglect, interparental violence, and inconsistent discipline to maximize statistical power in the data analyses described below.

RISK OF CONDUCT DISORDER IN ASSOCIATION WITH MAO-A GENOTYPE AND EXPOSURE TO CHILDHOOD ADVERSITY
When we modeled exposure to childhood adversity as an ordinal variable, there was a significant main effect of childhood adversity but not MAO-A on risk for conduct disorder (Table 1). Low MAO-A activity increased risk for conduct disorder only in the presence of an increasingly adverse childhood environment. After controlling for the interaction between low MAO-A activity and childhood adversity and the main effect of adversity, low MAO-A activity was associated with a lower risk of conduct disorder.

The prevalence of conduct disorder was plotted by level of adversity among boys with low vs high MAO-A activity to interpret the basis for the interaction (Figure). The raw data used to create this graph are given in Table 2. Most of our power to detect an interaction derives from the extremes of the distribution (Fisher exact test). Because of our sample size, we had low power to detect a statistically significant difference in the prevalence of conduct disorder in association with MAO-A genotype in children exposed to multiple adversities.

A statistical interaction such as we observed may result from a genotype-environment interaction or, under certain circumstances, from a genotype-environment correlation. This distinction is important because a genotype-environment interaction reflects genetically mediated sensitivity to environmental influences and/or environmentally mediated effect of genotype, whereby genes and environment together affect the phenotype. A genotype-environment correlation, in contrast, reflects a nonrandom distribution of environments among different geno-
types. In our specific case, this may be due to either a direct influence of the child’s genotype on experienced adversity (an evocative genotype-environment correlation) or an indirect influence of the child’s genotype on experienced adversity via correlated parental characteristics (a passive genotype-environment correlation).

If adverse parental treatment is elicited by a child with low MAO-A activity, this could create an evocative genotype-environment correlation. In a test for an evocative genotype-environment correlation, low MAO-A activity did not predict level of exposure to childhood adversity (linear regression analysis, \( \beta = .08, P = .38 \)). The child’s own genotype therefore had no discernible impact on their exposure to adversity in this study.

Children derive both genotype and familial environment from their parents. A passive genotype-environment correlation is present if parental characteristics associated with the child’s exposure to familial adversity are correlated with the child’s genotype. If a parent with a particular genotype is more likely to create a particular family environment, this will create a passive genotype-environment correlation in the child. We therefore tested if the observed interaction is attributable to a passive genotype-environment correlation. We have chosen to adjust for maternal symptoms of antisocial personality in our regression model because males inherit their X-linked MAO-A allele from their mother and because antisocial personality is associated with poor parenting and thus potentially with exposure to the adversities assessed in this study.

We found a significant correlation between the child’s exposure to adversities and maternal antisocial personality symptoms (Spearman rank correlation coefficient, \( r = 0.24, P = .001 \)); this was consistent with our expectation that antisocial personality is associated with poor parenting. Adjustment for the main effects of the child’s MAO-A genotype, the child’s level of exposure to adversity, and maternal antisocial personality symptoms in our regression model did not, however, attenuate the magnitude or the statistical significance of the association between conduct disorder and the interaction between MAO-A activity and adversity (Table 1).

A passive genotype-environment correlation therefore does not account for the observed association. Our findings in both tests for genotype-environment correlation are therefore consistent with a random distribution of low-activity genotypes among children exposed to different levels of childhood adversity.

When we modelled childhood adversity following Caspi and colleagues, there was a significant main effect of probable (OR, 2.76; 95% confidence interval [CI], 1.55-4.93; \( P < .001 \)) or definite exposure to childhood adversity (OR, 4.35; 95% CI, 1.4-13.5; \( P = .01 \)) but not a significant main effect of MAO-A (OR, 0.63; 95% CI, 0.33-1.22; \( P = .18 \)) on risk for conduct disorder (Table 2). There was also a marginally significant association between risk for conduct disorder and the interaction between low MAO-A activity and definite (OR, 7.56; 95% CI, 0.59-95.95; \( P = .059 \)) but not probable exposure to childhood adversity (OR, 1.32; 95% CI, 0.32-5.41; \( P = .34 \)) after controlling for the main effect of definite (OR, 2.67; 95% CI, 0.69-10.23; \( P = .15 \)) or probable exposure to childhood adversity (OR, 2.62; 95% CI, 1.35-5.05; \( P = .004 \)) and low MAO-A activity (OR, 0.48; 95% CI, 0.17-1.3; \( P = .15 \)). In a test for a passive genotype-environment correlation, there was still a marginally significant association between conduct disorder and the interaction between low MAO-A activity and definite (OR, 5.84; 95% CI, 0.44-77.97; \( P = .09 \)) but not probable exposure to childhood adversity (OR, 1.36; 95% CI, 0.32-5.72; \( P = .33 \)) after controlling for maternal symptoms of antisocial personality disorder (OR, 1.18; 95% CI, 0.94-1.5; \( P = .14 \)) and the main effect of definite (OR, 2.22; 95% CI, 0.54-9.07; \( P = .26 \)) or probable exposure to childhood adversity (OR, 2.45; 95% CI, 1.22-4.93; \( P = .01 \)) and low MAO-A activity (OR, 0.5; 95% CI, 0.18-1.35; \( P = .17 \)). In a test for an evocative genotype-environment correlation, low MAO-A

![Prevalence of conduct disorder as a function of monoamine oxidase A activity and level of exposure to childhood adversities.](image-url)

### Table 1. Odds Ratio (95% CI) for Conduct Disorder in Association With MAO-A Genotype and Childhood Adversity*

<table>
<thead>
<tr>
<th>Predictors of Conduct Disorder</th>
<th>Test for Main Effects</th>
<th>Test for Interaction</th>
<th>Test for Passive rGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood adversity</td>
<td>1.55 (1.21-1.97) [( P &lt; .001 )]</td>
<td>1.36 (1.04-1.78) [( P = .02 )]</td>
<td>1.27 (0.94-1.70) [( P = .11 )]</td>
</tr>
<tr>
<td>Low MAO-A activity</td>
<td>0.62 (0.33-1.17) [( P &lt; .14 )]</td>
<td>0.36 (0.13-0.97) [( P = .04 )]</td>
<td>0.38 (0.14-1.003) [( P = .05 )]</td>
</tr>
</tbody>
</table>
| Childhood adversity \(
| \times\) low MAO-A activity   | 1.69 (0.95-3.03) [\( P = .04 \)] | 1.64 (0.92-2.92) [\( P = .04 \)] | 1.21 (0.96-1.53) [\( P = .10 \)] |
| Maternal antisocial personality symptoms |                      |                     |                     |

Abbreviations: CI, confidence interval; MAO-A, monoamine oxidase A; OR, odds ratio.

*Childhood adversity coded as N of 7 items used to survey parental neglect, exposure to interpersonal violence, and inconsistent parental discipline. Passive rGE refers to a test for a passive genotype-environment correlation indexed by maternal symptoms of Antisocial Personality Disorder.
activity did not predict level of exposure to childhood adversity handled as a categorical variable ($\chi^2 = 0.69, P = .7$).

### Table 2. Prevalence of Conduct Disorder by MAO-A Genotype and Level of Exposure to Childhood Adversity*

<table>
<thead>
<tr>
<th>Level of Exposure to Childhood Adversity, No. (%)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low MAO-A</td>
<td>4/99 (4.04)</td>
<td>3/19 (15.79)</td>
<td>3/27 (11.11)</td>
<td>2/5 (40)</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>High MAO-A</td>
<td>22/249 (8.84)</td>
<td>13/53 (24.53)</td>
<td>10/47 (21.28)</td>
<td>1/10 (10)</td>
<td>0/4 (0)</td>
</tr>
<tr>
<td>$P$ Value, 2-tailed Fisher exact test</td>
<td>$P = .17$</td>
<td>$P = .53$</td>
<td>$P = .35$</td>
<td>$P = .24$</td>
<td>$P = .20$</td>
</tr>
</tbody>
</table>

Abbreviation: MAO-A, monoamine oxidase A.  
*Level of exposure to childhood adversity refers to 7 items used to survey parental neglect, exposure to interparental violence, and inconsistent parental discipline.

**COMMENT**

This study replicates the report by Caspi et al1 of a genotype-environment interaction that predicts individual variation in risk for antisocial behavior. We detect an interaction between MAO-A and exposure to a different set of childhood adversities in those surveyed by Caspi and colleagues. This suggests a relatively robust effect of childhood adversities in those surveyed by Caspi and colleagues. This suggests a relatively robust effect of MAO-A in combination with exposure to environmental adversity on risk for conduct disorder. Both sets of findings are also consistent with reports from adoption studies describing an increased risk for antisocial behavior in boys in association with an interaction between MAO-A and exposure to childhood adversity. In fact, in that model, the low-activity MAO-A genotype was associated with significantly lower risk for conduct disorder. This is an important finding because it suggests that specific genotypes may be associated with increasing or decreasing risks for psychiatric disorder contingent on environmental exposures. Moreover, relevant genetic factors may not be detected at all unless the target sample is stratified by salient environmental risk factors.

If genotype-environment interactions are generalized phenomena, there are several implications for psychiatric genetic studies. The effects of genotype may be small (or nonexistent) in gene-phenotype association studies if variability in exposure to environmental adversity is not taken into account. The absence of an independent effect of MAO-A on risk for conduct disorder in both the Dunedin and the Virginia studies underscores this point. It will therefore be important to collect detailed environmental histories as well as DNA on subjects participating in projects designed to identify genetic risk factors for psychiatric disorder. When samples differ in the prevalence of exposure to salient environmental risk factors, failures to replicate may remain the rule. Epidemiological samples are therefore likely to play an increasingly important role in the detection of genes for psychiatric disorder because they routinely sample a diversity of environments in unselected subjects from a representative range of families. Identification of a reordering of genotypic effects contingent on environmental exposure also requires subjects with a broad range of genetic and environmental risk and protective factors, including subjects who lack the environmental risk factors that may moderate genotypic effects.

A reordering of genotypic effects contingent on environmental exposure has been described in domesticated animal and plant species,17,18 and such effects may reflect selection for a variable response to environmental factors.17 This seems quite plausible for behavioral outcomes and may explain why specific environmental risk factors for juvenile disorders have been consistently replicated across studies,19 whereas the identification of specific genetic risk factors has been disappointingly elusive. In our own study, low MAO-A activity should not be considered a high-risk genotype per se, but it is perhaps poorly suited to tolerating specific forms of environmental adversity.

Many previous genetically informative studies have focused on estimating the main effects of genes on risk
for psychiatric disorders independent of environmental exposures. This paradigm assumes a direct path from genes to disorders with no interaction between genetic and environmental risk factors. In the case of measured genetic effects, this approach has yielded very disappointing results despite significant investment. Most candidate gene findings have failed consistent replication, and even those that have been verified account for only a very small fraction of variation in risk. If genes primarily exert effects on risk for psychiatric disorders contingent on environmental exposures, this may explain the very limited success of studies directed at detecting the main effects of genes via traditional linkage or association studies. Given the importance of epigenetics in human brain development and the complexity of human behavioral repertoires, it should not be surprising if complex genetic effects on psychiatric phenotypes are more readily discerned when relevant environmental contexts are taken into account. The implications for twin and family studies are not trivial. If a genotype-environment interaction is present but not modeled explicitly, it will be confounded with estimates of the main effects of genes or the environment in twins reared together. An interaction between genetic and environmental risk factors unshared by relatives will be confounded with estimates of the environment and will be identified as a main effect of the environment unique to individuals. An interaction between genes and environmental factors shared by relatives will be confounded with estimates of both genetic effects and common environmental effects, and will be identified as a main effect of both genes and the common environment.

Genotype-environment interactions have been reported to be important for the development of depression as well as antisocial behaviors in studies estimating aggregate genetic effects, and Caspi et al have recently reported that a functional polymorphism in the promoter region of the serotonin transporter gene moderates the influence of stressful life events on depression. There has traditionally been a strong emphasis on the likely importance of the independent effects of genes and environments on risk for complex disease in humans, but the findings of Caspi et al, which are replicated here, suggest that analysis of the joint effects of measured genes and environments may indicate 1 important way forward for psychiatric genetics.

The results presented here should be interpreted in light of the following limitations and caveats. First, the male twins who are the subject of the current report are not representative of all male twins in the VTSAKD. At entry into the VTSAKD, participants in the current study had a significantly lower prevalence of conduct disorder, and had mothers with significantly fewer symptoms of antisocial personality disorder, than twins who did not participate in the current study. However, any associated bias would likely serve to attenuate rather than overstate the magnitude of effects reported here. Second, the VTSAKD did not survey the variables that were used to construct the maltreatment index used by Caspi et al, and we therefore cannot estimate the association between their maltreatment index and our own adversity index. It is likely, however, that these 2 measures are significantly correlated, and they may indicate an overlapping set of environmental risks. Third, our findings are consistent with a reordering of genotypic effects contingent on environmental exposure, but a larger study is needed to confirm this possibility. Fourth, population stratification was not formally evaluated by a genomic control analysis, but we have partly allowed for the effects of stratification by controlling for the effects of maternal antisocial personality in our test for a passive genotype-environment correlation. Fifth, previous twin studies have largely focused on estimating the main effects of autosomal genes on risk for conduct disorder. However, MAO-A is an X-linked gene, and an increased risk for conduct disorder in association with an interaction between MAO-A and exposure to an adverse childhood environment suggests that there are sex differences in the heritable transmission of risk to male and female offspring. It will therefore be important to determine if the pattern of familial resemblance in extended (twins) family data is consistent with the presence of an X-linked gene with a large effect and if such effects are discernible only when samples are stratified by salient environmental exposures. Sixth, analysis of other psychiatric outcomes and a broader range of environmental adversities are required to determine the specificity of the effects on psychiatric disorder of MAO-A contingent on variation in exposure to salient environmental risk factors.

Submitted for publication November 28, 2003; final revision received February 19, 2004; accepted February 26, 2004.

This work was supported by grants MH-45268 (Dr Eaves) and MH-57761 (Dr Foley) from the National Institute of Mental Health, Bethesda, Md; the Carman Trust for Scientific Research, Richmond, Va (Dr Silberg); and by a MacArthur Junior Faculty Award (Dr Silberg). We acknowledge the contribution of the Virginia Twin Study for Adolescent Behavioral Development, now part of the Mid-Atlantic Twin Registry, Richmond, to ascertainment of subjects for this study. The Mid-Atlantic Twin Registry, directed by Linda Corey, PhD, has received support from the National Institutes of Health, Bethesda; the Carman Trust for Scientific Research, Richmond; the John T. and Katherine D. MacArthur Foundation, Chicago, Ill; the W. M. Keck Foundation, Los Angeles, Calif; the John Templeton Foundation, Radnor, Pa; and The Robert Wood Johnson Foundation, Princeton, NJ.

We thank Adrian Angold, MD, for his helpful comments on an earlier version of the manuscript.

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