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www.sciencemag.org/cgi/content/full/1070824/DC1
Figs. S1 and S2

12 February 2002; accepted 28 May 2002
Published online 13 June 2002;
10.1126/science.1070824
Include this information when citing this paper.

Role of Genotype in the Cycle of Violence in Maltreated Children

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We studied a large sample of male children from birth to adulthood to determine why some children who are maltreated grow up to develop antisocial behavior, whereas others do not. A functional polymorphism in the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A (*MAOA*) was found to moderate the effect of maltreatment. Maltreated children with a genotype conferring high levels of *MAOA* expression were less likely to develop antisocial problems. These findings may partly explain why not all victims of maltreatment grow up to victimize others, and they provide epidemiological evidence that genotypes can moderate children's sensitivity to environmental insults.

Childhood maltreatment is a universal risk factor for antisocial behavior. Boys who experience abuse—and, more generally, those exposed to erratic, coercive, and punitive parenting—are at risk of developing conduct disorder, antisocial personality symptoms, and of becoming violent offenders (*1*, *2*). The earlier children experience maltreatment, the more likely they are to develop these problems (*3*). But there are large differences between children in their response to maltreatment. Although maltreatment increases the risk of later criminality by about 50%, most maltreated children do not become delinquents or adult criminals (*4*). The reason for this variability in response is largely unknown, but it may be that vulnerability to adversities is conditional, depending on genetic susceptibility factors (*5*, *6*). In this study, individual differences at a functional polymorphism in the promoter of the monoamine oxidase A (*MAOA*) gene were used to characterize genetic susceptibility to maltreatment and to test whether the *MAOA* gene modifies the influence of maltreatment on children's development of antisocial behavior.

The *MAOA* gene is located on the X chromosome (Xp11.23–11.4) (*7*). It encodes the *MAOA* enzyme, which metabolizes neurotransmitters such as norepinephrine (NE), serotonin (5-HT), and dopamine (DA), rendering them inactive (*8*). Genetic deficiencies in *MAOA* activity have been linked with aggression in mice and humans (*9*). Increased aggression and increased levels of brain NE, 5-HT, and DA were observed in a transgenic mouse line in which the gene encoding *MAOA* was deleted (*10*), and aggression was normalized by restoring *MAOA* expression (*11*). In humans, a null allele at the *MAOA* locus was linked with male antisocial behavior in a Dutch kindred (*12*). Because *MAOA* is an X-linked gene, affected males with a single copy produced no *MAOA* enzyme—effectively, a human knockout. However, this mutation is extremely rare. Evidence for an association between *MAOA* and aggressive behavior in the human general population remains inconclusive (*13*–*16*).

Circumstantial evidence suggests the hypothesis that childhood maltreatment predisposes most strongly to adult violence among children whose *MAOA* is insufficient to constrain maltreatment-induced changes to neurotransmitter systems. Animal studies document that maltreatment stress (e.g., maternal deprivation, peer rearing) in early life alters NE, 5-HT, and DA neurotransmitter systems in ways that can persist into adulthood and can influence aggressive behaviors (*17*–*21*). In humans, altered NE and 5-HT activity is linked to aggressive behavior (*22*). Maltreatment has lasting neurochemical correlates in human children (*23*, *24*), and although no study has ascertained whether *MAOA* plays a role, it exerts an effect on all aforementioned neurotransmitter systems. Deficient *MAOA* activity may dispose the organism toward neural hyperreactivity to threat (*25*). As evidence, phenelzine injections, which inhibit the action of monoamine oxidase, prevented rats from habituating to chronic stress (*26*). Low *MAOA* activity may be particularly prob-

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lematic early in life, because there is insufficient *MAOB* (a homolog of *MAOA* with broad specificity to neurotransmitter amines) to compensate for an *MAOA* deficiency (*8*).

Based on the hypothesis that *MAOA* genotype can moderate the influence of childhood maltreatment on neural systems implicated in antisocial behavior, we tested whether antisocial behavior would be predicted by an interaction between a gene (*MAOA*) and an environment (maltreatment). A well-characterized variable number tandem repeat (VNTR) polymorphism exists at the promoter of the *MAOA* gene, which is known to affect expression. We genotyped this polymorphism in members of the Dunedin Multidisciplinary Health and Development Study, a sample without population stratification confounds (*27*). This birth cohort of 1,037 children (52% male) has been assessed at ages 3, 5, 7, 9, 11, 13, 15, 18, and 21 and was virtually intact (96%) at age 26 years.

The study offers three advantages for testing gene-environment ($G \times E$) interactions. First, in contrast to studies of adjudicated or clinical samples, this study of a representative general population sample avoids potential distortions in association between variables (*28*, *29*). Second, the sample has well-characterized environmental adversity histories. Between the ages of 3 and 11 years, 8% of the study children experienced "severe" maltreatment, 28% experienced "probable" maltreatment, and 64% experienced no maltreatment (*27*). (Maltreatment groups did not differ on *MAOA* activity, $\chi^2(2) = 0.38$, $P = 0.82$, suggesting that genotype did not influence exposure to maltreatment.) Third, the study has ascertained antisocial outcomes rigorously. Antisocial behavior is a complicated phenotype, and each method and data source used to measure it (e.g., clinical diagnoses, personality checklists, official conviction records) is characterized by different strengths and limitations. Using information from independent sources appropriate to different stages of development, we examined four outcome measures (*27*). Adolescent conduct disorder was assessed according to criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV); convictions for violent crimes were identified via the Australian and New Zealand police; a personality disposition toward violence was measured as part of a psychological assessment at age 26; symptoms of antisocial personality disorder were ascertained at age 26 by collecting information about the study members from people they nominated as "someone who knows you well." A common-factor model fit the four measures of antisocial behavior well (*27*), with factor loadings ranging from 0.64 to 0.74, showing that all four measures index liability to antisocial behavior.

Using moderated regression analysis, we predicted scores on a composite antisocial index comprising the four measures of antisocial behavior (*27*) (Fig. 1). The main effect of *MAOA* activity on the composite index of

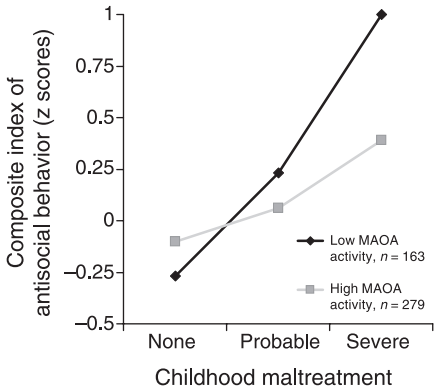

Fig. 1. Means on the composite index of antisocial behavior as a function of *MAOA* activity and a childhood history of maltreatment (*27*). *MAOA* activity is the gene expression level associated with allelic variants of the functional promoter polymorphism, grouped into low and high activity; childhood maltreatment is grouped into 3 categories of increasing severity. The antisocial behavior composite is standardized (*z* score) to a M = 0 and SD = 1; group differences are interpretable in SD unit differences (d).

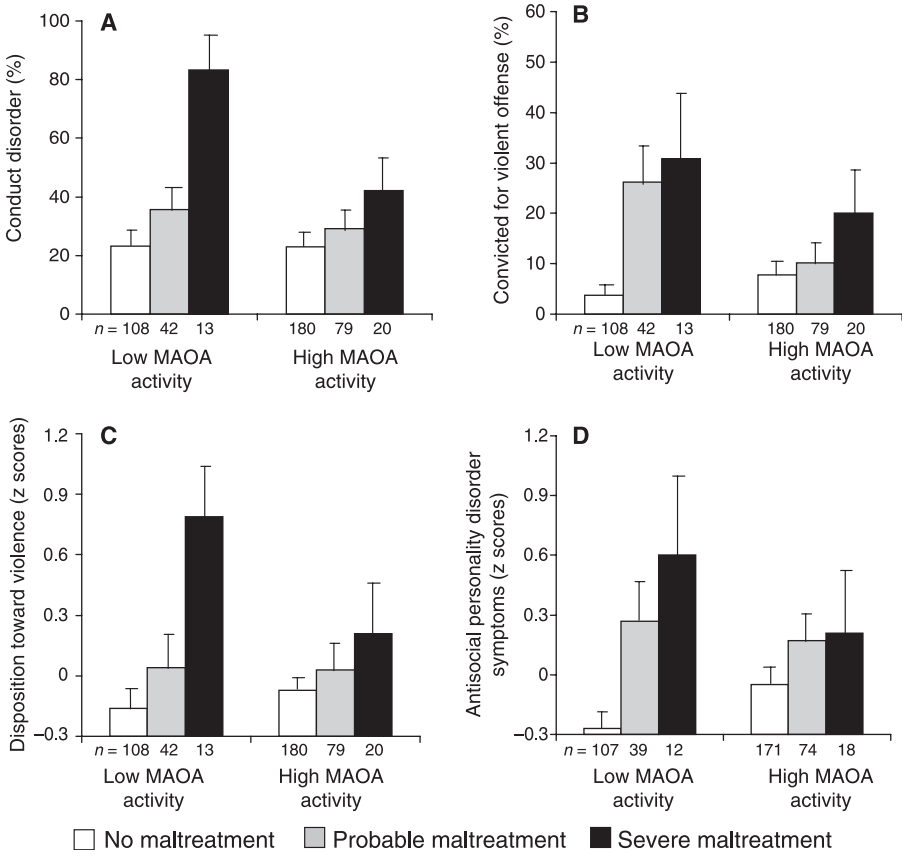

Fig. 2. The association between childhood maltreatment and subsequent antisocial behavior as a function of *MAOA* activity. (**A**) Percentage of males (and standard errors) meeting diagnostic criteria for Conduct Disorder between ages 10 and 18. In a hierarchical logistic regression model, the interaction between maltreatment and *MAOA* activity was in the predicted direction, $b = -0.63$, SE = 0.33, $z = 1.87$, $P = 0.06$. Probing the interaction within each genotype group showed that the effect of maltreatment was highly significant in the low–*MAOA* activity group ($b = 0.96$, SE = 0.27, $z = 3.55$, $P < 0.001$), and marginally significant in the high-*MAOA* group ($b = 0.34$, SE = 0.20, $z = 1.72$, $P = 0.09$). (**B**) Percentage of males convicted of a violent crime by age 26. The $G \times E$ interaction was in the predicted direction, $b = -0.83$, SE = 0.42, $z = 1.95$, $P = 0.05$. Probing the interaction, the effect of maltreatment was significant in the low–*MAOA* activity group ($b = 1.20$, SE = 0.33, $z = 3.65$, $P < 0.001$), but was not significant in the high *MAOA* group ($b = 0.37$, SE = 0.27, $z = 1.38$, $P = 0.17$). (**C**) Mean *z* scores (M = 0, SD = 1) on the Disposition Toward Violence Scale at age 26. In a hierarchical ordinary least squares (OLS) regression model, the $G \times E$ interaction was in the predicted direction ($b = -0.24$, SE = 0.15, $t = 1.62$, $P = 0.10$); the effect of maltreatment was significant in the low–*MAOA* activity group ($b = 0.35$, SE = 0.11, $t = 3.09$, $P = 0.002$) but not in the high *MAOA* group ($b = 0.12$, SE = 0.07, $t = 1.34$, $P = 0.17$). (**D**) Mean *z* scores (M = 0, SD = 1) on the Antisocial Personality Disorder symptom scale at age 26. The $G \times E$ interaction was in the predicted direction ($b = -0.31$, SE = 0.15, $t = 2.02$, $P = 0.04$); the effect of maltreatment was significant in the low–*MAOA* activity group ($b = 0.45$, SE = 0.12, $t = 3.83$, $P < 0.001$) but not in the high *MAOA* group ($b = 0.14$, SE = 0.09, $t = 1.57$, $P = 0.12$).

antisocial behavior was not significant (b = 0.01, SE = 0.09, t = 0.13, P = 0.89), whereas the main effect of maltreatment was significant (b = 0.35, SE = 0.07, t = 4.82, $P <$ 0.001). A test of the interaction between *MAOA* activity and maltreatment revealed a significant $G \times E$ interaction (b = −0.36, SE = 0.14, t = 2.53, P = 0.01). This interaction within each genotype group showed that the effect of childhood maltreatment on antisocial behavior was significantly weaker among males with high *MAOA* activity (b = 0.24, SE = 0.11, t = 2.15, P = 0.03) than among males with low *MAOA* activity (b = 0.68, SE = 0.12, t = 5.54, $P <$ 0.001).

We conducted further analyses to test if the $G \times E$ interaction was robust across each of the four measures of antisocial behavior that made up the composite index. For all four antisocial outcomes, the pattern of findings was consistent with the hypothesis that the association between maltreatment and antisocial behavior is conditional, depending on the child's *MAOA* genotype ($G \times E$ interaction P = 0.06, 0.05, 0.10, and 0.04, respectively). For adolescent conduct disorder (Fig. 2A), maltreated males (including probable and severe cases) with the low–*MAOA* activity genotype were more likely than nonmaltreated males with this genotype to develop conduct disorder by a significant odds ratio (OR) of 2.8 [95% confidence interval (CI): 1.42 to 5.74]. In contrast, among males with high *MAOA* activity, maltreatment did not confer significant risk for conduct disorder (OR = 1.54, 95% CI: 0.89 to 2.68). For adult violent conviction (Fig. 2B), maltreated males with the low–*MAOA* activity genotype were more likely than nonmaltreated males with this genotype to be convicted of a violent crime by a significant odds ratio of 9.8 (95% CI: 3.10 to 31.15). In contrast, among males with high *MAOA* activity, maltreatment did not confer significant risk for violent conviction (OR = 1.63, 95% CI = 0.72 to 3.68). For self-reported disposition toward violence (Fig. 2C) and informant-reports of antisocial personality disorder symptoms (Fig. 2D), males with the low–*MAOA* activity genotype who were maltreated in childhood had significantly elevated antisocial scores relative to their low-*MAOA* counterparts who were not maltreated. In contrast, males with high *MAOA* activity did not have elevated antisocial scores, even when they had experienced childhood maltreatment.

These findings provide initial evidence that a functional polymorphism in the *MAOA* gene moderates the impact of early childhood maltreatment on the development of antisocial behavior in males. Replications of this $G \times E$ interaction are now needed. Replication studies should use valid and reliable ascertainments of maltreatment history and should obtain multiple measures of antisocial outcomes, in large samples of males and females (*30*). If replicated, the findings have implications for research and clinical practice. With regard to research in psychiatric genetics, knowledge about environmental context might help gene-hunters refine their phenotypes. Genetic effects in the population may be diluted across all individuals in a given sample, if the effect is apparent only among individuals exposed to specific environmental risks. With regard to research on child health, knowledge about specific genetic risks may help to clarify risk processes. Numerous biological and psychological processes have been put forward to explain why and how experiences of maltreatment are converted into antisocial behavior toward others (*17*, *24*, *31*–*34*), but there is no conclusive evidence that any of these processes can account for the progression from childhood maltreatment to later criminal violence. Moreover, some youngsters make the progression, but others do not, and researchers have sought to understand why (*35*). The search has focused on social experiences that may protect some children, overlooking a potential protective role of genes. Genes are assumed to create vulnerability to disease, but from an evolutionary perspective they are equally likely to protect against environmental insult (*36*). Maltreatment studies may benefit from ascertaining genotypes associated with sensitivity to stress, and the known functional properties of *MAOA* may point toward hypotheses, based on neurotransmitter system development, about how stressful experiences are converted into antisocial behavior toward others in some, but not all, victims of maltreatment.

Until this study's findings are replicated, speculation about clinical implications is premature. Nonetheless, although individuals having the combination of low-activity *MAOA* genotype and maltreatment were only 12% of the male birth cohort, they accounted for 44% of the cohort's violent convictions, yielding an attributable risk fraction (11%) comparable to that of the major risk factors associated with cardiovascular disease (*37*). Moreover, 85% of cohort males having a low-activity *MAOA* genotype who were severely maltreated developed some form of antisocial behavior. Both attributable risk and predictive sensitivity indicate that these findings could inform the development of future pharmacological treatments.

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30. This study focused on males because their single X chromosome yields two straightforwardly characterized *MAOA* genotypes: high activity (63% in this sample) and low activity (37%). Females, having two copies of the X chromosome, fall into two homozygous groups, high-high (42% in this sample), low-low (12%), and a third heterozygous group, low-high (46%), that cannot be characterized with certainty because it is not possible to determine which of the two alleles is inactivated for each female participant. Given the rarity in females of both the low-low genotype (12%) and severe antisocial outcomes, such as violent conviction (2%), our cohort of 481 females, 11% of whom were severely maltreated, was too small to support all of the analyses reported here for males. However, adolescent conduct disorder could be analyzed, revealing that girls with the low–*MAOA* activity genotype were more likely to develop conduct disorder by a significant odds ratio of 5.5 (95% CI: 1.0 to 32.0) if they were maltreated. In contrast, among girls with high *MAOA* activity, maltreatment did not confer significant risk for conduct disorder (OR = 1.7, 95% CI: 0.75 to 4.2). This suggests that high *MAOA* activity exerts a protective influence against maltreatment for girls as well as boys, and raises the possibility that further research into X-linked genotypes may help to explain one of the least understood facts about serious antisocial behavior: the sex difference (*38*).
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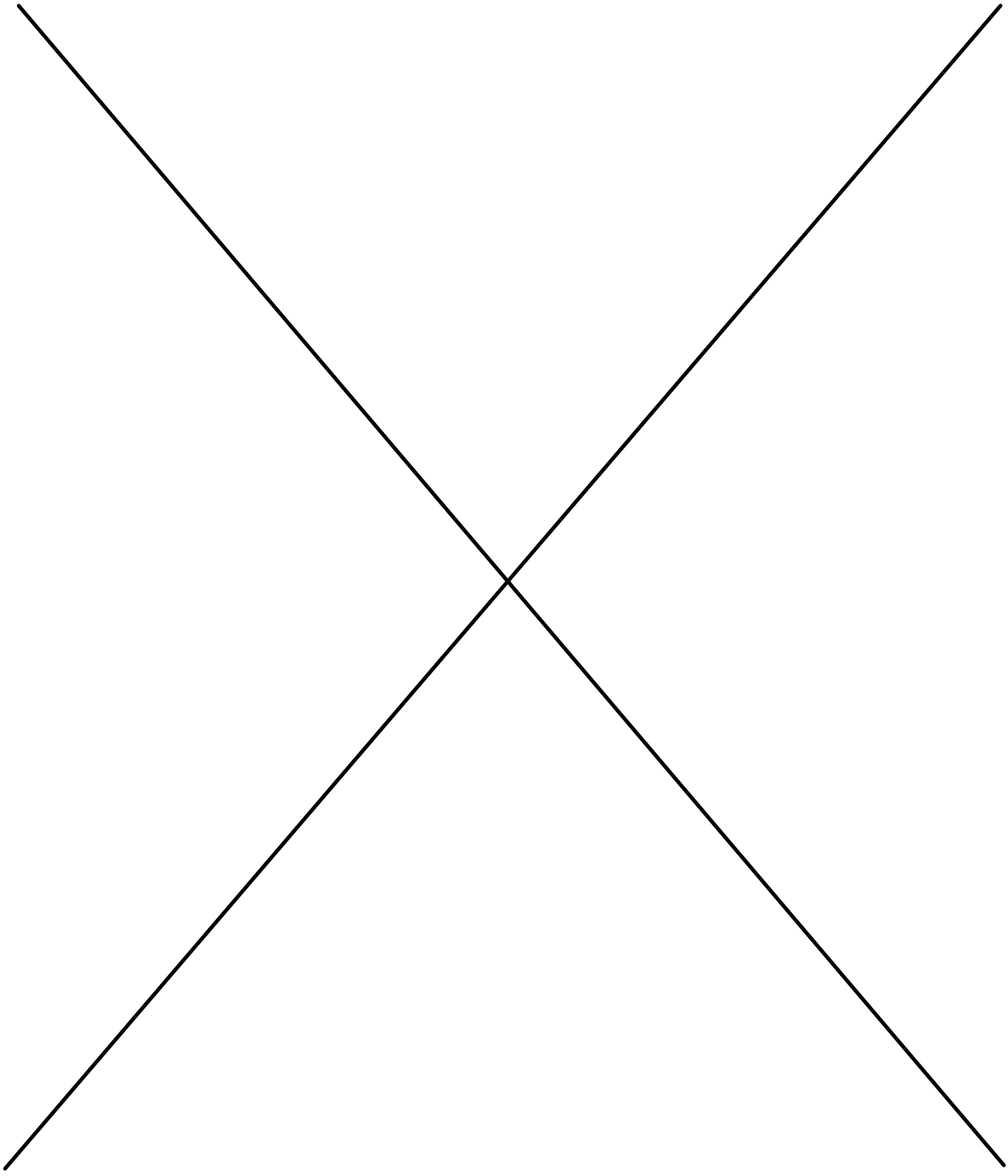
39. We thank P. Silva, founder of the Dunedin Multidisciplinary Health and Development Study, Air New Zealand, and the study members, their families, and friends. Supported by the Health Research Council of New Zealand, the University of Wisconsin Graduate School, and by grants from the U.K. Medical Research Council and the U.S. National Institute of Mental Health (MH49414, MH45070). The study protocol was approved by the institutional review boards of the participating universities.



Description of Methods and Measurements used in the Dunedin Multidisciplinary Health and Development Study

Materials and Methods

Research sample. The Dunedin longitudinal study was constituted when participants were age 3 when the investigators enrolled 91% of the consecutive births between April 1972 and March 1973 in Dunedin, New Zealand (*S1*). Cohort families represent the full range of socioeconomic status in the general population of New Zealand's South Island. Follow-ups have been carried out at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, and, most recently, at age 26, when we assessed 96% of the living cohort members (N = 499 males). At each age, participants are brought back to the research unit within 60 days of their birthday for a full day of individual tests and interviews. These data are supplemented by questionnaires completed by persons who know the study members well and by official record searches.

DNA extraction and genotyping. At age 26, DNA was obtained from 953 study members (97% of those assessed at that age; 51% male); 93% of DNA samples were obtained via blood and 7% via buccal swabs for those not wishing to undergo phlebotomy. DNA was extracted from blood samples using standard procedures (*S2*, *S3*). A modified procedure was used to extract DNA from buccal cells (*S4*). Primer sequences are described by Sabol *et al*. (*S5–S7*), namely MAO APT1 (5'-ACAGCCTGACCGTGGAGAAG-3') and MAO APB1 (5′-GAACGGACGCTCCATTCGGA-3′), although here MAO APT1 was 5′-labeled with the TET fluorophore. PCR was carried out on a PTC-225 DNA engine (MJ Research), using the following cycling conditions: initial 2-min denaturing step at 95°C, followed by 35 cycles of 94°C for 1 min, 58.2°C for 1 min and 72°C for 1 min 30 s, and a final extension phase of 72°C for 5 min. Reactions were performed in 25:l GeneAmp PCR Buffer I (PE Applied Biosystems), 1.5 mM $MgCl_2$, 50 ng of genomic DNA, 10 pmols of each primer, 0.33 mM dNTPs and 1.5 units of Native *Taq* (Promega). PCR products were assayed on an Applied Biosystems 377 genetic analyzer (PE Applied Biosystems), set up in genotyping mode, using 4.25% w/v polyacrylamide gel (Amresco) and TAMRA-labeled GS500 (PE Applied Biosystems) size standard. Results were analyzed using GeneScan v2.1 and Genotyper v1.1 software (Applied Biosystems).

Supporting Table S1 shows the allele frequencies observed among non-Maori members of our study. The genotypes were classified according to previous results showing that an optimum sequence length of 3.5 or 4 repeats results in high expression levels. In terms of expression, all studies (*S5–S7*) agree on the functional classification of the two most common alleles, i.e., 3 repeats (low activity) and 4 repeats (high activity). These two alleles account for 95.7% of our sample. Of rare alleles, both Sabol *et al*. (*S5*) and Deckert *et al*. (*S7*) assayed the 3.5 repeat with the same result (high activity), whereas a discrepancy arises for the 5 repeat. We chose the classification of Sabol *et al*. (*S5*) as they assayed 3 cell lines as opposed to one. However, we carried out analyses using both classifications and observed the same effects. The rare 2 repeat, of which only 1 exists in our sample, was classified as low activity due to its short length.

Population stratification can probably be ruled out as a confounding factor in this study. First, cohort members reporting Maori ethnicity (7%) were not included in our analysis. Second, Caucasian study members reported the ethnicity of all four grandparents, and only 4% reported 1 or 2 non-European grandparents. Third, allele frequencies among Caucasian study members matched closely frequencies reported in Caucasian samples. As a final check for stratification we adopted a genomic control approach based on latent class analysis (*S8*). One hundred individuals were selected at random from the sample and typed for 40 unlinked microsatellite markers. In a stratified sample one would expect to observe Hardy-Weinberg disequilibrium and linkage disequilibrium across the unlinked markers: our genomic control approach aimed to identify subpopulations (latent classes) such that within each there is Hardy-Weinberg and linkage equilibrium. In the current sample, however, there was no support for having more than one latent class, which is consistent with the sample being homogeneous.

Childhood maltreatment. Evidence of childhood maltreatment during the first decade of life (ages 3 to 11 years) was ascertained using behavioral observations, parental reports, and retrospective reports by study members once they reached adulthood (*S9*, *S10*). First, mother-child interactions were observed during the child's age-3 assessment. The mother was rated by an observer on eight categories: mother's affect toward the child was consistently negative; harshness toward the child; rough, awkward handling of the child; no effort to help child; unaware or unresponsive to child's needs; indifferent to child's performance; demanding of child's attention; soiled, unkempt appearance of child). Mothers engaging in 2 or more such behaviors were classified as rejecting (16%), based on evidence that such maternal behavior is associated with increased risk of children's later antisocial behavior (*S11*). Second, harsh discipline was measured at ages 7 and 9 using a checklist on which parents indicated if they engaged in ten disciplinary behaviors such as "smack him or hit him with something." Parents scoring in the top decile of the sample-wide distribution were classified as unusually harsh, relative to the culture in which this cohort grew up (10%), based on evidence that such parenting styles are associated with subsequent antisocial behavior of children (*S12*). Third, changes in the person occupying the role of the child's primary caregiver were ascertained at each assessment. Children who experienced 2 or more such changes during the first decade of life were classified as having suffered disruptive caregiver changes (6%), based on evidence that such family changes are predictive of later antisocial behavior (*S13*). Fourth, exposure to child physical abuse was assessed retrospectively at age 26 as part of an interview about victimization. Study members were classified as physically abused if they reported multiple episodes of severe physical punishment (e.g., strapping leaving welts; whipping with electric cords) resulting in lasting bruising or injury before age 11 (3%). Fifth, unwanted sexual contact was assessed retrospectively at age 26 as part of an interview about reproductive health. Study members were classified as sexually abused if they reported having their genitals touched, touching another's genitals, or attempted and/or completed sexual intercourse before age 11 (5%). The percentages of males experiencing physical and sexual abuse are consistent with rates reported elsewhere (*S14*). We examined these maltreatment experiences based on evidence that they too are linked to antisocial behavior (*S15*). We derived a cumulative exposure index for each child by counting the number of maltreatment experiences during the first decade of life; 64% of the children experienced no maltreatment, 28% experienced 1 indicator of

maltreatment (hereafter referred to as "probable maltreatment"), and 8% experienced 2 or more indicators of maltreatment (hereafter "severe maltreatment").

Antisocial behavior outcomes in adolescence and in adulthood. We examined four different outcome measures of antisocial behavior, using information from independent data sources that were appropriate at different stages of development.

Conduct disorder was measured according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), which identify adolescents displaying a persistent pattern of behavior that violates the rights of others, including physical harm (*S16*). A diagnosis of conduct disorder (using a 12-month reporting period for symptoms) was made in our longitudinal study when we assessed the research participants at each of four ages: ages 11, 13, 15, and 18. A 'lifetime' diagnosis was arrived at by establishing whether a study member received the diagnosis at one or more of the four ages (according to the DSM, conduct disorder is not normally diagnosed after age 18).

Court records of violent convictions in adulthood were searched via the Australian and New Zealand Police for 97% of male study members. Among study males, 11% received 174 convictions for violent crimes (e.g., common assault, aggravated assault with intent to injure with weapon, domestic violence, manslaughter, rape).

A disposition toward violence was ascertained at age 26 as part of the Multidimensional Personality Questionnaire (MPQ) Aggression scale (*S17*) (e.g., "When I get angry I am ready to hit someone," "I admit that I sometimes enjoy hurting someone physically"). ∀ reliability of the summed scale was 0.71.

Symptoms of antisocial personality disorder were ascertained at age 26, when informant reports about 95% of male study members were collected by mailing a questionnaire to persons they nominated as "someone who knows you well" (*S18*). Informants were friends, partners, or family members. Informants described the study members on seven cardinal symptoms: "has problems controlling anger," "blames others for own problems, "does not show guilt after doing something bad," "impulsive, rushes into things without thinking," "good citizen (reversed)," "does things against the law," and "gets into fights." Response options were "not a problem, "a bit of a problem," and "yes, a problem." ∀ reliability of the summed scale was 0.84.

Intercorrelations between the four outcomes ranged from 0.32 to 0.46. We fitted a common factor model to the four measures of antisocial behavior, using methods appropriate to the mixture of categorical and continuous measures (*S19*). According to multiple fit indices, the model fit well (Π^2 (2) = 2.56, P = 0.28, CFI = 0.99, RMSEA = 0.02), with factor loadings ranging from 0.64 to 0.74, showing that all four measures index liability to antisocial behavior. On the basis of the factor analysis, we created a composite index of antisocial behavior by counting the number of antisocial outcomes observed for each study member. This summary index counts whether they (a) met diagnostic criteria for adolescent conduct disorder, (b) were convicted for a violent crime, (c) scored in the top quartile of the distribution on a self-reported disposition toward violence, and (d) scored in the top quartile of the distribution on informant-reported antisocial personality disorder symptoms. We created this composite because the most reliable way to measure antisocial behavior is to aggregate multiple sources of information. We also report separate analyses of each of the four measures of antisocial

behavior, in order to test whether the observed findings were robust or sensitive to the four different ways in which the antisocial phenotype was measured. A robust finding is one whose pattern should be observed irrespective of how antisocial behavior is measured (*S20*).

The effects of *MAOA* activity, maltreatment, and their interaction on antisocial behavior were estimated in a moderated regression framework, using logistic regression for categorical outcomes (e.g., conduct disorder) and ordinary least squares (OLS) for continuous measures (e.g., personality disposition toward violence). The full results are contained in Supporting Table S2. The interaction effect was consistent with the hypothesis that *MAOA* activity moderated the effect of maltreatment on antisocial outcomes. As shown in the Report (Fig. 1), the dose-response association between maltreatment and antisocial behavior was significantly weaker in the high–*MAOA* activity group than in the low–*MAOA* activity group. We probed the gene × environment interaction further (*S21*) and found that the difference in antisocial behavior between the high and low *MAOA* groups became larger at increasing levels of maltreament. T tests for these differences are as follows: $t = –1.48$, $P = 0.14$ at no maltreatment, $t = 1.62$, $P = 0.11$ at probable maltreatment, and $t = 2.31$, $P = 0.02$ at severe maltreatment.

We further considered the possibility that the observed protective effect of high *MAOA* activity could have been brought about because of individual differences in IQ. We considered this alternative hypothesis because complete and selective deficiency of enzymatic activity of *MAOA* was associated with mild mental retardation in the Dutch kindred (*S22*), and low IQ is linked to high levels of antisocial behavior in the general population (*S23*), including in this sample ($r = –0.28$, $P < 0.001$). Therefore, the observed protective effect of high *MAOA* activity could have been an epiphenomenon of higher IQ among males with this genotype. However, we found no IQ differences between males with low- and high *MAOA* activity (M = 107 (SD = 14) vs. M = 108 (SD = 13), $t(430) = –0.70$, $P = 0.48$), and no significant linear association between maltreatment and IQ in either the low–*MAOA* activity group, $t(157) = –0.87$, $P = 0.38$, or the high–*MAOA* activity group, $t(269) = 0.93$, $P = 0.34$. We repeated the regression analysis shown in Supplementary Table S2 (first row), with the addition of IQ as a covariate. The interaction effect between *MAOA* and maltreatment remained statistically significant and of equivalent magnitude after controlling for IQ ($b = –0.34$, SE = 0.14, $t = 2.43$, $P = 0.015$).

Finally, we considered the possibility that the observed protective effect of high *MAOA* activity could be brought about if children with this genotype were likely to be reared in favorable environments. As such, we introduced into our analyses a further environmental covariate, social class, that is associated with antisocial behavior (*S24*), including in this sample ($r = –0.46$, $P < 0.001$). The childhood social class variable used in our analyses is the average of the highest social class level of either parent, assessed repeatedly at the study member's birth and ages 3, 5, 7, 9, 11, 13, and 15. This variable reflects the socioeconomic conditions experienced by the study members while they grew up (*S25*). There were no social class differences between males with low and high *MAOA* activity, $t\ (439) = 0.90$, $P = 0.37$. We repeated the regression analysis shown in Supplementary Table S2 (first row), with the addition of social class as a covariate. The interaction effect between *MAOA* and maltreatment remained statistically significant and

of equivalent magnitude after controlling for childhood social class origins (b = –0.33, SE = 0.14, t = 2.36, P = 0.019).

Table S1. The Dunedin sample does not differ significantly from published frequencies of alleles (*S5*, *S7*) at the *MAOA* promoter locus, $\chi^2(4) = 6.21$, $P = 0.184$.

Number (and percent) of alleles in	Number of repeats at *MAOA* promoter polymorphism				
	2	3	3.5	4	5
Dunedin sample males, *n* (chromosomes) = 442	1 (0.2)	149 (33.7)	5 (1.1)	274 (62.0)	13 (2.9)
Caucasian controls, *n* (chromosomes) = 1940	3 (0.2)	658 (33.9)	9 (0.5)	1238 (63.8)	32 (1.6)

Table S2. Results of final regression analyses testing $G \times E$ interaction effects on antisocial outcomes. The table presents final models with main effects and interactions entered simultaneously. Childhood maltreatment was handled as a single quantitative variable in the regression analyses, ranging from no maltreatment to severe maltreatment.

Antisocial outcomes	Predictor variables											
	MAOA				Maltreatment				*MAOA* × Maltreatment			
	b	SE	*t/z*	*p*	*b*	SE	*t/z*	*p*	*b*	SE	*t/z*	*p*
Composite Antisocial Index	.16	.11	1.45	.15	.54	.11	4.73	.001	-.36	.14	2.53	.01
Conduct Disorder (%)	.06	.28	.20	.84	.96	.27	3.55	.001	-.63	.33	1.87	.06
Violence Conviction (%)	.32	.46	.70	.48	1.2	.33	3.65	.001	-.83	.42	1.95	.05
Disposition Toward Violence Scale	.11	.11	.95	.35	.35	.12	3.04	.003	-.24	.15	1.62	.10
Antisocial Personality Symptoms Scale	.22	.12	1.90	.06	.45	.12	3.74	.001	-.31	.15	2.02	.04

SUPPORTING REFERENCES AND NOTES

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