Published in final edited form as:
Compr Psychiatry. 2011 ; 52(2): 188–194. doi:10.1016/j.comppsych.2010.05.005.

MAOA regulates antisocial personality in Caucasians with no history of physical abuse

Irving M. Reti[1], **Jerry Z. Xu**[1], **Jason Yanofski**[1], **Jodi McKibben**[2], **Magdalena Uhart**[1], **Yu-Jen Cheng**[2], **Peter Zandi**[1,2], **Oscar J. Bienvenu**[1], **Jack Samuels**[1], **Virginia Willour**[1], **Laura Kasch-Semenza**[1], **Paul Costa**[1,3], **Karen Bandeen-Roche**[2], **William W. Eaton**[1,2], and **Gerald Nestadt**[1,2]

[1] The School of Medicine, Johns Hopkins University, Baltimore, MD, USA

[2] The Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA

[3] The National Institute on Aging, The National Institutes of Health, Baltimore, MD, USA

Abstract

Objective—Preclinical and human family studies clearly link MAOA to aggression and antisocial personality. The 30bp VNTR in the MAOA promoter regulates MAOA levels but its effects on antisocial personality (ASP) in humans are unclear.

Methods—We evaluated the association of the VNTR of the MAOA promoter with DSM-IV antisocial personality disorder (ASPD) traits in a community sample of 435 participants from the Hopkins Epidemiology of Personality Disorders Study

Results—We did not find an association between the activity of the MAOA allele and ASPD traits, however amongst Caucasians, when subjects with a history of childhood physical abuse were excluded, the remaining subjects with low activity alleles had ASPD trait counts that were 41% greater than those with high activity alleles ($p<0.05$).

Conclusion—The high activity MAOA allele is protective against ASP amongst Caucasians with no history of physical abuse, lending support to a link between MAOA expression and antisocial behavior.

Keywords

association study; polymorphism; promoter; conduct disorder; NEO

Correspondence should be addressed to: Irving Reti, MBBS, Associate Professor, Psychiatry and Neuroscience, Johns Hopkins University, 600 N. Wolfe St., Meyer 3-181, Baltimore, MD 21205, Phone: 410-955-1484, Fax: 410-955-0152.

FINANCIAL DISCLOSURES

Paul Costa receives royalties from the NEO-PI-R. Irving M. Reti receives research support from Brainsway Inc and Neuronetics Inc. Jerry Z. Xu, Jason Yanofski, Jodi McKibben, Magdalena Uhart, Yu-Jen Cheng, Peter Zandi, Oscar J. Bienvenu, Jack Samuels, Virginia Willour, Laura Kasch-Semenza, Karen Bandeen-Roche, William W. Eaton, Gerald Nestadt report no biomedical financial interests or potential conflicts of interest.

INTRODUCTION

The etiology of many psychiatric conditions is multifactorial with genetic and environmental influences interacting to produce psychopathology. As antisocial personality (ASP) traits are so pervasive and have such deleterious effects on society, there has been intense interest in identifying genetic and environmental etiologic factors that could be treated, ameliorated or prevented.[1,2] However, gene-environment interactions contributing to ASP are complex and poorly understood. For example, although maltreatment as a child increases the risk of developing antisocial personality disorder (ASPD) by about 50%, most maltreated children do not develop ASPD,[3,4] suggesting other factors such as genetic vulnerability play a role in susceptibility to the adverse consequences of child abuse.

The monoamine oxidase A (MAOA) enzyme metabolizes norepinephrine, serotonin and dopamine at the synapse. As early as the 1960s a link was made between decreased MAO activity and aggressive behavior in rodents administered MAOA inhibitors.[5] Pintar et al.[6] assigned the MAOA gene to the human X chromosome and some years later deficient MAOA activity was linked to antisocial behavior in males with an X chromosome deletion[7] and a point mutation at the MAOA gene.[8] Confirming the association between decreased MAOA activity and antisocial behavior, Cases et al.[9] reported that mice lacking the MAOA gene manifested increased levels of brain norepinephrine, serotonin and dopamine and increased aggression.

Sabol et al.[10] first reported a variable number tandem repeat (VNTR) polymorphism, 30 base pairs (bp) in length, located in the promoter of the MAOA gene which they demonstrated affects transcriptional activity in gene reporter assays. “High activity” alleles (which mostly have 4 repeats of the 30bp sequence) transcribe at 2–10×’s the rate at which “low activity” alleles transcribe (which mostly have 3 repeats of the 30bp sequence). Denney et al.[11] reported MAOA activity in human fibroblast cultures obtained from 11 donors correlated with whether subjects had high or low activity VNTR alleles. However, ASPD traits and/or substance abuse have inconsistently demonstrated an association between the low activity MAOA alleles and antisocial or conduct disordered behavior in human behavioral studies enriched for subjects with histories of being abused.[12,13,14,15,16,17] Two recent community samples have also failed to find an association between MAOA alleles alone and conduct disordered behaviors[18] and ASP traits,[19] however both these studies suggest that low activity MAOA alleles increase the risk of conduct disorder and ASP traits in the presence of an adverse childhood environment. Other studies, however, have failed to find such a gene-environment interaction.[17,20]

In this study we used a community sample, from the Hopkins Epidemiology of Personality Disorders Study[1] (HEPS), to evaluate the association between the MAOA promoter VNTR alleles and ASPD traits. We studied Caucasians and African Americans separately as they have different rates of high and low activity alleles[10,15] and because race may differentially affect how MAOA and abuse history predict ASP.[15] We first examined whether Caucasians and African Americans in our sample with low activity MAOA alleles have significantly higher rates of ASP traits than those with high activity alleles. We then evaluated the association after excluding subjects with an environmental factor known to regulate ASP, namely childhood physical abuse,[19,21,22,23] which could obscure or mask any genetic mediation of ASP by MAOA. Finally, we also made parallel assessments of the association of MAOA alleles with childhood conduct disorder and adult NEO-PI-R personality traits.[24]

MATERIALS AND METHODS

Sample

The sample used for evaluating population genetic substructure is a subset of the Baltimore ECA Program and includes all subjects in the HEPS. In 1981, 175–211 adult residents of East Baltimore were sampled probabilistically for participation in the Baltimore site of the ECA Program.[25,26] From 1993 through June 1996, 1920 of those interviewed in 1981 were interviewed again as part of the Baltimore ECA Follow-up survey.[27] In 2004 and the first half of 2005, 1071 of those interviewed in 1993–6 were interviewed again ("wave 4") and DNA samples were obtained from subjects who consented. Genetic analyses for population substructure were conducted on this sample as well as on any HEPS subjects who were not evaluated in 2004.

The 742 subjects who participated in the HEPS were selected from the 1920 subjects re-interviewed between 1993 and 1996. From these 1920 subjects, we selected all those who were examined by psychiatrists in 1981 as well as all subjects who were identified by the Diagnostic Interview Schedule as having a lifetime diagnosis of any of six Axis 1 diagnoses (mania, depression, panic disorder, obsessive-compulsive disorder, alcohol use disorder or drug use disorder) at follow-up in 1993. In addition, a 25% (222/884) random sample was selected from the remaining subjects.

Informed consent was obtained from each subject for participation in the study including for the collection of DNA samples as described below. The research reported in this study was approved by the Johns Hopkins University Institutional Review Board.

DNA isolation

Subjects from wave 4 who agreed to provide DNA in 2004/5 were sampled by venous blood or cheek swab if they did not want to provide a venous sample. HEPS subjects who agreed to provide DNA were sampled by finger-stick onto a specially formulated "Isocode®" Card. DNA was isolated from peripheral blood leukocytes using Puregene Blood Kit chemistry on an Autopure LS automated DNA purification instrument (Qiagen, Valencia, CA). Buccal swabs were isolated manually using a Puregene DNA isolation kit (Qiagen) following manufacturer's protocol. Blood collected on Isocode Cards was isolated according to the manufacturer's instructions by heating hole punches (made by the American Red Cross) in distilled water at 95C for 30 minutes. DNA concentrations were determined by spectrophotometry using a DU 530 Life Science UV/Vis Spectrophotometer (Beckman Coulter).

For both the population substructure and MAOA analyses presented here only DNA collected by venous sample or finger-stick was used. Genotyping for population substructure was successfully conducted on 906 subjects with 81.7% of samples being from venous collection and 19.3% from finger-stick. For the MAOA analysis, 618 individuals were successfully genotyped, with 71.7% of samples being from venous collection and 28.3% from finger-stick.

Population substructure

As this is the first of a series of association studies we are conducting, we initially looked for population genetic substructure in our sample using 23 markers with high efficiency at clustering individuals into population subgroups.[28] STR markers D1S252, D2S319, D12S352, D17S799, D8S272, D1S196, D7S640, D8S1827, D7S657, D22S274, D5S407, D2S162, D10S197, D11S935, D9S175, and D5S410 were selected from Applied Biosystems Linkage Mapping Set v2.5 and amplified following manufacturer's protocol.

Markers D7S2469, D16S3017, D10S1786, D15S1002, D6S1610, and D1S2628 were synthesized by Applied Biosystems with fluorophore PET to allow genotyping in the same lane with the other markers. Amelogenin was included to determine gender. PCR products were pooled prior to electrophoresis on a 3730 DNA Analyzer (Applied Biosystems). Data was collected and analyzed with GeneMapper software (Applied Biosystems) that calculates fragment length in reference to an internal lane standard (Genescan-500 labeled with LIZ). The last of the 23 markers genotyped was the Duffy SNP rs#2814778 performed using pre-designed TaqMan® SNP Genotyping Assays C__15769614 (Applied Biosystems, Foster City, CA) following manufacturers supplied protocols. PCR and endpoint detection of fluorescence was carried out in a ABI Prism7900HT Sequence Detection System (Applied Biosystems, Foster City, CA) using default settings. Fluorescence data was analyzed with ABI Prism 7900 allelic discrimination software. All genotypes were manually checked.

We used population analysis software Structure 2.2 to identify population substructure within the sample and found 2 genetically distinct clusters that largely correspond to self-reported race, namely Caucasian and African American (see Supplementary Data). Accordingly, we therefore assigned subjects their self-reported race.

MAOA genotyping

Primer sequences were MAO APT1 (5′-ACAGCCTGACCGTGGAGAAG-3′) and MAO APB1 (5′-GAACGGACGCTCCATTCGGA-3′) described by Sabol et al. (1998), The MAO APT1 was 5′-labeled with 6FAM fluorophore. PCR was carried out in 10ul containing 0.1μM primers, 0.16 mM each dNTP (Amersham), 10 mM Tris (pH8.3); 50 mM KCL, 1.5 mM MgCl, 0.6 units of Ampli Taq Gold DNA polymerase (Applied Biosystems, Foster City, CA), 0.1% BSA, 10% DMSO, and 40ng DNA. Amplification was carried out in a Thermo Hybaid MBS 0.2S (Needham Heights, MA) using the following cycling conditions: initial 8 min denaturing step at 94°C, followed by 35 cycles of 94°C for 30 sec, 58°C for 30 sec and 72°C for 30 sec followed by a final extension of 72°C for 10 min. PCR products were assayed on a 3730 DNA Analyzer (Applied Biosystems). Data was collected and analyzed with GeneMapper software (Applied Biosystems) that calculates fragment length in reference to an internal lane standard (Genescan-500 labeled with LIZ) and quantifies the amount of fluorescence in each fragment.

Based on self-reported race, our sample consisted of: Caucasian – 59.1%, African American – 37.5%, Hispanic – 1%, Asian – 0.6%, Native American – 0.2% and Other – 1.6%. Since individuals self-identified as Asian, Native American, Hispanic and ‘Other’ are genetically similar to Caucasians according to our population substructure analysis, we included MAOA data from these subjects with data from Caucasian subjects and henceforth the term Caucasian in this study includes these minorities in our sample. African American subjects were considered separately. The allele frequencies for Caucasian and African American are shown in table 1. As has been reported previously, allele frequency rates differ between the 2 populations.[10,15] We used the classification of Sabol et al.[10] and Caspi et al.[19] to designate rare alleles as either low or high activity. Accordingly, 2 and 5 repeats were grouped with those with 3 repeats (ie “low activity”). Those with 3.5 repeats were grouped with those with 4 repeats (ie high activity”). As the MAOA gene is X-linked, females who are heterozygous (46% of our female sample) cannot be characterized with certainty as it is not possible to tell which of the two alleles is inactivated. Therefore the subsequent analyses included 224 males and 211 females.

Childhood physical abuse

As part of a battery of questions focused on parenting behavior and childhood experiences, subjects in the HEPS sample were asked, ‘Did a parent or other care provider discipline you

excessively?' If a positive response was elicited the subject was asked to provide details and the rater was instructed to code based on judgment of presence or absence of childhood physical abuse. This is a dichotomous variable, with the presence or absence of physical abuse based on the answer to those questions. In earlier work we found strong correlations between our measure of physical abuse and other measures we obtained of parenting behavior including punishment and restrictive rules[22].

Adult antisocial personality traits

As described in Reti et al.[22] the assessment of ASPD traits was conducted using the International Personality Disorder Examination (IPDE),[29] a semistructured instrument designed for administration by clinicians that detects all relevant criteria for DSM-IV personality disorders. There are seven items pertaining to adult ASPD traits. The psychologists were directed to evaluate abnormal traits manifest over the subject's entire adult life. Each criterion was rated '0' (absent), '1' (accentuated or exaggerated), '2' (criterion level or pathological), or '9' (missing or unknown), based on the responses of both the subject and at least one knowledgeable informant who had known the individual for most of his/her adult life. In reliability exercises, the intraclass correlation coefficient for number of ASPD traits rated present was 0.8.[1]

A scale for adult ASPD traits was constructed by assigning a score of zero to ratings of '0' and a score of one point to ratings of either '1' or '2' for the seven relevant items. In this way, the metric for the scale was the number of antisocial traits present. If four or more items were recorded, the diagnostic algorithm operated by assigning the value of '0' to data items that were missing or unknown. If fewer than four items were recorded an adult ASPD trait scale score was not calculated for that individual; this was the case for six individuals.

Childhood conduct disorder traits

Conduct disorder traits were also assessed using the IPDE. There are 15 items pertaining to childhood conduct disorder traits and each criterion was rated in a similar manner to ASPD traits. In reliability exercises, the intraclass correlation coefficient for number of conduct disorder traits rated present was 0.92. Two conduct disorder trait scales were constructed with a score of zero being assigned to a rating of '0' for both scales. One scale was constructed like the ASPD trait scale with a score of one point to ratings of either '1' or '2'. The second scale was constructed by assigning a score of zero to rating of '1', thereby creating a scale which only reflected severe childhood conduct pathology.

Assessment of personality traits

The NEO-PI-R is a 240-item, self-report questionnaire designed to measure the five factor model of personality. The NEO-PI-R measures six specific traits, or facets, that define each of the five broad factors, and uses a 5-point Likert response scale ranging from 'Strongly disagree' to 'Strongly agree'. Details regarding the instrument's reliability, validity and longitudinal stability can be found in Costa and McCrae.[23] Most subjects in the HEPS (89.5%) completed the NEO-PI-R.

RESULTS

We first checked, in each population, whether there was a difference in ASPD trait scores between high and low activity subjects (table 2). Amongst Caucasians, the mean ASPD trait score for low activity subjects was 2.14 whereas it was 1.9 for high activity subjects, which was not significantly different. Amongst African Americans, the mean ASPD trait score for low activity subjects was 2.2 whereas it was 2.15 for high activity subjects, which was also not significantly different.

We had previously observed both high reports of childhood physical abuse in the HEPS sample and a strong correlation between it and later ASP.[22] To determine whether MAOA alleles modified the risk of ASP after childhood physical abuse, we analyzed this relationship separately in subjects who reported abuse and those that did not (table 2). We did not find that MAOA activity modified the number of ASPD traits in subjects who had been physically abused. In fact, ASPD trait scores were non-significantly lower amongst Caucasians with a history of abuse and low activity MAOA activity. However, in Caucasian subjects with no history of childhood physical abuse, mean ASPD trait score was 1.38 in high activity subjects and 1.94 in low activity subjects ($p<0.05$), an increase of 41%. When Native Americans, Hispanics, Asians and 'Other' were excluded from the analysis, the results were very similar with the ASPD trait score amongst "true" Caucasians at 1.37 for high activity allele subjects and at 1.97 ($p<0.05$) for low activity allele subjects, an increase of 44%. Similar trends were also obtained when Caucasian males and females were analyzed separately, although the results did not reach statistical significance. ASPD trait scores amongst African Americans with no history of abuse were virtually identical in low and high MAOA activity subjects. Also the chances of experiencing childhood physical abuse were not significantly affected by MAOA allele length in either Caucasians or African Americans.

To further evaluate the relative roles of physical abuse and the MAOA allele in ASPD trait scores amongst Caucasians, we performed a multiple linear regression analysis with ASPD trait score as the dependent variable and physical abuse, the MAOA allele and a physical abuse × MAOA allele interaction term as independent variables. The results shown in table 3 support the stratification analysis although the effect of the interaction term did not reach statistical significance. The data suggest reporting a history of childhood physical abuse is associated with an approximately one point higher ASPD trait score on average than not reporting physical abuse regardless of MAOA allele type, consistent with the stratification analysis. Among those not reporting a history of childhood physical abuse, the high activity allele is associated with approximately a half-point lower ASPD trait score than that of the low activity allele, also consistent with the stratification analysis. The data also suggest that the effect of physical abuse is stronger for those with the high activity MAOA allele compared with those the low activity allele. As the ASPD trait score is a right-skewed score running from 0–7 and thus not normally distributed, we also performed ordinal logistic regression to assess sensitivity to failure of normality, and findings were qualitatively and quantitatively similar.

We also evaluated how MAOA allele activity influences the likelihood of each ASPD trait in Caucasians and African Americans who had not suffered physical abuse (table 4). Amongst Caucasians, the proportion of subjects positive on each trait was higher in those with the low activity allele compared with those with the high activity allele. The difference was statistically significant at the 0.05 level for "Impulsivity to plan ahead" and for "Lack of remorse", and significant at the 0.1 level for "Reckless disregard for safety of self and others". Amongst African Americans, there was no pattern or trend regarding likelihood of being positive on a trait amongst individuals with low versus high allele activity genotypes.

We also used an alternate methodology to confirm our finding that MAOA genotype influences ASPD trait score in Caucasians who have not suffered physical abuse. We checked NEO trait scores by MAOA allele activity in Caucasians who had not suffered childhood physical abuse (using a two-tailed unpaired t test). We found that individuals with low activity alleles had higher neuroticism factor scores than those with high activity alleles ($p<0.1$). Several neuroticism facet scores, namely vulnerability ($p<0.1$), angry hostility ($p<0.05$) and anxiety ($p<0.05$) were higher in individuals with low activity compared with high activity alleles. Individuals with low activity alleles also had lower scores on the

agreeableness factor ($p<0.05$) and lower agreeableness facet scores on trust ($p<0.05$), altruism ($p<0.05$) and compliance ($p<0.1$). We also evaluated whether an expert generated prototypic ASPD profile generated by Lynam and colleagues varied by MAOA allele. Prototypes formed by experts have been used to verify the facets that capture pure antisocial traits.[30,31] Miller et al.[32] developed a NEO-PI-R index which captures DSM-IV antisocial personality disorder criteria, comprising the sum of 17 individual facets (see Supplementary Data). We found that individuals with low activity alleles had higher scores on the scale than those with high activity alleles ($p<0.1$).

We also checked whether the MAOA polymorphism influenced childhood conduct disorder scores in Caucasians with no history of childhood physical abuse. We did not find MAOA genotype influenced conduct disorder scores when scores of '1' and '2' were assigned a value of one. However, when scores of '1' were assigned a value of zero and scores of '2' were assigned a value of one, creating a scale which reflected severe childhood conduct pathology, those with low activity MAOA alleles had significantly higher scores than those with high activity alleles ($p<0.01$, Mann-Whitney U test). Amongst childhood conduct disorder traits, those that were significantly more like to score '2' compared with '0' or '1' amongst low activity individuals were "Lied/conned" ($p<0.01$), "Destroy property" ($p<0.1$), "Burglary" ($p<0.05$) and "Truant" ($p<0.05$). (For these calculations we used a Pearson's chi-square test to compare rates between MAOA alleles except when a cell contained less than 5 subjects in which case we used a Fisher's exact test.)

DISCUSSION

Preclinical studies of MAOA function as well as studies of human families with deficient MAOA activity strongly suggest the gene plays a key role in mediating aggression and antisocial personality. As the 30bp VNTR promoter polymorphism of MAOA regulates the expression of MAOA in vitro[10,33] and probably in vivo,[11] researchers have predicted it would also regulate human ASP. However, studies evaluating an association between this VNTR and ASP have yielded mixed results. In this study we found that this MAOA polymorphism did not significantly regulate ASPD trait scores in either Caucasians or African Americans when each population as a whole was analyzed. However, since environmental factors known to regulate ASP, including a history of childhood physical abuse,[19,21,22,23] could obscure or mask any genetic mediation of ASP by MAOA, we also analyzed our sample excluding subjects with a history of physical abuse. In subjects without a history of childhood physical abuse we found the VNTR MAOA promoter polymorphism did predict ASP in Caucasians, but not African Americans. Caucasians with low activity alleles had ASP scores that were on average 41% higher than subjects with high activity alleles. As far as we are aware, this is the first study to find that the high activity MAOA allele is protective in subjects without a history of childhood physical abuse.

Unlike some other recent studies,[15,19] we failed to find that the MAOA VNTR promoter polymorphism is associated with ASPD traits in those who suffered childhood physical abuse. In fact amongst Caucasians, those with high activity MAOA alleles had (non-significantly) higher levels of ASPD traits than those with low activity alleles. Other studies have also failed to find such a gene-environment interaction [17,20], however Weder et al., (2009) recently showed that MAOA was only protective if the abuse was moderate [34]. Unfortunately, we do not have data about the severity of physical abuse suffered by each subject in our study. As we have reported previously,[22] we also found in these new analyses that HEPS subjects who experienced childhood physical abuse have significantly higher levels of ASP than those who did not.

We found an effect of the MAOA polymorphism on ASPD trait scores in Caucasians with no history of childhood physical abuse, but not in African Americans. The explanation for the racial difference we observed may lie in a combination of genetic and environmental factors. Like us, other studies have also reported racial differences in both MAOA allele distribution[10,21] and in the effect of MAOA on ASP traits. For example, Widom and Brzustowicz[21] found high levels of MAOA activity were protective only in Caucasians but not in non-Caucasian populations. In addition there may be other genetic factors modulating MAOA expression and other genes that differ by race influencing antisocial behavior. Environmental factors that differ by race may also play a role in generating the racial difference we observed including economic and other disparities in the childhood of African Americans and Caucasians[35]; racial disparities have been noted as early as birth, with African American infants being at higher risk for low birth weight[36]. Additionally, deciding whether to record an antisocial personality trait (especially trait number 1) as present or absent may have been influenced by the subject's report of legal problems including arrests which may be more likely amongst African American adults than Caucasian adults for an identical crime[37].

Our study is strengthened by 2 independent measures in the same subject that are related to the ASPD trait measure, confirming our finding that MAOA genotype influences ASP trait score in Caucasians who have not suffered physical abuse. We found the low activity MAOA allele was associated with significantly higher neuroticism and lower agreeableness facet scores in this population. Elevated neuroticism and lower agreeableness scores have been previously associated with higher ASPD trait scores[38,39]. We also found that the low activity MAOA allele was associated with higher scores on the childhood conduct disorder scale amongst Caucasians with no history of childhood physical abuse. However, the result was only significant for a childhood conduct disorders scale in which only severe or pathological behaviors were counted.

Our study is limited by childhood physical abuse being a retrospective measure. Nonetheless, we have previously shown it correlates strongly with other retrospective measures of parental behavior obtained in the HEPS survey including being beaten or receiving other harsh punishment.[22] On the other hand a significant strength of the study is that ratings were made by psychiatrists and outside informants to corroborate information from subjects.

In summary, we have shown that when we exclude subjects with an adverse environmental exposure clearly associated with later ASP, there is a significant association between the allele activity of the MAOA promoter VNTR polymorphism and ASP in Caucasians. These findings lend support to preclinical and human family studies showing a clear link between MAOA expression and antisocial behavior.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by the following NIH grants RO1 MH050616-09 (Nestadt), RO1 MH47447 (Eaton), K23 MH64543 (Bienvenu), K23 AA017466 (Uhart), as well as the Intramural Research Program of the NIA (Costa).

References

1. Samuels J, Eaton WW, Bienvenu OJ, Brown CH, Costa PT, Nestadt G. Prevalence and correlates of personality disorders in a community sample. Br J Psychiatry. 2002; 180:536–542. [PubMed: 12042233]
2. Mercy JA, Krug EG, Dahlberg LL, Zwi AB. Violence and health: the United States in a global perspective. Am J Publ Health. 2003; 92:256–261.
3. Luntz BK, Widom CS. Antisocial personality disorder in abused and neglected children grown up. Am J Psychiatry. 1994; 151:670–674. [PubMed: 8166307]
4. Widom, CS. Handbook of Antisocial Behavior. Stoff, DM.; Breiling, J.; Maser, JD., editors. Wiley; New York: 1997.
5. Aprison MH, Ferster CB. Neurochemical correlates of behavior: correlation of brain monoamine oxidase activity with behavioral changes after iproniazid and 5-hydroxytryptophan. J Neurochem. 1961; 6:350–357. [PubMed: 13683915]
6. Pintar JE, Barbosa J, Francke U, Castiglione CM, Hawkins M Jr, Breakefield XO. Gene for monoamine oxidase type A assigned to the human X chromosome. J Neurosci. 1981; 1:166–75. [PubMed: 7196439]
7. Sims KB, de la Chapelle A, Norio R, Sankila EM, Hsu YP, Rinehart WB, et al. Monoamine oxidase deficiency in males with an X chromosome deletion. Neuron. 1989; 2:1069–76. [PubMed: 2483108]
8. Brunner HG, Nelen M, Breakefield XO, Ropers HH, van Oost BA. Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. Science. 1993; 262:578–80. [PubMed: 8211186]
9. Cases O, Seif I, Grimsby J, Gaspar P, Chen K, Pournin S, et al. Aggressive behavior and altered amounts of brain serotonin and norepinephrine in mice lacking MAOA. Science. 1995; 268:1763–6. [PubMed: 7792602]
10. Sabol SZ, Hu S, Hamer D. A functional polymorphism in the monoamine oxidase A gene promoter. Hum Genet. 1998; 103:273–9. [PubMed: 9799080]
11. Denney RM, Koch H, Craig IW. Association between monoamine oxidase A activity in human male skin fibroblasts and genotype of the MAOA promoter-associated variable number tandem repeat. Hum Genet. 1999; 105:542–51. [PubMed: 10647887]
12. Samochowiec J, Lesch KP, Rottmann M, Smolka M, Syagailo YV, Okladnova O, et al. Association of a regulatory polymorphism in the promoter region of the monoamine oxidase: A gene with antisocial alcoholism. Psychiatry Res. 1999; 86:67–72. [PubMed: 10359483]
13. Schmidt LG, Sander T, Kuhn S, Smolka M, Rommelspacher H, Samochowiec J, Lesch KP. Different allele distribution of a regulatory MAOA gene promoter polymorphism in antisocial and anxious-depressive alcoholics. J Neural Transm. 2000; 107:681–9. [PubMed: 10943908]
14. Gerra G, Garofano L, Bosari S, Pellegrini C, Zaimovic A, Moi G, et al. Analysis of monoamine oxidase A (MAO-A) promoter polymorphism in male heroin-dependent subjects: Behavioural and personality correlates. J Neural Transm. 2004; 111:611–21. [PubMed: 15088154]
15. Widom CS. The cycle of violence. Science. 1989; 244:160–6. [PubMed: 2704995]
16. Nilsson KW, Sjöberg RL, Damberg M, Leppert J, Ohrvik J, Alm PO, et al. Role of monoamine oxidase A genotype and psychosocial factors in male adolescent criminal activity. Biol Psychiatry. 2006; 59:121–7. [PubMed: 16125147]
17. Young SE, Smolen A, Hewitt JK, Haberstick BC, Stallings MC, Corley RP, Crowley TJ. Interaction between MAO-A genotype and maltreatment in the risk for conduct disorder: failure to confirm in adolescent patients. Am J Psychiatry. 2006; 163:1019–25. [PubMed: 16741202]
18. Foley DL, Eaves LJ, Wormley B, Silberg JL, Maes HH, Kuhn J, Riley B. Childhood adversity, monoamine oxidase a genotype, and risk for conduct disorder. Arch Gen Psychiatry. 2004; 61:738–44. [PubMed: 15237086]
19. Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, et al. Role of genotype in the cycle of violence in maltreated children. Science. 2002; 297:851–4. [PubMed: 12161658]

20. Huizinga D, Haberstick BC, Smolen A, Menard S, Young SE, Corley RP, et al. Childhood maltreatment, subsequent antisocial behavior, and the role of monoamine oxidase A genotype. Biol Psychiatry. 2006; 60:677–83. [PubMed: 17008143]
21. Widom CS, Brzustowicz LM. MAOA and the "cycle of violence:" childhood abuse and neglect, MAOA genotype, and risk for violent and antisocial behavior. Biol Psychiatry. 2006; 7:684–9. [PubMed: 16814261]
22. Reti IM, Samuels JF, Eaton WW, Bienvenu OJ 3rd, Costa PT Jr, Nestadt G. Adult antisocial personality traits are associated with experiences of low parental care and maternal overprotection. Acta Psychiatr Scand. 2002; 106:126–33. [PubMed: 12121210]
23. Bierer LM, Yehuda R, Schmeidler J, Mitropoulou V, New AS, Silverman JM, Siever LJ. Abuse and neglect in childhood: relationship to personality disorder diagnoses. CNS Spectr. 2003; 8:737–54. [PubMed: 14712172]
24. Costa, PT., Jr; McCrae, RR. Psychological Assessment Resources. Odessa, FL: 1992. Revised NEO Personality Inventory (NEO-PI-R) and NEO Five-Factor Inventory (NEO-FFI): Professional Manual.
25. Eaton WW, Holzer CE III, Von Korff M, Anthony JC, Helzer JE, George L, et al. The design of the Epidemiologic Catchment Area surveys: the control and measurement of error. Arch Gen Psychiatry. 1984; 41:942–948. [PubMed: 6477054]
26. Regier DA, Myers JK, Kramer M, Robins LN, Blazer DG, Hough RL, et al. The NIMH Epidemiologic Catchment Area (ECA) Program: historical context, major objectives, and study population characteristics. Arch Gen Psychiatry. 1984; 41:934–941. [PubMed: 6089692]
27. Eaton WW, Anthony JC, Gallo J, et al. Natural history of diagnostic interview schedule/DSM-IV major depression: the Baltimore Epidemiologic Catchment Area follow-up. Arch Gen Psychiatry. 1997; 54:993–999. [PubMed: 9366655]
28. Yang BZ, Zhao H, Kranzler HR, Gelernter J. Practical population group assignment with selected informative markers: characteristics and properties of Bayesian clustering via STRUCTURE. Genet Epidemiol. 2005; 28:302–12. [PubMed: 15782414]
29. Loranger AW, Sartorius N, Andreoli A, et al. The International Personality Disorder Examination. Arch Gen Psychiatry. 1994; 51:215–224. [PubMed: 8122958]
30. Miller JD, Lynam DR, Widiger TA, Leukefeld C. Personality disorders as extreme variants of common personality dimensions: can the Five-Factor Model adequately represent psychopathy? J Pers. 2001; 69:253–276. [PubMed: 11339798]
31. Williams LM, Gatt JM, Kuan SA, Dobson-Stone C, Palmer DM, Paul RH, Song L, Costa PT, Schofield PR, Gordon E. A Polymorphism of the MAOA Gene is Associated with Emotional Brain Markers and Personality Traits on an Antisocial Index. Neuropsychopharmacology. Epub Feb 4, 2009.
32. Miller JD, Bagby RM, Pilkonis PA, Reynolds SK, Lynam DR. A simplified technique for scoring DSM-IV personality disorders with the Five-Factor Model. Assessment. 2005; 12:404–15. [PubMed: 16244121]
33. Deckert J, Catalano M, Syagailo YV, Bosi M, Okladnova O, Di Bella D, et al. Excess of high activity monoamine oxidase A gene promoter alleles in female patients with panic disorder. Hum Mol Genet. 1999; 8:621–4. [PubMed: 10072430]
34. Weder N, Yang BZ, Douglas-Palumberi H, Massey J, Krystal JH, Gelernter J, Kaufman J. MAOA genotype, maltreatment, and aggressive behavior: the changing impact of genotype at varying levels of trauma. Biol Psychiatry. 2009; 65:417–24. [PubMed: 18996506]
35. U.S. Department of Health and Human Services. Trends in the Well-Being of America's Children and Youth. U.S. Printing Office; Washington, DC: 1998.
36. Kleinman JC, Kessel SS. Racial differences in low birth weight: Trends and risk factors. N Engl J Med. 1987; 317:749–753. [PubMed: 3627185]
37. Golub A, Johnson BD, Dunlap E. The race/ethnicity disparity in misdemeanor marijuana arrests in New York City. Criminol Public Policy. 2007; 6:131–164. [PubMed: 18841246]
38. Derefinko KJ, Lynam DR. Convergence and divergence among self-report psychopathy measures: a personality-based approach. J Personal Disord. 2006; 20:261–80.

39. Ross SR, Benning SD, Patrick CJ, Thompson A, Thurston A. Factors of the Psychopathic Personality Inventory: Criterion-Related Validity and Relationship to the BIS/BAS and Five-Factor Models of Personality. Assessment. Aug 14.2008

Table 1

MAOA-VNTR allele frequencies

	MAOA VNTR repeats				
	2	**3**	**3.5**	**4**	**5**
Caucasians	0.50%	34.10%	1.20%	62.80%	1.40%
African Americans	4.70%	48.70%	0.20%	45.50%	0.90%

Table 2

Mean number of adult ASPD items scored “1” or “2” by MAOA allele.

	Caucasians		African Americans	
	Low activity	**High activity**	**Low activity**	**High activity**
Total population	2.14 (88)	1.9 (195)	2.2 (86)	2.15 (66)
Physical abuse history	3 (16)	3.33 (51)	3 (18)	3 (12)
No physical abuse history	1.94 (72)	1.38 (144)*	1.99 (68)	1.96 (54)

Mann-Whitney U test for comparing samples by MAOA allele. The number in brackets is the sample size.

*$p \leq 0.05$

Table 3

Multiple linear regression analysis of effects of physical abuse, MAOA allele and the interaction term physical abuse × MAOA allele on number of adult antisocial personality traits amongst Caucasians.

Variables influencing ASP	Regression coefficient	t	Significance	95% confidence interval	
Physical abuse	1.057	1.97	0.05	0.002	2.112
MAOA allele	0.558	−1.98	0.049	−1.114	−0.003
Physical abuse × MAOA allele	0.892	1.43	0.153	−0.333	2.117

$r^2 = 0.135$

Table 4

Proportion of subjects without a history of physical abuse scoring “1” or “2” on each antisocial personality disorder trait by MAOA allele.

	Caucasians		African Americans	
	Low activity	**High activity**	**Low activity**	**High activity**
1. Failure to conform to social norms - arrests	0.39	0.33	0.38	0.41
2. Deceitfulness	0.13	0.09	0.15	0.22
3. Impulsivity or failure to plan ahead	0.1	0.03*	0.05	0.09
4. Irritability and aggressiveness - fights	0.37	0.27	0.4	0.29
5. Reckless disregard for safety of self and others	0.5	0.36#	0.27	0.3
6. Consistent irresponsibility	0.24	0.2	0.53	0.44
7. Lack of remorse	0.29	0.14*	0.31	0.31

Pearson’s chi-square test to compare rates between MAOA alleles. Fisher’s exact test when any cell contains less than 5 subjects.

$p \leq 0.1$

* $p \leq 0.05$