Psychiatr Q (2014) 85:257–265
DOI 10.1007/s11126-013-9287-x

ORIGINAL PAPER

The 2-Repeat Allele of the MAOA Gene Confers an Increased Risk for Shooting and Stabbing Behaviors

Kevin M. Beaver · J. C. Barnes · Brian B. Boutwell

Published online: 11 December 2013

Abstract There has been a great deal of research examining the link between a polymorphism in the promoter region of the MAOA gene and antisocial phenotypes. The results of these studies have consistently revealed that low activity MAOA alleles are related to antisocial behaviors for males who were maltreated as children. Recently, though, some evidence has emerged indicating that a rare allele of the MAOA gene—that is, the 2-repeat allele—may have effects on violence that are independent of the environment. The current study builds on this research and examines the association between the 2-repeat allele and shooting and stabbing behaviors in a sample of males drawn from the National Longitudinal Study of Adolescent Health. Analyses revealed that African-American males who carry the 2-repeat allele are significantly more likely than all other genotypes to engage in shooting and stabbing behaviors and to report having multiple shooting and stabbing victims. The limitations of the study are discussed and suggestions for future research are offered.

Keywords Add Health · MAOA · Shooting · Stabbing

K. M. Beaver (✉)
College of Criminology and Criminal Justice, Florida State University, 634 W. Call Street, Tallahassee, FL 32306-1127, USA
e-mail: kbeaver@fsu.edu

K. M. Beaver
Center for Social and Humanities Research, King Abdulaziz University, Jeddah, Saudi Arabia

J. C. Barnes
School of Economic, Political, and Policy Sciences, University of Texas at Dallas, Richardson, TX 75080, USA

B. B. Boutwell
College of Criminal Justice, Sam Houston State University, Huntsville, TX 77341-2296, USA

Introduction

Serious violent crime represents a pressing public health and safety concern to citizens in the United States and around the world. To illustrate, there are approximately 5 million violent victimization events that occur annually in the United States and a large percentage of these crimes involve the use of lethal weapons, such as guns and knives [29]. Although statistically rare, murder remains one of the leading causes of death for adolescents and young adults [13] and the commission of a violent act that does not culminate in a murder can still leave the victim physically as well as emotionally damaged [17]. The resulting financial burden that is produced by serious violent behavior, moreover, is astounding, with some upper-limit estimates indicating that each murder costs taxpayers more than $17 million [6].

Although the consequences associated with personal violence are relatively well-known, the causes of these extreme violent acts remain poorly understood. There has been increasing evidence, however, indicating that serious physical violence is the result of a complex arrangement of neurobiological, genetic, and environmental factors acting individually and synergistically [20]. Findings from recent neuroimaging research, for example, have identified structural and functional differences in regions of the prefrontal cortex and areas of the limbic system in offenders compared to non-offenders [21–23]. In addition to neurobiological correlates to extreme violence, including murder, there is now a wealth of evidence underscoring the role that genetic factors play in the etiology of serious violent behaviors. The results of a string of meta-analyses have revealed, for instance, that genes account for approximately 50 % of the variance in antisocial behaviors and serious violence [7, 16, 19, 26].

Despite the sizeable body of research indicating that violence is highly heritable, the precise genetic polymorphisms that are related to extreme acts of violence have remained somewhat elusive. The most promising candidate gene in relation to extreme acts of violence is the MAOA gene. The MAOA gene has been mapped to the X chromosome at location Xp11.23-11.4 [15] and has a 30 base pair (bp) variable number of tandem repeats (VNTR) polymorphism in the promoter region of the gene. The MAOA gene is responsible for coding for the production of the MAOA enzyme that degrades certain neurotransmitters, such as dopamine and serotonin [28]. This is a functional polymorphism, wherein different alleles are related to different activity levels for the MAOA enzyme [27]. The most common way of dividing these alleles is by creating two groups: a group consisting of alleles that correspond to low MAOA activity and a group consisting of alleles that correspond to high MAOA activity. Usually, the 2-repeat allele and the 3-repeat allele are grouped together to create the low MAOA activity genotype while the 3.5-repeat allele, 4-repeat allele, and 5-repeat allele are grouped together to create the high MAOA activity genotype [5].

A wide range of studies have examined the potential association between MAOA genotype and antisocial behaviors [14] and theoretical models tying the MAOA genotype to brain functioning have been supported [3, 18]; but see [8]. The results of these studies have been relatively consistent in that they tend to indicate that the low MAOA activity alleles confer an increased risk to antisocial behaviors, but only among males who were exposed to environmental liabilities, such as childhood maltreatment, abuse, and neglect [5]. Although the link between antisocial behavior and MAOA has been the most replicated finding in the study of the genetic underpinnings to antisocial phenotypes, there has been limited evidence bearing directly on whether MAOA is linked to specific acts of violent behavior. Most studies examining the effects of MAOA tend to examine non-

specific antisocial behavioral scales or scales that include a wide range of antisocial traits (e.g., [30]). While such an approach is useful to establish a link between MAOA and antisocial behavior in general, it is not an appropriate strategy for determining whether MAOA has behavioral-specific effects. Using an additive scale of antisocial behaviors may mask important heterogeneity that exists between the individual behaviors and MAOA genotype such that MAOA may be related to certain types of antisocial behaviors, but not others. As a result, to further unpack the nexus between MAOA genotype and serious violence, the current study examines only extreme violence as measured by shooting and stabbing behaviors.

Another potential shortcoming of the available MAOA research is the way in which the alleles are broadly grouped into two categories (i.e., a high MAOA activity group and a low MAOA activity group). Beaver et al. [1] grouped the MAOA genotype into the high/low dichotomy and reported that the low activity genotype correlated with violent behavior among gang members. This measurement strategy could mask important variation that exists for each of the individual alleles and recent research by Guo et al. [9] provides some support for this possibility. Guo et al. examined the association between MAOA and delinquent behavior in a longitudinal sample of adolescents and young adults. Unlike prior research examining MAOA, these researchers estimated the effects of the 2-repeat allele against all other alleles in data drawn from the National Longitudinal Study of Adolescent Health (Add Health). Their statistical models revealed that the 2-repeat allele conferred an increased risk of serious and violent behaviors in both adolescence and early adulthood. Importantly, Guo et al. also performed a functional analysis and reported that the 2-repeat allele had a lower level of promoter activity when compared against the 3-repeat and 4-repeat alleles.

In another study, also analyzing the Add Health data, Beaver et al. [2] reported a link between the 2-repeat allele and the odds of being arrested, the odds of being incarcerated, and a lifetime measure of antisocial behavior. Unfortunately, neither the Beaver et al. study nor the Guo et al. [9] study specifically examined the most serious and violent types of criminal behaviors, but rather grouped together a wide range of antisocial behaviors, some of which are violent and some of which are non-violent. Given that research has revealed that violent and non-violent criminal behaviors might have different etiologies [4], the next important step in the 2-repeat research is to examine this allele's association with some of the most violent types of behaviors. Against this backdrop, the current study examines the effect of the 2-repeat allele on two highly violent behaviors: shooting and stabbing someone. The findings will help to reveal whether the 2-repeat allele has effects on violent criminal behaviors rather than antisocial behavior broadly defined.

Materials and Method

Participants

Data for this study were drawn from the DNA subsample of the National Longitudinal Study of Adolescent Health (Add Health; [10]). Detailed information about the Add Health, including its sampling design, has been published previously [11, 12, 24]. Briefly, the Add Health is a longitudinal four-wave study of a nationally representative sample of American adolescents who were attending 132 middle or high schools during the 1994–1995 academic school year. The first (N = 20,745) wave of data was collected when respondents were at home along with their primary caregivers. The second wave of data

was collected approximately one-and-a-half years later (N = 14,738). The third round of interviews were completed in 2001–2002 when the respondents were in early adulthood (N = 15,197). The fourth wave of data commenced in 2007–2008 when the respondents were between the ages of 24–32 years old (N = 15,701).

A subsample of subjects was genotyped for a number of genes related to neurotransmission at wave 3. Eligibility was based on whether the respondents were part of a sibling pair included in the data; respondents who also had a sibling participating in the study were asked to submit buccal cells for genotyping. Overall, 2,574 subjects agreed to participate. Genotyping was conducted in a coordinated effort between Add Health and researchers at the Institute of Behavioral Genetics in Boulder, Colorado [12].

Genotyping Procedures

A variant of a previously developed assay was used to genotype subjects for the MAOA-uVNTR polymorphism [27]. Primer sequences were as follows: forward, 5′ACAGCCT GACCGTGGAGAAG-3′ (fluorescently labeled), and reverse, 5′-GAACGTGACGCT CCATTCGGA-3′. This assay resulted in PCR products of 291 (2-repeat allele), 321 (3-repeat allele), 336 (3.5-repeat allele), 351 (4-repeat allele), and 381 (5-repeat allele) bps. Two independent raters scored the genotypes. MAOA genotypes were divided into two groups: one group consisted of subjects who possessed the 2-repeat allele and the other group consisted of subjects who possessed the 3-repeat, 3.5-repeat, 4-repeat, and 5-repeat alleles. Because MAOA is X-linked and because shooting and stabbing tend to be almost exclusively carried out by males, the current study excludes females from the analyses.

Measures

Shooting and stabbing were measured with two interrelated items. During each of the four waves of data collection, respondents were asked to indicate whether they had shot or stabbed someone during the previous 12 months. Responses were coded dichotomously, where 0 = did not shoot or stab someone in the past 12 months and 1 = shot or stabbed someone in the past 12 months. The first shooting and stabbing measure was a dichotomous measure that indicated whether the respondent had ever shot or stabbed someone across all four waves of data. This item was coded such that 0 = did not shoot or stab someone and 1 = shot or stabbed someone. Overall, 5.6 % of the sample reported having shot or stabbed someone at some time during the first four waves of data collection. The second shooting and stabbing item was designed to measure repeat shooting or stabbing. This item was created by summing across all four wave-specific shooting and stabbing items. The resulting value indicated the total number of waves for which the respondent indicated they had shot or stabbed someone. In total, 4.7 % of the sample reported shooting or stabbing someone at one wave, 0.8 % of the sample reported shooting or stabbing someone at two waves, and 0.1 % of the sample reported shooting or stabbing someone at three waves. There were no subjects who reported shooting or stabbing someone at all four waves.

To take into account the potentially confounding effects of race, a single-item variable was included to measure racial status. During wave 1 interviews, interviewers indicated which race best described each subject. The data for the current study were analyzed using subjects who were either Caucasian or African-American.

Findings

Findings from previous research have indicated that the frequency of the 2-repeat allele varies significantly across races (e.g., [25, 30]). As a result, the analysis begins by examining the frequency of the 2-repeat allele separately for Caucasians and African Americans. Overall, the 2-repeat allele was carried by 0.1 % of Caucasian males and by 5.2 % of African-American males. These frequencies were double-checked using self-reports of race instead of interviewer-reported race and the results were nearly identical. Importantly, these allelic frequencies parallel those reported in other samples (e.g., [25, 30]). Given the extremely low prevalence of the 2-repeat allele in Caucasian males, all of the subsequent analyses were conducted within the African-American male subsample. After cases were excluded for missing data, the final analytical sample size was N = 133 African-American males, including 6.0 % who possessed the 2-repeat allele (three 2-repeat carriers were dropped because of missing data on the shooting or stabbing variables).

Next, the association between the 2-repeat allele and the dichotomous shooting or stabbing variable was examined by estimating a binary logistic model. The results of this analysis are presented in Fig. 1, where the predicted probabilities are contained as bar graphs and the parameter estimates are included in the caption. As can be seen, the predicted probability of shooting or stabbing someone for respondents with alleles other than the 2-repeat allele was 0.07. In contrast, the predicted probability of shooting or stabbing someone for subjects with the 2-repeat allele was 0.50. The parameter estimates for this equation revealed that the 2-repeat allele exerted a statistically significant effect on the odds of shooting or stabbing someone (OR = 12.89, $p < 0.05$).

The last analysis that was conducted was designed to examine the association between the 2-repeat allele and the total number of waves that the subject reported shooting or stabbing someone. Given that this measure was highly skewed, the association was examined by estimating a negative binomial regression equation. Figure 2 contains a graphical depiction of the predicted rate of change along with the parameter estimates in the caption. As this figure shows, the predicted rate of change is 0.10 for respondents who

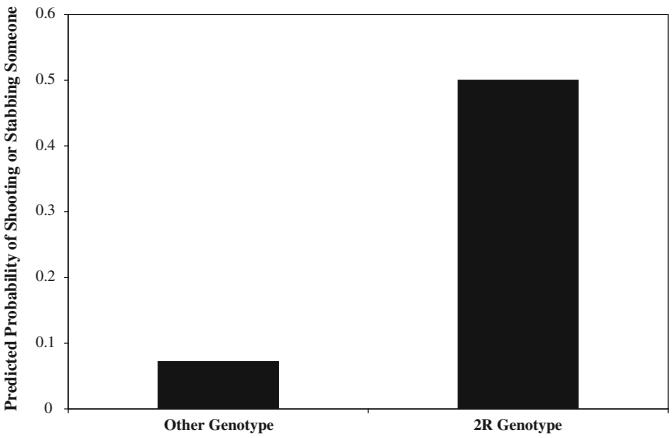

Fig. 1 Predicted probabilities of lifetime prevalence of shooting or stabbing someone (N = 133). *Note* Parameter estimates for logit equation: b = 2.56, SE = .79, OR = 12.89, $p < 0.05$; all equations corrected for the clustering of observations in families by using the "cluster" command in STATA10.0; any cases missing a family ID number were dropped from the analyses

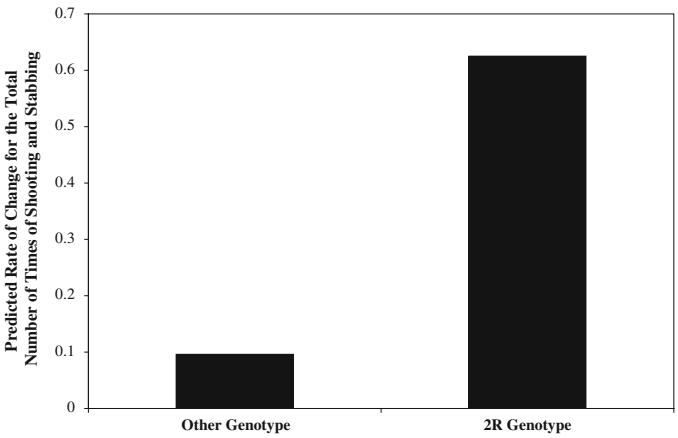

Fig. 2 Predicted rate of change for the total number of times of shooting or stabbing someone (N = 133). *Note* Parameter estimates for negative binomial equation: b = 1.87, SE = .54, exp(b) = 6.51, $p < 0.05$; all equations corrected for the clustering of observations in families by using the "cluster" command in STATA10.0; any cases missing a family ID number were dropped from the analyses

possess alleles other than the 2-repeat allele, but the predicted rate of change is 0.63 for respondents who carry the 2-repeat allele. The parameter estimates generated from the negative binomial analysis indicate that this association between the 2-repeat allele and the total number of shooting or stabbing incidents is statistically significant (exp(b) = 6.51, $p < 0.05$).

Discussion

There has been a great deal of interest in examining the specific genetic polymorphisms that are associated with antisocial behavior in general and specific categories of antisocial behavior, such as violence or aggression, in particular [5, 14]. Even so, there has been comparatively less empirical attention paid to the potential link between certain genetic markers and specific antisocial behaviors. The current study partially addressed this gap in the literature by examining whether MAOA genotype was related to shooting and stabbing behaviors during adolescence and adulthood. Analysis of data drawn from the National Longitudinal Study of Adolescent Health revealed two key findings. First, carriers of the 2-repeat allele of MAOA were significantly more likely than carriers of all other alleles to report having shot or stabbed someone at least once during their lifetime. Second, the 2-repeat allele was also related to the total number of waves in which the subject reported shooting or stabbing someone. In short, the 2-repeat allele confers an increased risk of shooting and stabbing multiple victims over the entire life course.

Although to our knowledge, this is the first study to link a specific genetic polymorphism to shooting and stabbing behaviors and to having multiple shooting and stabbing victims, there are a number of issues that should be addressed in future studies to determine the robustness of the results. First, almost all of the prior research examining the effects of MAOA on antisocial behaviors has pooled the 2-repeat allele together with the 3-repeat allele [14]. As the results of this study indicate, however, this approach may be misguided as the most powerful effects may be found within the 2-repeat allele and combining the

2-repeat allele with the 3-repeat allele may attenuate the main effects of MAOA [9]. Supplemental analyses (not reported) revealed that when the 2-repeat allele and the 3-repeat allele were combined, this genotype was unrelated to the odds of shooting or stabbing someone.

Second, and relatedly, analysis of the Add Health data revealed that the 2-repeat allele conferred an increased risk of shooting and stabbing behaviors and that these effects were independent of environmental factors. These findings stand in stark contrast to much of the extant MAOA research which has revealed that MAOA only has effects on antisocial behaviors in the presence of environmental liabilities. The differential effects, however, could be because the 2-repeat allele has independent effects whereas the 3-repeat allele only has effects when paired with an environmental risk factor. Future research needs to explore this possibility in much greater detail.

Third, and importantly, all of the existing research examining the effects of the 2-repeat allele on antisocial behaviors has analyzed data from the Add Health. While the current study extends previous research by showing that the 2-repeat allele has relatively strong effects on some of the most violent types of criminal behaviors, the findings should be viewed cautiously because they do not represent a completely independent analyses from those conducted by Guo et al. [9] and Beaver et al. [2]. Future research is needed that examines the effects of the 2-repeat allele in a sample that is distinct from the Add Health. Moreover, the study focused on a rare event, in a small sample, with a low base rate of the 2R allele. While the findings are statistically significant, they could have been influenced by small changes in the cell sizes of the 2×2 table (between the 2R allele and shooting/stabbing). Thus, the reader should exercise appropriate caution when interpreting the exact values presented here.

Last, the analyses for the current study were confined to African-American males because of the low base rate of Caucasian males carrying the 2-repeat allele which precluded the ability to calculate any multivariate statistical models. Future studies should expand on these findings and examine the effects of MAOA for African Americans, Caucasians, and other racial/ethnic groups. Since approximately 5.5 % of African-Americans and less than 1 % of Caucasians carry this rare allele [25, 30], the sample sizes will need to be sufficiently large to increase the statistical power needed to detect small-to-moderate effects of the 2-repeat allele. Until studies are conducted that are able to simultaneously examine both African Americans and Caucasians, it would be premature to speculate as to the potential ramifications of the 2-repeat allele in explaining any of the well-known crime trends.

Acknowledgments This research uses data from Add Health, a program project designed by J. Richard Udry, Peter S. Bearman, and Kathleen Mullan Harris, and funded by P01-HD31921 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, with cooperating funding from 17 other agencies. Special acknowledgement is due to Ronald R. Rindfuss and Barbara Entwisle for assistance in the original design. Persons interested in obtaining data files from Add Health should contact Add Health, Carolina Population Center, 123 W. Franklin Street, Chapel Hill, NC 27516-2524 (addhealth@unc.edu). No direct support was received from grant P01-HD31921 for this analysis.

References

1. Beaver KM, DeLisi M, Vaughn MG, Barnes JC: Monoamine oxidase A genotype is associated with gang membership and weapon use. Comprehensive Psychiatrcy 51:130–134, 2010.
2. Beaver KM, Wright JP, Boutwell BB, Barnes JC, DeLisi M, Vaughn MG: Exploring the association between the 2-repeat allele of the MAOA gene promoter polymorphism and psychopathic personality

traits, arrests, incarceration, and lifetime antisocial behavior. Personality and Individual Differences 54:164–168, 2013.
3. Buckholtz JW, Meyer-Lindenberg A: MAOA and the neurogenetic architecture of human aggression. Trends in Neurosciences 31:120–129, 2008.
4. Burt SA: Are there meaningful etiological differences within antisocial behavior? Results of a meta-analysis. Clinical Psychology Review 29:163–78, 2009.
5. Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R: Role of genotype in the cycle of violence in maltreated children. Science 297:851–854, 2002.
6. DeLisi M, Kosloski A, Sween M, Hachmeister E, Moore M, Drury A: Murder by numbers: Monetary costs imposed by a sample of homicide offenders. The Journal of Forensic Psychiatry and Psychology 21:501–513, 2010.
7. Ferguson CJ: Genetic contributions to antisocial personality and behavior: A meta- analytic review from an evolutionary perspective. Journal of Social Psychology 150:1–21 2010.
8. Fowler JS, Alia-Klein N, Kriplani A, et al.: Evidence that brain MAO A does not correspond to MAO A genotype in healthy male subjects. Biological Psychiatry 62, 355–358, 2007.
9. Guo G, Ou X-M, Roettger M, Shih JC: The VNTR 2 repeat in MAOA and delinquent behavior in adolescence and young adulthood: Association and MAOA promoter activity. European Journal of Human Genetics 16:626–634, 2008.
10. Harris KM: The National Longitudinal Study of Adolescent Health (Add Health), Waves I & II, 1994–1996; Wave III, 2001–2002; Wave IV, 2007–2009 [machine-readable data file and documentation]. Chapel Hill, Carolina Population Center, University of North Carolina at Chapel Hill, 2009.
11. Harris KM, Florey F, Tabor J, Bearman PS, Jones J, Udry JR. The National Longitudinal Study of Adolescent Health: Research Design [www document]. URL: http://www.cpc.unc.edu/projects/addhealth/design, 2003.
12. Harris KM, Tucker Halpern C, Smolen A, Haberstick BC: The national longitudinal study of adolescent health (add health) twin data. Twin Research and Human Genetics 9:988–997, 2006.
13. Heron M: Deaths: Leading causes for 2007. National Vital Statistics Reports 59:1–95, 2011.
14. Kim-Cohen J, Caspi A, Taylor A, Williams B, Newcombe R, Craig IW, Moffitt TE: MAOA, maltreatment, and gene-environment interaction predicting children's mental health: New evidence and a meta-analysis. Molecular Psychiatry 11:903–913, 2006.
15. Levy ER, Powell JF, Buckle VJ, Hsu YP, Breakefield XO, Craig IW: Localization of human monoamine oxidase-A gene to Xp11.23-11.4 by in situ hybridization: Implications for Norrie disease. Genomics 5:368–370, 1989.
16. Mason DA, Frick PJ: The heritability of antisocial behavior: A meta-analysis of twin and adoption studies. Journal of Psychopathology and Behavioral Assessment 16:301–323, 1994.
17. Menard S: Short- and long-term consequences of adolescent victimization. Youth Violence Research Bulletin:1–16, 2002.
18. Meyer Lindenberg A, Buckholtz JW, Kolachana B, et al.: Neural mechanisms of genetic risk for impulsivity and violence in humans. Proceedings of the National Academy of Sciences 103:6269–74, 2006.
19. Miles DR, Carey G: Genetic and environmental architecture of human aggression. Journal of Personality and Social Psychology 72:207–217, 1997.
20. Raine A: From genes to brain to antisocial behavior. Current Directions in Psychological Science 17:323–328, 2008.
21. Raine A, Buchsbaum MS, Stanley J, Lottenberg S, Abel L, Stoddard J: Selective reductions in prefrontal glucose metabolism in murders. Biological Psychiatry 36:365–373, 1994.
22. Raine A, Buchsbaum M, LaCasse L: Brain abnormalities in murderers indicated by positron emission tomography. Biological Psychiatry 42:495–508, 1997.
23. Raine A, Meloy JR, Bihrle S, Stoddard J, LaCasse L, Buchsbaum MS: Reduced prefrontal and increased subcortical brain functioning assessed using positron emission tomography in predatory and affective murderers. Behavioral Sciences and the Law 16:319–332, 1998.
24. Resnick M, Bearman P, Blum R, Bauman K, Harris K, Jones J, Tabor J, Beuhring T, Sieving R, Shew M, Ireland M, Bearinger L, Udry J: Protecting adolescents from harm: Findings from the National Longitudinal Study of Adolescent Health. Journal of the American Medical Association 278:823–832, 1997.
25. Reti IM, Jerry Z Xu, Jason Yanofski, Jodi McKibben, Magdalena Uhart, Yu-Jen Cheng, Peter Zandi, Oscar J Bienvenu, Jack Samuels, Virginia Willour, Laura Kasch-Semenza, Paul Costa, Karen Bandeen-Roche, William W Eaton, Gerald Nestadt: Monoamine oxidase A regulates antisocial personality in whites with no history of physical abuse. Comprehensive Psychiatry 52:188–194, 2011.

26. Rhee S-H, Waldman ID: Genetic and environmental influences on antisocial behavior: A meta-analysis of twin and adoption studies. Psychological Bulletin 128:490–529, 2002.
27. Sabol S, Hus S, Hamer D: A functional polymorphism in the monoamine oxidase A gene promoter. Human Genetics 103:273–279, 1998.
28. Shih JC, Chen K, Ridd MJ: Monoamine oxidase: From genes to behavior. Annual Review of Neuroscience 22:197–217, 1999.
29. Truman JL, Rand MR: Criminal victimization, 2009. Washington, DC: Bureau of Justice Statistics, US Department of Justice, 2010.
30. Widom CS, Brzustowicz LM: MAOA and the "cycle of violence:" Childhood abuse and neglect, MAOA genotype, and risk for violent and antisocial behavior. Biological Psychiatry 60:684–689, 2006.

Author Biographies

Kevin M. Beaver, PhD is a professor in the College of Criminology and Criminal Justice at Florida State University and a visiting distinguished professor at King Abdulaziz University.

J. C. Barnes, PhD is an assistant professor in the School of Economic, Political, and Policy Sciences at the University of Texas at Dallas.

Brian B. Boutwell, PhD is an assistant professor in the Department of Criminal Justice and Criminology at Sam Houston State University.