MAOA Genotype, Maltreatment, and Aggressive Behavior: The Changing Impact of Genotype at Varying Levels of Trauma

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Background: Childhood adversity has been shown to interact with monoamine oxidase-A (*MAOA*) genotype to confer risk for antisocial behavior. Studies examining this gene-by-environment (G×E) association, however, have produced mixed results.

Methods: Relevant research is reviewed, and results of a study with 114 children (73 maltreated and 41 control subjects) are presented. The maltreated children represent the extreme on a continuum of adversity and were assessed at a time of extreme stress—shortly after removal from their parents' care due to abuse. Measures of aggressive behavior were obtained using standard research instruments, and monoamine oxidase-A *MAOA* genotypes were obtained from saliva-derived DNA specimens. Population structure was controlled for using ancestral proportion scores computed on the basis of genotypes of ancestry informative markers.

Results: Many prior investigations appear to have had reduced power to detect the predicted G×E interaction because of low base rates of maltreatment and antisocial behavior in their samples and failure to use optimal procedures to control for population structure in ethnically diverse cohorts. In this investigation, a significant interaction was detected between exposure to moderate trauma and the "low-activity" *MAOA* genotype in conferring risk for aggression. Children with exposure to extreme levels of trauma, however, had high aggression scores regardless of genotype.

Conclusions: Our study suggests that problems in aggressive behavior in maltreated children are moderated by *MAOA* genotype, but only up to moderate levels of trauma exposure. Extreme levels of trauma appear to overshadow the effect of *MAOA* genotype, especially in children assessed at time of acute crisis.

Key Words: Aggression, antisocial, child abuse, gene–environment interaction, maltreatment, *MAOA*

Child maltreatment has been consistently associated with antisocial behavior in children who were abused (1–9). However, not all maltreated children develop problems with aggression or rule breaking, core symptoms associated with the diagnoses of conduct disorder and antisocial personality disorder. A groundbreaking study by Caspi *et al.* (1) suggested that resilience shown by some maltreated children relates to a polymorphism in the monoamine oxidase-A (*MAOA*) gene promoter. *MAOA* is an X-linked gene encoding an enzyme responsible for metabolizing neurotransmitters, such as serotonin and norepinephrine. The absence of a functional *MAOA* gene has been associated with aggression in animals (2) and humans (3). The number of copies in this variable number of tandem repeats (VNTR) *MAOA* polymorphism affects gene expression and efficiency of gene transcription (4,5). Caspi *et al.* (1) found that adults who were maltreated as children with "low-activity" *MAOA* alleles *(MAOA- L)* were more likely to develop conduct disorder, antisocial personality symptoms, and violence than adults maltreated as children with "high-activity" *MAOA* alleles (*MAOA-H)*, with this latter group having rates of these problems that were comparable to nonmaltreated control subjects.

Subsequent studies examining this gene-by-environment (G×E) interaction, however, have yielded mixed results. Replications (6–9), partial replications (10–13), negative findings (14–16), and even opposite findings (17) have been reported. Two recent meta-analyses reported small to medium effect sizes for the *MAOA* genotype and maltreatment interaction in conferring risk for antisocial behavior. The first (12) included five studies and reported an effect size of .18. The second, which included a total of eight studies, including the five studies in the original meta-analysis (12), showed an effect size of .17 for the G×E interaction involving the *MAOA* gene (18).

Studies included in these meta-analyses differ in terms of sample characteristics and phenotypes examined. Table 1 summarizes findings and key study characteristics of the 13 relevant published studies. Two of four replications included epidemiologic samples with Caucasian males (6,8), similar to the Caspi study (1), and one of the other replication studies was performed with Caucasian males who were referred to a forensic clinic (9). The fourth replication study included Native American females and reported an interaction between *MAOA* genotype and experiences of child maltreatment in conferring risk for antisocial personality (7). No other published articles that included non-Caucasian subjects replicated this G×E interaction for antisocial personality and aggression (10,14,16).

Among the partial replications, Widom (11) studied an ethnically diverse cohort but only found a significant G×E interaction for aggression among Caucasian subjects. Frazzetto's study (13) was limited to Caucasian male and female psychiatric outpatients and control subjects, but the G×E interaction was only significant for male participants (13). In the last two studies classified as partial replications, neither Huang (10) nor Kim-Cohen (12) detected a G×E interaction in predicting aggression or antisocial

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Table 1. Characteristics and Findings of Published Studies Examining MAOA Genotype and Maltreatment in Conferring Risk for Antisocial Behavior

Reference	Sample (*n*)	Cohort	Ethnicity	Sex	Prevalence Maltreatment (%)	Number High-Risk Subjects[a]	Phenotypes Examined	Prevalence Antisocial Behavior (%)	Findings
					Replications				
Caspi 2002[1]	442 adults	Epidemiological	Caucasian	Males	8	13	Conduct disorder, violent disposition, violent offenses, antisocial symptoms	25	G×E (low-activity allele)
Foley 2004[6]	514 children and adolescents	Epidemiological	Caucasian	Males	3.5	6	Conduct disorder	11.5	G×E (low-activity allele)
Nilsson 2006[8]	81 adolescents	Epidemiological	Caucasian	Males	14	5	Violence, vandalism, stealing, total Criminality Index	37	G xE (low-activity allele)
Reif 2007[9]	184 adults	Forensic evaluation referrals	Caucasian	Males	50	63	Recurrent violent behavior	39	G×E (low-activity allele)
Ducci 2007[7]	291 adults	168 alcoholic and 123 control subjects	Native Americans	Females	51	13	Alcohol use disorders and ASPD, ASPD symptoms	13	G×E (low-activity allele)
					Partial Replications				
Widom 2006[11]	409 adults	Maltreated and control subjects	Mixed	Both	50	NR	Juvenile and adult violence	42	G×E only in Caucasians (low-activity allele)
Frazzetto 2007[13]	235 adults	90 psychiatric outpatients and 145 control controls	Caucasian	Both	34	38	Aggression	NR	G×E only in men (low activity allele)
Huang 2004[10]	766 adults	663 Psychiatric outpatients with a mood disorder and 103 healthy controls	Mixed	Both	21	53	Aggression, hostility impulsivity, suicide attempts	NR	G×E for aggression both sexes (ns), positive for impulsivity in men and for suicide attempts in women (low-activity allele); in men, low-activity allele also associated with history of abuse
Kim-Cohen 2006[12]	975 children	Epidemiological	Caucasian	Males	4.7	16	Mental health composite score with antisocial, inattention, and emotional problem subscales	7	G×E negative for aggression, positive for inattention (low-activity allele)
					Negative or Opposite Reports				
Huizinga 2006[15]	277 adults	Epidemiological	Caucasian	Males	9	9	Violence, antisocial behavior	27	ns
Sjoberg 2007[17]	119 adolescents	Epidemiological	Caucasian	Females	11	1	Criminality risk index	38	G×E (high-activity allele, opposite finding)