Criminal Behavior and Single Nucleotide Polymorphism in Genes Related to Monoamine Regulation

Gabriella Cansino, BS[a]*; Peyton Gandy, MS[a]; Jessica Motl, MS[a]; Todd Armstrong, PhD[b]; Matthew Nobles, PhD[b]; Brian Boutwell, PhD[b]; David Gangitano, PhD[a]

[a]*Department of Forensic Science, Sam Houston State University, Huntsville, TX 77340*

[b]*Department of Criminal Justice and Criminology, Sam Houston State University, Huntsville, TX 77340*

INTRODUCTION

Since antisocial behavior is closely associated with criminal activity, understanding the etiology of antisocial behavior may be highly significant for criminal behavior analysts and profilers [1]. The genes regulating two closely associated neurotransmitters, serotonin (5-HT) and dopamine (DA), are of significant interest due to their involvement in social and behavioral regulation. For example, an imbalance in dopaminergic levels leads to variation in emotional regulation in an individual. Previous studies have shown that high levels of DA have been implicated in impulsive aggressive behaviors as well as emotional dysregulation [2,3]. Indeed, low serotonergic function has been associated with an increased likelihood for aggression and impulsivity [2-4].

There are numerous regulatory genes that affect the levels of each neurotransmitter within the central nervous system. DA is metabolized by catechol O-methyltransferase (COMT), monoamine oxidase A (MAOA), and monoamine oxidase B (MAOB) enzymes and is converted to norepinephrine via a dopamine β-hydroxylase (DβH) enzyme [5]. Tryptophan hydroxylase 1 (TPH1) converts tryptophan into 5-HT and then is broken down by MAOA and COMT into its metabolites [6].

Previous studies have shown that single nucleotide polymorphisms (SNPs) within the targeted genes are associated with changes in emotional behavior [5-11]. For this study, thirteen SNPs of interest were analyzed due to their direct link to the DA and 5-HT pathways. Therefore, examining SNPs within various genes responsible for regulating neurotransmitter levels may reveal a genetic predisposition for criminal and antisocial behavior.

MATERIALS AND METHODS

Sample Collection: Buccal swabs were collected from male inmates (N=100) within a jail located in southeastern Texas and from male students at Sam Houston State University (N=93). All the protocols used in this study were approved by the IRB of Sam Houston State University.

DNA Extraction and Quantification: DNA from buccal swabs was isolated using an enzymatic-organic extraction method. DNA was quantified in a StepOne™ Real-Time PCR System (Life Technologies, Foster City, CA) with D21S11 Primers (IDT-DNA, Coralville, IA), and SYBR® Green Master Mix (Life Technologies).

DNA Amplification: A multiplex PCR was performed using 1 ng DNA with the Hot Start Taq Polymerase kit (Qiagen, Hilden, Germany) in an Eppendorf Mastercycler Gradient PCR system (Eppendorf, New York, NY). PCR primers were designed using the software Primer3 Plus and AutoDimer. The two multiplex systems consisted of a 5-plex containing MAOA and MAOB SNPs (rs3788862, rs909525, rs979605, rs2283729, rs1799836) and an 8-plex with COMT, DβH, and TPH1 SNPs (rs740603, rs737865, rs165599, rs4680, rs129882, rs739398, rs1611115, rs1800532).

RESULTS

Table 1. Allele frequencies, standard deviations (in parentheses), and Hardy-Weinberg Equilibrium p-values (control, inmate) for the control (N = 93) and inmate (N = 100) samples. [a] Indicates a difference between allele frequencies of the two samples that failed to survive correction for multiple comparisons (p = 0.004). [b] (p < 0.01).

Gene (location)/SNP	Alleles	Control (SD)	Inmate (SD)	HWE
MAOA (Xp11.3)				
rs909525	A	.699 (.046)	.722 (.046)	----------
rs3788862	G	.699 (.046)	.742 (.045)	----------
rs979605	C	.710 (.046)	.680 (.048)	----------
MAOB (Xp11.3)				
rs1799836	A	.538 (.050)	.378[a] (.050)	----------
rs2283729	G	.742 (.044)	.663 (.049)	----------
COMT (22q11.21)				
rs4680	G	.529 (.050)	.586 (.051)	.515, .831
rs740603	A	.590 (.050)	.520 (.051)	1.00, .841
rs737865	T	.802 (.040)	.862 (.035)	1.00, .684
rs165599	A	.541 (.050)	.452 (.051)	.394, 1.00
DβH (9q34)				
rs129882	C	.843 (.037)	.805 (.041)	.424, .335
rs739398	C	.634 (.049)	.690 (.048)	.108, .007[b]
rs1611115	C	.762 (.043)	.793 (.042)	.233, .534
TPH1				
rs1800532	C	.680 (.047)	.760 (.044)	.055, .273

Table 2. Haplotype frequencies for MAOA, MAOB and COMT SNPs for control and inmate samples. [a] Permutation p-value generated with 500 shufflings. [b] Statistically significant differences at 0.05 levels. [c] Statistically significant differences at 0.01 levels.

Haplotype Blocks	Frequency	Control, Inmate Ratios	P-value	Permutation P-value[a]
MAOA (Xp11.3)				
GAT	0.089	0.011, 0.165	0.0002[c]	0.0007[c]
MAOB (Xp11.3)				
AG	0.405	0.505, 0.309	0.0059[c]	0.034[b]
COMT (22q11.21)				
TGAA	0.145	0.078, 0.205	0.0006[c]	0.0007[c]

Fig. 1. Evaluation of linkage disequilibrium (LD) between loci using D' (coefficient of LD). D' ≥ 60 indicates a moderate degree of LD, D' ≥ 80 indicates a strong degree of LD. Distances between loci are shown in parentheses. a) D' values between MAOA markers (Block 1) and MAOB markers (Block 2). b) D' values between COMT markers.

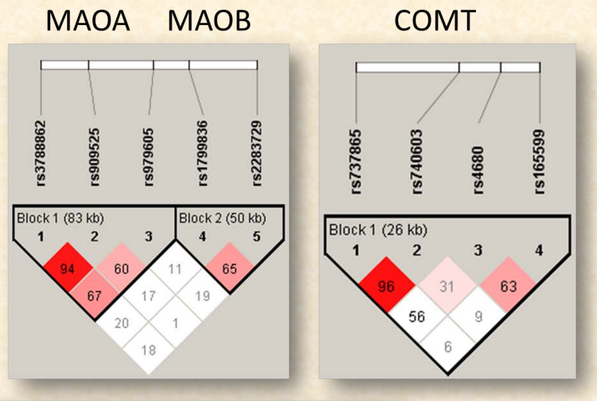
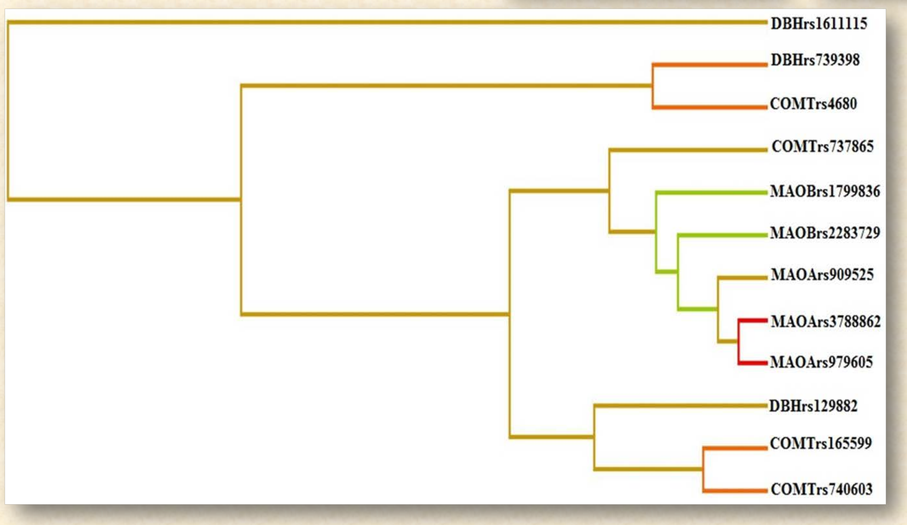


Fig. 2. Interaction dendogram for the thirteen analyzed SNP markers. The length of the line connecting two SNPs represents the degree of interaction. Shorter lines indicate stronger interactions between two SNPs. The color of the line represents the type of interaction. Red and orange represents a synergistic relationship or positive information gain (epistasis) between markers, whereas blue and green indicates redundancy, correlation or a negative information gain between markers.



MATERIALS AND METHODS

Genotyping: The SNPs were analyzed with the SNaPshot Multiplex Kit (Life Technologies). SNaPshot products were detected with the 3500 Genetic Analyzer using POP 7 and a 50 cm capillary array platform (Life Technologies). Allele calling was performed using the software GeneMapper v. 4.1 (Life Technologies). A custom bin set was designed to allow automation of genotyping.

Data Analysis: Allele frequencies were generated with PowerStats v. 1.2 software. Hardy-Weinberg Equilibrium (HWE), overall linkage disequilibrium (LD) and homogeneity of allele frequencies of control and inmates were assessed using GENEPOP v. 4.1 software. Haplotype and interaction analyses were performed using Haploview and Multifactorial Dimensionality Reduction software (MDR), respectively.

CONCLUSIONS

- Statistically significant differences were identified in haplotype combinations of linked markers (MAOA, MAOB, and COMT) between inmate and control groups.
- SNP-SNP interactions were detected between COMT and DBH and individually among MAOA and COMT SNPs.
- Fst value indicates genetic population differentiation between control and inmate groups.
- This study implicates additional genes related to monoamine metabolism, other than MAOA, may be associated with criminal behavior.
- Future studies need to address population-specific differences for the studied SNP markers.

ACKNOWLEDGEMENTS

This project was partially funded by the SHSU Enhancement Research Grant awarded to Matthew Nobles, PhD.

REFERENCES

1. Loeber R, Hay DF. Key issues in the development of aggression and violence from childhood to early adulthood. *Annu Rev Psychol* 1997;48:371–410.
2. Seo D, Patrick CJ, Kennealy P. Role of serotonin and dopamine system interactions in the neurobiology of impulsive aggression and its comorbidity with other clinical disorder. *Aggress Violent Behav* 2008;13:383-95.
3. van Erp AMM, Miczek KA. Aggressive behavior, increased accumbal dopamine, and decreased cortical serotonin in rats. *J Neurosci* 2000;20:9320-5.
4. Sora I, Wichems C, Takahashi N, Li XF, Zeng ZZ, Revay R, et al. Cocaine reward models: Conditioned place preference can be established in dopamine- and in serotonin-transporter knockout mice. *Proc Natl Acad Sci USA* 1998;95:7699-704.
5. Grigorenko EL, DeYoung CG, Eastman M, Getchell M, Haeffel GJ, Klinteberg Ba, et al. Aggressive behavior, related conduct problems, and variation in genes affecting dopamine turnover. *Aggressive Behav* 2010;36:158-76.
6. Rujescu D, Giegling I, Bondy B, Gietl A, Zill P, Möller H-J. Association of anger-related traits with SNPs in the TPH gene. *Mol Psychiatr* 2002;7:1023-9.
7. Rujescu D, Giegling I, Sato T, Hartmann AM, Moller HJ. Genetic variations in tryptophan hydroxylase in suicidal behavior: analysis and meta-analysis. *Biol Psychiat* 2003;54:465–73.
8. 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.
9. 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. *Pers Indiv Differ* 2013;54:164–8.
10. Tammimäki A, Käenmäki M, Kambur O, Kulesskaya N, Keisala T, Karvonen E et al. Effect of S-COMT deficiency on behaviour and extracellular dopamine concentrations in mice. *Psychoph S* 2010;211:389–401.
11. Bortolato M, Godar SC, Davarian S, Chen K, Shih JC. Behavioral disinhibition and reduced anxiety-like behaviors in monoamine oxidase B-deficient mice. *Neuropsychopharmacol* 2009;34:2746–57.