Genetic Study of Single Nucleotide Polymorphisms in the Oxytocin Receptor

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ABSTRACT

Oxytocin plays an important role in social behavior and is associated with empathy, bonding, and trust. Previous studies have found that both gene expression and environment impact the development of certain behaviors. Furthermore, behavior is influenced by neurotransmitters and the expression of their receptors. While the relationship between genotype and gender has been explored, there is limited information on the influence of ethnicity on genotype. This study analyzed four single nucleotide polymorphisms associated with the oxytocin receptor in the three main ethnic groups within the United States. It was concluded that genotypic differences between ethnic groups resulted in phenotypic or behavioral differences. More specifically, it was found that oxytocin receptor polymorphisms for rs53576 and rs1042778 affect behaviors such as aggression and empathy.

INTRODUCTION

Behavioral genetics is the study of how the environment and genetic factors play a role in human behavior. Previous studies have shown that these factors can influence the development of certain behaviors in young adults (1). Behavior is also influenced by neurotransmitters and the expression of their receptors in the brain. Understanding the complex mechanisms of neurotransmitters and their interaction is the base knowledge for the design of antidepressants and drugs of abuse (2).

One key neurotransmitter that affects social behavior is oxytocin. Oxytocin is synthesized in the hypothalamus and after secretion, is stored or circulated throughout the blood stream (3-4). Although it is a key component in the birthing process, equal concentrations are found in the posterior pituitary and plasma in both men and women (5). Oxytocin is involved in social memory, affiliation, aggression, learning and memory, as well as anxiety and depression (4-7). The function of oxytocin in humans can be assessed by studying polymorphisms within the oxytocin receptor (OXTR) gene. The OXTR gene has many polymorphic sites making genotyping with single nucleotide polymorphisms (SNPs) ideal. SNPs are single base variations found at specific locations on the genome and considered to be the most abundant type of polymorphism in humans (8-9).

Polymorphisms within OXTR markers have been linked to different emotional and behavioral traits, such as psychopathy, aggression, and empathy. While genotypic differences between males and females have been reported, the influence of ethnic background on genotype still remains unknown (10).

This study analyzed four OXTR SNPs (rs11476, rs53576, rs6770632, and rs1042778) for the three main ethnic groups in the United States in order to determine if there is an association between genotype and behavior. Furthermore, this study aimed to identify any differences in allele frequencies observed between the three main ethnic groups.

RESULTS

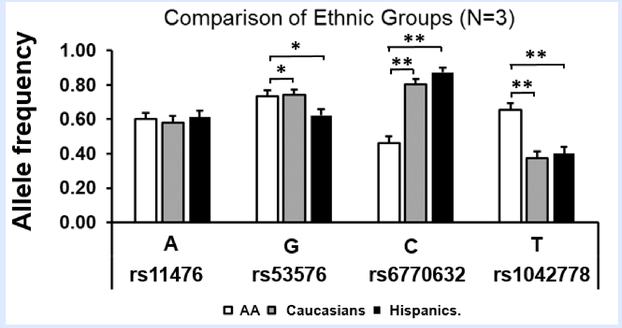

Figure 1: Major allele frequencies comparison for the three major ethnic groups. *p<0.05, **p<0.0008.

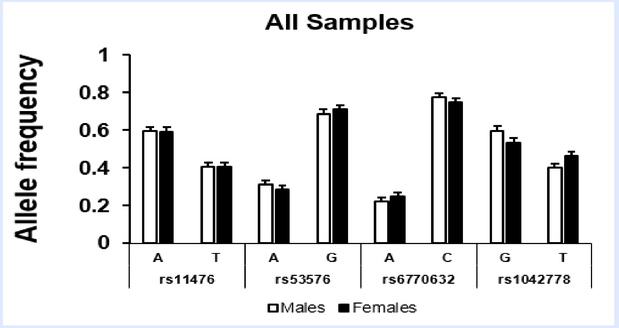

Figure 2: Comparison of male and female major allele frequencies for the four OXTR SNPs.

	Caucasian Aggression			African American Aggression			Hispanic Aggression		
	b	SE	Exp(b)	b	SE	Exp(b)	b	SE	Exp(b)
Rs53576 AA	.16	.57	1.17	-.25	.84	.78	.09	.56	1.09
Rs53576 GA	.68*	.29	1.97	.05	.49	1.05	-.15	.40	.86
Age	-.01	.01	1.00	.01	.02	1.01	-.04	.09	.96
Sex	.88**	.29	2.41	.77	.47	2.15	1.23**	.37	3.42
Constant	-1.07**	.33	.34	-.59	.51	.55	-.12	1.79	.89
Nagelkerke R^2		.09			.07			.12	

Note: *p<.05, **p<.01, ***p<.001

Figure 3: Logistic regression results for OXTR rs53576 and aggression.

	Caucasian Aggression			African American Aggression			Hispanic Aggression		
	b	SE	Exp(b)	b	SE	Exp(b)	b	SE	Exp(b)
Rs1042778 GG	.40	.46	1.49	-1.07	.78	.34	-1.34*	.60	.26
Rs1042778 GT	.22	.44	1.25	-.71	.50	.49	-.97	.55	.38
Age	-.00	.01	1.00	.01	.02	1.01	-.04	.09	.97
Sex	.89**	.29	2.42	.93	.50	2.53	1.32**	.38	3.74
Constant	-1.09*	.48	.34	-.24	.50	.79	.56	1.87	1.75
Nagelkerke R^2		.07			.11			.16	

Note: *p<.05, **p<.01, ***p<.001

Figure 4: Logistic regression results for OXTR rs1042778 and aggression.

	Caucasian Empathy			African American Empathy			Hispanic Empathy		
	b	SE	Exp(b)	b	SE	Exp(b)	b	SE	Exp(b)
Rs53576 AA	-.14	.59	.87	-1.74	.98	.18	.25	.55	1.28
Rs53576 GA	.84**	.29	2.31	-1.60**	.58	.20	-.33	.38	.72
Age	.03	.04	1.03	-.02	.03	.99	-.13	.09	.88
Sex	-.97**	.29	.38	-1.87	.57	.15	-.75*	.36	.48
Constant	-.49	.89	.62	1.77*	.73	5.86	3.29	1.83	26.84
Nagelkerke R^2		.12			.31			.09	

Note: *p<.05, **p<.01, ***p<.001

Figure 5: Logistic regression results for OXTR rs53576 and empathy.

	Caucasian Empathy			African American Empathy			Hispanic Empathy		
	b	SE	Exp(b)	b	SE	Exp(b)	b	SE	Exp(b)
Rs1042778 GG	1.51**	.53	4.53	.70	.80	2.02	-.47	.57	.63
Rs1042778 GT	1.50**	.51	4.48	.13	.52	1.14	-.28	.54	.76
Age	.05	.04	1.05	-.02	.04	.99	-.13	.09	.88
Sex	-.97**	.29	.38	-1.62**	.53	.20	-.71*	.36	.49
Constant	-1.96	1.03	.14	.78	.88	2.17	3.45	1.85	31.41
Nagelkerke R^2		.13			.19			.09	

Note: *p<.05, **p<.01, ***p<.001

Figure 6: Logistic regression results for OXTR rs1042778 and empathy.

DISCUSSION & CONCLUSIONS

- SNP allele frequency data was in agreement with previously reported data
- Statistically significant differences were detected in allele frequencies for three of the SNP markers when the ethnic groups were compared
- Logistic regression analysis revealed statistically significant differences in rs53576 and rs1042778 SNP markers for empathy and aggression
- Genotypic differences between the ethnic groups resulted in phenotypic or behavioral differences

MATERIALS AND METHODS

Sample Collection: Buccal swabs were collected from Sam Houston State University students who agreed to participate in a survey aimed at collecting information about the students' behavior. It consisted of 31 sections, including psychopathy, empathy, and antisocial behavior. All protocols used were approved by the Institutional Review Board at Sam Houston State University.

DNA Extraction and Quantification: DNA was extracted on the QIAcube (Qiagen, Hilden, Germany) using the QIAamp® DNA Investigator Kit (Qiagen) as per manufacturer's instruction. DNA quantitation was performed on a StepOne™ PCR System (ThermoFisher, Waltham, MA), using SYBR® Green Master Mix (ThermoFisher) and D21S11 primers.

DNA Amplification: PCR primers were designed using the software Primer3Plus and AutoDimer. Samples were amplified using the Type-it ® Microsatellite PCR Kit (Qiagen) with a DNA target of 0.2ng. PCR amplification was performed on the GeneAmp® PCR System 9700 (ThermoFisher).

Genotyping: Single base extension (SBE) was performed using the SNaPshot® Multiplex Kit (ThermoFisher) according to manufacturer's instructions. Purified SBE products were run on a 3500 Genetic Analyzer (ThermoFisher). Allele calling was performed using GeneMapper® Software v4.1 (ThermoFisher).

DNA Analysis: Allele frequencies were estimated by allele counting using the PowerStats v1.2 software. Hardy-Weinberg equilibrium and linkage disequilibrium were assessed using the software Genetic Data Analysis. Gender differences in allele frequencies were estimated with Fisher's exact tests using GenePop'007 software. Haploview v4.2 was used to perform single marker and haplotype analysis and permutation p-values. Logistic regression analysis was performed using SPSS software version 22. For this, selection of risk alleles was performed according to Malik et al. (11).

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