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Research paper

# The association of 22 Y chromosome short tandem repeat loci with initiative–aggressive behavior

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ABSTRACT

Aggressive behavior represents an important public concern and a clinical challenge to behaviorists and psychiatrists. Aggression in humans is known to have an important genetic basis, so to investigate the association of Y chromosome short tandem repeat (Y-STR) loci with initiative–aggressive behavior, we compared allelic and haplotypic distributions of 22 Y-STRs in a group of Chinese males convicted of premeditated extremely violent crimes ($n = 271$) with a normal control group ($n = 492$). Allelic distributions of DYS533 and DYS437 loci differed significantly between the two groups ($P < 0.05$). The case group had higher frequencies of DYS533 allele 14, DYS437 allele 14, and haplotypes 11–14 of DYS533–DYS437 compared with the control group. Additionally, the DYS437 allele 15 frequency was significantly lower in cases than controls. No frequency differences were observed in the other 20 Y-STR loci between these two groups. Our results indicate a genetic role for Y-STR loci in the development of initiative aggression in non-psychiatric subjects.

## 1. Introduction

Aggression is any form of behavior that intends to inflict damage upon another individual or object, and can be divided into non-premeditated impulsive aggression and premeditated initiative aggression (Chen et al., 2014). Aggression and violence are major causes of invalidism, death, and property loss worldwide (Vassos et al., 2014). Every year, > 1.6 million people are killed through violence, which is almost twice the number killed in armed conflicts in 2002 (Zwi et al., 2002; Chen et al., 2015). Therefore, preventing violence and aggression has become one of the most urgent and important global concerns.

Both environmental and genetic factors have been shown to be associated with aggressive behavior (Craig and Halton, 2009; Chen et al., 2015). For example, major mental disorders such as schizophrenia, bipolar disorders, and antisocial personality disorder have been shown to increase the risk of violence (Longato-Stadler et al., 2002). Substance and alcohol abuse, and the use of violent video games also appear to be crucial risk factors for violence (Holcomb and Ahr, 1988; Steadman et al., 1998). Moreover, the family growth environment, economic conditions, and education are associated with the occurrence of aggressive behaviors (Guo, 2014).

Previous studies have shown that the heritability of aggressive behavior is about 50% (Miles and Carey, 1997; Ferguson, 2010). Therefore, the identification of associated genetic factors is imperative to our understanding of the biological causes and mechanisms behind the formation and occurrence of crime. Molecular genetic studies have identified many candidate genes related to aggression and violence, such as: (1) the serotonin pathway-related genes tryptophan hydroxylase, monoamine oxidase A (*MAOA*), and serotonin transporter; (2) the stress response pathway-related genes dopamine beta-hydroxylase, and catechol-*O*-methyltransferase; and (3) the sex steroid-related genes estrogen receptor, and androgen receptor (Craig and Halton, 2009;

*Abbreviations:* Y-STRs, Y chromosome short tandem repeats; *TPH*, tryptophan hydroxylase; *MAOA*, monoamine oxidase A; *DBH*, dopamine-beta- hydroxylase; *COMT*, catechol-*O*-methyltransferase; *ESR*, estrogen receptor; *AR*, androgen receptor

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Pavlov et al., 2012). However, these findings are controversial.

Epidemiologic studies have shown that males are more likely to be aggressive and demonstrate antisocial behaviors than females (Craig and Halton, 2009), so the Y chromosome was predicted to provide a genetic basis for this (Hesselbrock, 1991; Carey, 1992). Lee et al. proposed that the male-specific gene sex-determining region on the Y chromosome (*SRY*) contributed to heightened sympathetic reactivity to stress and the "fight–flight" response to aggression in males (Lee and Harley, 2012). Haplogroups *R2* and *R1a1* of the human Y chromosome were also reported to be associated with aggressive behavior (Shah et al., 2009). Therefore, we speculated that other loci on the Y chromosome might be associated with human aggression and violence.

Short tandem repeat (STR) loci are composed of repeats (10–30 times) of 3–7 core base pair sequences that are located throughout the chromosome (Edwards et al., 1991). STR loci have been widely used in gene mapping, paternity testing, linkage analysis of disease mechanisms, tumor biology, and population genetics (Butler, 2006). Most STR loci are located in the non-recombination regions of the Y chromosome, and undergo haploid paternal inheritance. Our group previously discovered that autosomal STR loci *TH01* and *TPOX* were associated with impulsive aggression, and that *Penta D* and *Penta E* were associated with initiative aggression (Yang Chun et al., 2014; † et al., 2015). However, until now there has been no report on the relationship between STR loci on the Y chromosome and initiative aggression. Therefore, in this study, we genotyped 22 Y-STR loci in subjects who have committed premeditated criminal offenses and normal controls to determine if the Y-STR loci are associated with initiative–aggressive behavior.

## 2. Materials and methods

### 2.1. Participants

The present study included 271 individuals who were imprisoned for initiative–aggressive behavior (assault $n = 54$; robbery $n = 204$; homicide $n = 13$) between 2003 and 2014. The mean age of the subjects was 31.7 years ($SD = 10.6$). A total of 43, 197, 24, and six individuals had attained primary, junior, high school, and university diplomas, respectively; one individual was illiterate. The subjects had no history of neurological or psychiatric diseases that were diagnosed by psychiatrists. Furthermore, no subjects were reported to have either substance use disorders or a history of brain trauma. The controls consisted of 492 age-matched (mean age = 33.4 years, $SD = 14.3$) nonviolent blood donors who were recruited from the No. 102 Hospital of People's Liberation Army (PLA) in Changzhou, China. The controls had no family history of criminal offenses, violent activities, or other evident mental disorders.

All participants were unrelated, Han Chinese males living in Jiangsu Province. There were no significant differences in the distributions of age ($t = 1.72$, $P = 0.09$) or place of residence ($\chi^2 = 3.33$, $P = 0.07$) between the two groups. All participants were fully informed about the scope and procedure of the study, and provided their written informed consent. This study was approved by the Ethics Committee of Changzhou No.102 Hospital of PLA, and all experiments were carried out in accordance with approved guidelines.

### 2.2. Y-STR loci selection and genotyping

DNA was extracted from peripheral blood using the conventional Chelex-100 extraction method (Walsh et al., 1991). The 22 Y-STR loci (DYS576, DYS389 I, DYS448, DYS389 II, DYS19, DYS391, DYS481, DYS549, DYS533, DYS438, DYS437, DYS570, DYS635, DYS390, DYS439, DYS392, DYS643, DYS393, DYS458, DYS385a/b, DYS456, and DY_GATA_H4) were genotyped using the PowerPlex® Y23 fluorescent-labeled multiplex amplification system (Promega, USA) which is widely applied in forensic laboratories worldwide (supplementary Table S1). The 22 Y-STR loci included in this kit can be amplified simultaneously in one amplification system (Thompson et al., 2013). The haploids of the 22 Y-STR loci from the same paternal inheritance can be conservatively delivered (except for mutations). PCR was performed using 0.2 ng of template DNA, 2 μL 5× Master Mix, 1 μL 10× Primer Pair Mix, and $dH_2O$ a final volume of 10 μL. Amplification was performed on automated thermal cycler AB 9700 (Life, USA) using the following protocol: initial denaturation at 96 °C for 2 min, followed by 27 cycles of 94 °C for 10 s, 61 °C for 1 min, and 72 °C for 30 s, with a final extension at 60 °C for 20 min. For genotyping, 1 μL of the PCR product was mixed with 0.5 μL CC5 Internal Lane Standard (Promega) and 14 μL deionized formamide in a 96-well plate, then analyzed on the AB3500xL Genetic Analyzer. We used 3500 Data Collection v1.0 software (Life) to collect inspection data. Raw data were further analyzed by GeneMapper ID-X v1.3 software (Life) for allelic discrimination.

### 2.3. Statistical analyses

We used PowerSats software (Promega) to obtain allele and genotype frequencies of the 22 Y-STR loci. Statistical analyses were performed using SPSS software version 19.0. A $P$-value of $< 0.05$ was considered statistically significant. R × C chi-square tests were used to compare the frequencies of alleles and genotypes of each STR between subjects and controls. The exact $p$-values were calculated using Fisher's exact test, and the significance level was set after performing the Bonferroni correction. Odds ratios (*ORs*) with 95% confidence intervals (*CIs*) of different allele and genotype frequencies were determined as a measure of the association strength. We created haplotype groups of the Y-STR loci containing alleles with significantly different frequency, by manually counting the number of each allele combinations, and compared haplotype frequencies by analysis mentioned above.

## 3. Results

### 3.1. Two Y-STRs had differences in allele frequency distributions

As shown in Tables 1 and 2, three allelic frequencies of two Y-STR loci demonstrated significant differences between subjects and controls. The frequencies of allele 14 of DYS533 (2.21% vs. 0.20%; $P < 0.01$ and allele 14 of DYS437 (68.63% vs. 58.94%; $P < 0.0125$) were significantly higher in subjects compared with controls, while allele 15 of DYS437 had a significantly lower frequency in subjects compared with controls (29.15% vs. 38.01%; $P < 0.0125$).

No significant differences were found in the allele frequencies of the other 20 Y-STR loci between subjects and controls (Supplementary Information).

**Table 1**
Comparison of allele frequencies at the DYS533 locus between subjects and controls (frequency, %).

| Alleles | Subjects ($n = 271$) | Controls ($n = 492$) | $\chi^2$ | *P*-value | Odds ratio | 95%*CI* |
|---|---|---|---|---|---|---|
| 10 | 12 (4.43) | 41 (8.33) | 4.12 | 0.0423 | 0.51 | 0.26–0.99 |
| 11 | 174 (63.84) | 294 (59.76) | 1.46 | 0.2270 | 1.21 | 0.89–1.64 |
| 12 | 64 (23.99) | 131 (26.63) | 0.83 | 0.3617 | 0.85 | 0.60–1.20 |
| 13 | 13 (4.80) | 23 (4.67) | 0.01 | 0.9392 | 1.03 | 0.51–2.06 |
| 14 | 6 (2.21) | 1 (0.20) | 7.77 | 0.0095 | 11.12 | 1.33–92.83 |
| $\chi^2$ | 12.74 | | | | | |
| *P*-value | 0.013 | | | | | |

*Note:* Figures in brackets indicate frequencies. Allele frequencies < 1% in both subjects and controls were removed. The level of statistical significance for these pairwise tests was set at 0.05/5 = 0.01.