Interaction between Serotonin Transporter and Serotonin Receptor 1 B genes polymorphisms may be associated with antisocial alcoholism

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Abstract

Background: Several studies have hypothesized that genes regulating the components of the serotonin system, including serotonin transporter (5-HTTLPR) and serotonin 1 B receptor (5-HT1B), may be associated with alcoholism, but their results are contradictory because of alcoholism’s heterogeneity. Therefore, we examined whether the 5-HTTLPR gene and 5-HT1B gene G861C polymorphism are susceptibility factors for a specific subtype of alcoholism, antisocial alcoholism in Han Chinese in Taiwan.

Methods: We recruited 273 Han Chinese male inmates with antisocial personality disorder (ASPD) [antisocial alcoholism (AS-ALC) group (n = 120) and antisocial non-alcoholism (AS-N-ALC) group (n = 153)] and 191 healthy male controls from the community. Genotyping was done using PCR-RFLP.

Results: There were no significant differences in the genotypic frequency of the 5-HT1B G861C polymorphism between the 3 groups. Although AS-ALC group members more frequently carried the 5-HTTLPR S/S, S/LG, and LG/LG genotypes than controls, the difference became non-significant after controlling for the covarying effects of age. However, the 5-HTTLPR S/S, S/LG, and LG/LG genotypes may have interacted with the 5-HT1B G861C C/C polymorphism and increased the risk of becoming antisocial alcoholism.

Conclusion: Our study suggests that neither the 5-HTTLPR gene nor the 5-HT1B G861C polymorphism alone is a risk factor for antisocial alcoholism in Taiwan’s Han Chinese population, but that the interaction between both genes may increase susceptibility to antisocial alcoholism.

Keywords: Antisocial alcoholism, Serotonin, Serotonin transporter gene, 5-HT1B gene

Background

Alcoholism (also: alcohol dependence) is a complex, heterogeneous disorder that is influenced by multiple genes as well as sociocultural factors [1,2]. Twin studies have shown that genetic factors account for about 50-60% of the overall variance in alcoholism [3-5]. Many candidate genes have been studied; however, the results are controversial. Therefore, to reduce the heterogeneity of alcoholism by proper subtyping is important. In addition, a gene-to-gene interaction approach may be more revealing than a single-gene approach for studying alcoholism. By using appropriate subtypes of alcoholism and the gene-to-gene interaction approach, the results may be more conclusive.

Cloninger (1987) identified two subtypes of alcoholism. Type I alcoholism is characterized by late onset, more psychological dependence, and anxious/depressed personality traits. Individuals with type II alcoholism are characterized by early onset, a higher familial risk for alcoholism, and antisocial personality traits [1]. We previously subdivided alcoholism into three categories: pure, anxious/depressive, and antisocial (AS) [6]. We showed that antisocial alcoholism (AS-ALC; alcoholism comorbid
with antisocial personality disorder), which overlaps to some extent with Cloninger’s type II alcoholism, have a strong genetic predisposition to alcoholism and different genetic polymorphisms than do other subtypes of alcoholism. The protective effect of the ADH1B*2 allele against alcoholism vanished in antisocial alcoholics [6], and the protective effect of the ALDH2*2 allele might disappear in individuals with antisocial personality disorder (ASPD) and carrying the MAOA-uVNTR 4-repeat allele [7]. Antisocial alcoholics had higher novelty-seeking scores with an interaction between the DRD2 TaqI A1 (A1A1 or A1/A2) and 5-HTTLPR S/S genotype [8]. Moreover, antisocial alcoholics had different polymorphisms of the serotonin (5-HT) transporter both in vivo imaging study [20] and in postmortem brain study [21]. Human SPECT study showed that homoyzgous carriers of the long allele (L/L) had an increase in the availability of raphe serotonin transporter [20]. Serotonin transporter mRNA levels in subjects with S/L and S/S genotypes were also lower than in subjects with the L/L genotype in postmortem brain study [21]. Although the S allele has been linked to a risk of alcoholism [22,23] and to antisocial alcoholics or type II alcoholics [24-26], this link is still controversial [20,27,28]. In addition to the long and short alleles, other subtypes of the L allele have been described [29]. The long variant with an adenosine at single nucleotide polymorphism (SNP) rs25531 (Lc) has been reported to have higher activity than the long variant with a guanine at rs25531 (Lc) [30,31]. Furthermore, other uncommon alleles that are longer than the L variant were found in several studies [29,32-35]. The extra-long allele or “novel allelic variant” were called XL variants with 15, 18,19, 20 or 22 repeats with unknown function [29,32-35]. Hence, the past dichotomous classification of SHTTLPR into S and L allele may not be sufficient and the association between the tri-allelic 5-HTTLPR polymorphism (S, Lc, Lc) and the risk of alcoholism or antisocial alcoholism remains unknown.

The serotonin 1B receptors (5-HT1B) are located on presynaptic and postsynaptic terminals and function as both autoreceptors and heteroreceptors that mediate the release of serotonin [36]. The 5-HT1B gene has been associated with alcohol intake and aggression in animal and human studies. An alcohol preference locus has been mapped in mice to the region where 5-HT1B is located [37]. 5-HT1B receptor knockout mice were found to have increased aggressive behavior [38] and increased spontaneous alcohol consumption [39]. In human studies, of 16 reported polymorphisms of 5-HT1B, the results of association studies that used the G861C polymorphism remain inconsistent [40]. Some studies associated polymorphisms of 5-HT1B G861C with alcoholism [41] or antisocial alcoholism [42]. People with the 5-HT1B 861C allele also had 20% fewer 5-HT1B binding sites in the prefrontal cortex, which was the same as the alcoholism group [43,44]. However, subsequent studies did not confirm the association [45-47]. The heterogeneity of alcoholism, as well as different populations and ethnicities, may cause the discrepancy.

The prevalence rate of ASPD and antisocial behaviors in individuals with alcohol use disorders ranges from 20% to 33% [48-50]. Because of their high comorbidity, most studies have not distinguished the effects of ASPD from those of alcoholism in Western populations [51]. Being able to specify whether the genes were involved in pure ASPD (ASPD not comorbid with alcoholism (AS-N-ALC)) or AS-ALC, or both, may clarify the nature of these disorders and elucidate whether past genetic associations with AS-ALC were merely contributed by ASPD.

The aims of current study is to (1) investigate whether the tri-allelic 5-HTTLPR polymorphism and 5-HT1B G861C polymorphism are associated with AS-ALC in the Han Chinese population in Taiwan, and (2) assess the serotonergic genetic interaction between 5-HTTLPR and 5-HT1B G861C polymorphisms and antisocial alcoholism.

Methods
Participants and clinical assessments
This study was approved by the Institutional Review Boards for the Protection of Human Subjects at the Tri-Services General Hospital and National Cheng Kung...
University Hospital. Because of the low prevalence (0.1%) of ASPD in Han Chinese in Taiwan [52], it is difficult to recruit study participants with ASPD from clinics or from the community. Instead, we recruited 273 Han Chinese men with ASPD from a prison in Taipei (northern Taiwan) \((n = 173)\) and a prison in Tainan (southern Taiwan) \((n = 100)\). The research protocol was reviewed and approved by the Taiwan Ministry of Justice, which permitted us to collect blood samples from the participants. The procedures were fully explained to each participant before they gave written informed consent; however, there were no advocates for the inmates present when they were asked to sign the consent form. Participants were told that they were free to drop out of or to join the study at any time. We offered several compensatory benefits: 1) a free physical examination, 2) liver and renal function tests, and 3) free treatment or assistance in transferring those with psychiatric or physical illnesses to hospitals. Each participant was initially evaluated by an attending psychiatrist and then interviewed by a psychologist well-trained in using the DSM-IV and the Modified Chinese Version of the Modified Schedule of Affective Disorder and Schizophrenia-Life Time (SADS-L) [53,54]. The inter-rater reliability of the Chinese version of the modified SADS-L was good with the kappa values range from 0.71 to 1.00 in several major mental illness [54]. The SADS-L was also found to be adequate for diagnosing ASPD with or without alcoholism [6,55-57]. Participants with major mental illnesses including schizophrenia, bipolar disorder, multiple substance abuse, or other organic mental disorders, and those who refused to participate \(< 10\%\) were excluded from the study. None of the participants was taking any kind of medication. All who met the criteria for a diagnosis of antisocial personality disorder with or without alcoholism were assigned to the AS-ALC group \((n = 120)\) or the AS-N-ALC group \((n = 153)\), respectively.

The healthy control group included 191 male volunteers recruited from the community. The Chinese version of the SADS-L was used to screen their psychiatric conditions. All controls were free of present and past major and minor mental illness (affective disorder, schizophrenia, anxiety disorder, personality disorder, alcohol abuse and dependence, and illegal substance use disorder), and none had a family history of psychiatric disorders among their first-degree relatives.

**Blood samples and genotyping for 5-HTTLPR and 5-HT1B G861C polymorphisms**

Twenty milliliters of blood was drawn from each participant, and standard methods were used to extract genomic DNA from the leukocytes. The genotypes of 5-HTTLPR functional polymorphisms were genotyped using polymerase chain reaction plus restriction fragment length polymorphism (PCR-RFLP) analysis [18]. The A/G SNP of the \(L\) allele were determined using a modified protocol [58]. The G861C polymorphism of the 5-HT1B gene was genotyped using a modified protocol [42].

**Statistical analyses**

One-way analysis of variance (ANOVA) and the Bonferroni Post Hoc Test were used to determine the mean age differences between the subgroups. The difference in genotype frequency of 5-HTTLPR and 5-HT1B G861C polymorphisms between three groups was calculated using the Pearson \(\chi^2\) test (2-tailed). The 5-HTTLPR polymorphisms in AS-ALC and AS-N-ALC groups were further stratified by the 5-HT1B G861C polymorphism using the \(\chi^2\) tests. Logistic regression analysis was used to examine the main effect and gene-to-gene interaction of the 5-HTTLPR and 5-HT1B G861C polymorphisms for the risk of antisocial alcoholism. Both the \(S_A\) and the \(S_G\) alleles were recorded as the \(S\) allele because there is no functional difference in the SNPs [59]. Because past studies found that \(S\) and \(LG\) carrier had lower function and expression of serotonin transporter [18-20,60], we divided the 5-HTTLPR polymorphisms into 2 groups, low-functional \((S/S, S/LG, LG/LG)\) and high-functional \((S/LA, LG/LA, LA/LA, S/XL, LA/XL, LG/XL)\), for data analysis. There was only 8 participants carried the \(LA/LA\) genotype in our study, so we did not separate the homozygous \(LA\) carries from heterozygous \(L_A\) carriers into another group. SPSS for Windows 17.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

The power estimation was calculated using G-power 3.1 software [61,62]. Our total sample size \((n = 464)\) had a power of 0.58 to detect a small effect (effect size = 0.1), of 0.99 to detect a medium effect (effect size = 0.3), and of 1.00 to detect a large effect (effect size = 0.5) of genotype distributions.

**Results**

Healthy controls were significantly older than those in the AS-ALC \((P = 0.004)\) and AS-N-ALC groups \((P = 0.009)\;\text{mean age: } F = 6.87; df = 2, 461 (Table 1). A Bonferroni post hoc test did not show a significant age difference between the AS-ALC and AS-N-ALC groups.

Genotype distributions of 5-HTTLPR and 5-HT1B G861C were in Hardy-Weinberg equilibrium \((5-HTTLPR: P = 0.75 \text{ in AS-ALC and } P = 0.22 \text{ in AS-N-ALC}; 5-HT1B G861C: P = 0.07 \text{ in AS-ALC and } P = 0.72 \text{ in AS-N-ALC}). The distribution of the 5-HTTLPR and 5-HT1B G861C genotypes was not significantly different between the three groups (Table 2). However, there was a higher frequency of the low-functional 5-HTTLPR polymorphism \((S/S, S/LG, LG/LG)\) in the AS-ALC group than in the control group (Table 2). After stratifying the 5-HTTLPR polymorphisms with the 5-HT1B G861C polymorphism, a
significant difference in the frequency of 5-HTTLPR polymorphisms was found after controlling for the 5-HT1B G861C C/C genotype for both AS-ALC versus controls and AS-ALC versus AS-N-ALC (Table 3). A logistic regression analysis, done to control the possible covarying effect of age, showed that the 5-HTTLPR and 5-HT1B G861C genotypes were not significantly different between the AS-ALC and control groups or the AS-ALC and the AS-N-ALC groups (Table 4). However, the regression did reveal a significant interaction between the 5-HTTLPR and 5-HT1B G861C genes. Compared with AS-N-ALC and control groups, the interaction between the 5-HTTLPR low-functional group (S/S, S/LG, LG/LG genotype) and the 5-HT1B G861C C/C genotype may increase the risk of becoming an antisocial alcoholic (P = 0.04, odds ratio (OR) = 6.22 and 5.76, respectively) (Table 4).

Discussion
We found that interaction between the 5-HTTLPR S/S, S/LG, LG/LG genotypes and the 5-HT1B G861C C/C genotypes was associated with the AS-ALC group compared with the control and AS-N-ALC groups. Unlike past studies [24-26,43], we did not find an association between the 5-HTTLPR or the 5-HT1B G861C polymorphisms with AS-ALC. Although the AS-ALC group seemed to have a higher frequency of the 5-HTTLPR S/S, S/LG, LG/LG genotype than did the control group, when the effect of age was controlled by logistic regression, the difference was not significant.

The interaction between the 5-HTTLPR S/S, S/LG, LG/LG and the 5-HT1B G861C C/C genotypes may result in reduced brain serotonin function. Because patients with the 5-HT1B 861 C allele were found with fewer 5-HT1B binding sites in the prefrontal cortex [43,44] and the 5-HTTLPR S/S, S/LG, LG/LG was the low-functional group [30,31], our results imply that only the combined effect of serotonergic dysfunction from the studied genes, but not from individual genes, may be associated with risk for antisocial alcoholism. Several other reasons may also account for our positive finding. First, past studies compared the 5-HTTLPR polymorphism between antisocial alcohols and healthy (without ASPD and non-alcoholics) controls. Because ASPD has been linked to the 5-HTTLPR polymorphism [63-65], we tried to control for the confounding effect of ASPD by comparing antisocial alcohols with healthy controls and antisocial non-alcoholics. Second, our healthy control group belonged to a super-control group that excluded any other major or minor mental illness, while in other studies [25,26], the authors included only individuals from unscreened community controls and no antisocial non-alcoholics. Moreover, we used a tri-allelic functional 5-HTTLPR polymorphism instead of a bi-allelic polymorphism. All these factors may have caused results different from those of other reports.

We found no association between antisocial alcoholism and the 5-HT1B G861C polymorphism. A previous study [43] showed that the frequencies of the 5HTTLR 861 C allele varied widely among different ethnic groups, ranging from 20% in African-Americans to 36% in Hispanics and 42% in Asians. In our current study, the frequency of the 5-HT1B C allele (48.9% in the control group, 49.6% in the AS-ALC group, and 47.1% in the AS-N-ALC group) was higher than in previous reports. We also added an AS-N-ALC group to decrease the effect of ASPD. Different populations and ethnicities may also partially explain our different results.

Our past study [66] showed that antisocial alcohols and antisocial non-alcoholics shared a similar genetic vulnerability of dopamine-related genes, which was different from healthy controls. However, in the present study, we did not find the same distributions of the 5-HTTLPR and 5-HT1B genes in the three groups. It seems that the antisocial non-alcoholics and healthy

| Group     | n  | Age (years) | F  | P-value |
|-----------|----|-------------|----|---------|
| AS-ALC    | 120| 32.4 ± 7.6  | 6.87| 0.001   |
| AS-N-ALC  | 153| 32.8 ± 7.5  |     |         |
| Controls  | 191| 35.5 ± 9.4  |     |         |

Table 2 Genotype distribution and frequency of the 5HTTLPR and 5HT1B G861C polymorphism

| Group     | n  | S/S, S/LG, LG/LG | S/LG, LG/LG | LG/LG | S/S, S/LG, LG/LG | LG/LG | S/S, S/LG, LG/LG | LG/LG | χ² | P-value |
|-----------|----|----------------|-------------|-------|----------------|-------|----------------|-------|----|---------|
| AS-ALC    | 120| 90 (75.0)      | 30 (25.0)   |       | 30 (25.0)      |       | 25 (20.8)      |       | 5.39| 0.02**  |
| AS-N-ALC  | 153| 100 (65.4)     | 53 (34.6)   |       | 53 (34.6)      |       | 44 (28.8)      |       | 2.95| 0.09     |
| Controls  | 191| 119 (62.3)     | 72 (37.7)   |       | 72 (37.7)      |       | 55 (28.8)      |       | 5.50| 0.06*** |

α AS-ALC: Antisocial alcoholism; AS-N-ALC: Antisocial personality disorder without alcoholism.
β AS-ALC vs. Healthy Controls.
γ AS-ALC vs. AS-N-ALC.
δ AS-N-ALC vs. Controls.
α AS-N-ALC vs. AS-N-ALC.
Table 3 SHTTLPR genotype frequency after stratification of SHT1B G861C genotype

| G861C Genotype | Groups          | S/S, S/LG, Lg/LG, S/LA, Lg/LA, Lg/La, Lg/LXL, Lg/XL, Lg/XL | X² | P       |
|----------------|-----------------|------------------------------------------------------------|----|---------|
| AS-ALC vs. Controls |                 |                                                           |    |         |
| G/G            | AS-ALC          | 15 (60.0) 10 (40.0)                                        | 0.023 | 0.878  |
|                | Controls        | 32 (58.2) 23 (41.8)                                        |     |         |
| G/C            | AS-ALC          | 53 (75.7) 17 (24.3)                                        | 1.086 | 0.297  |
|                | Controls        | 60 (68.2) 28 (31.8)                                        |     |         |
| C/C            | AS-ALC          | 22 (88.0) 3 (12.0)                                         | 7.509 | 0.006* |
|                | Controls        | 27 (56.3) 21 (43.8)                                        |     |         |
| AS-ALC vs. AS-N-ALC |                 |                                                           |    |         |
| G/G            | AS-ALC          | 15 (60.0) 10 (40.0)                                        | 0.784 | 0.376  |
|                | AS-N-ALC        | 31 (70.5) 13 (29.5)                                        |     |         |
| G/C            | AS-ALC          | 53 (75.7) 17 (24.3)                                        | 3.075 | 0.079  |
|                | AS-N-ALC        | 46 (62.2) 28 (37.8)                                        |     |         |
| C/C            | AS-ALC          | 22 (88.0) 3 (12.0)                                         | 3.863 | 0.049* |
|                | AS-N-ALC        | 23 (65.7) 12 (34.3)                                        |     |         |

*P < 0.05
AS-ALC, antisocial alcoholism; AS-N-ALC, antisocial personality disorder without alcoholism.

Table 4 Logistic regression analysis of SHTTLPR gene and SHT1B receptor gene G861C polymorphism and their interaction for the risk of antisocial alcoholism (AS-ALC)

| Models | B   | OR  | 95% CI | P-value |
|--------|-----|-----|--------|---------|
| Model 1 |     |     |        |         |
| SHTTLPR low functional group | −0.47 | 0.62 | 0.22-1.75 | 0.37 |
| SHT1B G861C G/C | −0.21 | 0.81 | 0.29-2.27 | 0.69 |
| SHT1B G861C C/C | −1.13 | 0.32 | 0.07-1.36 | 0.14 |
| SHTTLPR low-functional group SHT1B G861C G/C | 1.09 | 2.97 | 0.84-10.44 | 0.09 |
| SHTTLPR low-functional group SHT1B G861C C/C | 1.83 | 6.22 | 1.10-35.27 | 0.04* |
| Model 2 |     |     |        |         |
| SHTTLPR low-functional group | 0.14 | 1.15 | 0.43-3.07 | 0.78 |
| SHT1B G861C G/C | 0.49 | 1.63 | 0.61-4.35 | 0.33 |
| SHT1B G861C C/C | −1.26 | 0.28 | 0.07-1.19 | 0.09 |
| SHTTLPR low-functional group SHT1B G861C G/C | 0.07 | 1.07 | 0.32-3.65 | 0.91 |
| SHTTLPR low-functional group SHT1B G861C C/C | 1.75 | 5.76 | 1.09-30.44 | 0.04* |

SHTTLPR low-functional group: S/S, S/LG, Lg/LG
SHTTLPR high-functional group: S/LA, Lg/LA, Lg/LA, S/XL, Lg/XL, Lg/XL
B, coefficients; CI, confidence interval; OR, odds ratio
Model 1, reference groups are: SHTTLPR low-functional group, SHT1B G861C G/G genotypes, and AS-N-ALC group; covarying for age
Model 2, reference groups are: SHTTLPR low-functional group, SHT1B G861C G/G genotypes, and controls; covarying for age

*P < 0.05. The SHTTLPR gene and its interaction with the SHT1B gene may be feasible to divide those with the SHTTLPR genotypes into a low-functional group for statistical analysis according to past study results [18-20,60]. Although the function of the SHTTLPR XL allele remains unknown, one study had speculated that it may function as an L allele [75]. However, additional study will be required to test its function since a significant proportion of Han Chinese carry this allele [75]. Finally, it is very likely that individuals with ASPD may belong to a specific group since members of both the AS-ALC and AS-N-ALC groups were all recruited from jail, which caused sampling biases. In addition, we used controls without any past psychiatric history from the community. Regardless of alcoholism, the inmate participants with ASPD were substantially different from the healthy community participants [75]. It is necessary to be aware of the possibility of false-positive results when comparing these phenotypes with super-normal controls [42].
Our results supported the notion that antisocial alcoholism is associated with the interaction between the 5-HTTLPR and 5-HT1B G861 polymorphisms. Additional studies to examine the 5-HTTLPR and 5HT1B G861C gene polymorphisms and their interaction effects with the dopaminergic gene in antisocial alcoholism are required.

Patient consent
Obtained.

Ethical approval
This study was approved by the Institutional Review Boards for the Protection of Human Subjects at the Tri-Service General Hospital and National Cheng Kung University Hospital.

Abbreviations
5-HTTLPR: Serotonin transporter; 5-HT1B: Serotonin 1 B receptor; ASPD: Antisocial personality disorder; AS-ALC: Antisocial alcoholism; AS-N-ALC: Antisocial non-alcoholism.

Competing interests
The authors declare no conflict of interests.

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Authors’ contributions
The author, TYW wrote the first draft of this manuscript and designed this study with the author RBL. The authors, SYL and Y-HC managed the statistical analyses. The authors, SLG, SHC, CHC and CLC managed the lab work. The authors, TYW, SYH, NST, IHL, TLY, YKY and RBL managed the patients recruitment. All authors read and approved the final manuscript.

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