

Association between serotonin transporter gene polymorphisms and heroin dependence: a meta-analytic study

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Background: Studies have examined the association between heroin dependence and serotonin transporter gene polymorphisms but yielded inconsistent results. The purpose of current study is to determine the overall effect of these polymorphisms on the risk for heroin dependence through a meta-analytic method.

Methods: A meta-analysis was conducted to examine the association of heroin dependence with two common polymorphisms of serotonin transporter gene, in the promoter (5-hydroxytryptamine transporter-linked promotor region [*5-httlpr*]) and intron 2 (a various number tandem repeat in serotonin transporter intron 2 [*STin2*]). Data from studies with *5-httlpr* (6 studies) and *STin2* (8 studies) were synthesized by random effects model.

Results: In the analysis, heroin dependence was found to be significantly associated with the S allele of *5-httlpr* (odds ratio [OR] = 1.22, 95% confidence interval [CI] = 1.08–1.41, $P=0.002$). The association between the S allele of *5-httlpr* and heroin dependence was significant in Caucasian subjects (OR = 1.37, 95% CI = 1.12–1.68, $P=0.003$), but not in non-Caucasian subjects. On the other hand, no association with *STin2* polymorphism was found (OR = 1.14, 95% CI = 0.91–1.42, $P=0.242$).

Conclusion: The results suggest an ethnic-specific effect of the *5-httlpr* polymorphism on the risk for heroin dependence, but the influence of the genetic variance in the patients with comorbidities or intermediate phenotypes of heroin dependence needs to be further examined.

Keywords: ethnicity, heroin, polymorphism, serotonin transporter, *STin2*

Introduction

Heroin dependence (HD) is associated with significant comorbidities (including viral hepatitis, human immunodeficiency virus infection, depression, and other substance abuse), serious socioeconomic consequences, and higher mortality rate.¹ Although its pathogenesis is complex, the drug dependence has its origins in both genetic and environmental risk factors.² However, the genetic factors contributing to the biological basis of HD have not yet been established. Previous literature has proposed that the serotonin (5-hydroxytryptamine, 5-HT) system, through modifying dopamine transmission, is involved in the deficiency in reward system in drug dependence.³ The study examining monoamine markers in the brains of chronic heroin users found decreased level of 5-hydroxyindoleacetic acid, a serotonin metabolite, in striatum.⁴ Neuroimaging studies have shown that the association between dopamine and serotonin transporter availability and addictive behaviors, indicating a role of serotonin in HD.^{5–7} Also, dysfunction of 5-HT system is associated with impulsivity, disordered behavioral inhibition, and depression, which are all frequently observed in drug addicts.⁸ Hence, in search

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of candidate genes for the susceptibility to HD, serotonergic pathway has received substantial attention in research.⁹

The 5-HT transporter (5-HTT), localized on the presynaptic membrane of serotonergic neurons, plays an important role in maintaining homeostasis of serotonin transmission by uptaking released serotonin from the synaptic cleft.¹⁰ The human 5-HTT protein is encoded by SLC6A4 gene, mapped to chromosome 17q11.1-q12.¹¹ The gene expression is regulated by a functional polymorphism in the 5' regulatory promotor region (termed *5-httlpr*, 5-hydroxytryptamine gene-linked polymorphic region), involving two common alleles that correspond to a 44-base pair deletion (S allele) or insertion (L allele).¹² The *5-httlpr* S allele was found to reduce efficiency of transcription, resulting in decreased expression of 5-HTT and serotonin uptake in lymphoblast cell lines.¹³ The other common polymorphic variant in SLC6A4 gene, located in intron 2, consists of a variable number of 17-bp repeats (9, 10, or 12-repeat) (serotonin transporter intron 2 [*STin2*]). Meta-analytic studies have indicated that serotonin gene is associated with the susceptibility of a few psychiatric disorders, such as the risk of developing violent suicide,¹⁴ affective disorders,¹⁵ antidepressant response,¹⁶ and schizophrenia.¹⁷

In the last few years, many studies have reported that association between heroin abuse and serotonin gene,^{18,19} but the evidence remains inconclusive. Some of them showed the association with 10-repeat allele in *STin2*²⁰ or with SS genotype in *5-httlpr*,²¹ but these positive findings were not replicated in other studies. The inconsistency may be due to insufficient statistical power in individual studies, poor phenotype definition, heterogeneity of subjects among different studies, or random error in the absence of a true association. To reconcile the discrepancy among studies, a meta-analysis was performed to determine the overall effect of these polymorphisms on the susceptibility to HD by synthesizing the results from all published articles.

Methods

Literature search

To identify studies eligible for this meta-analysis, a literature search was performed for all studies available up to April 2016 through PubMed at the National Library of Medicine using key words: (heroin OR opiate) AND (serotonin transporter OR SLC6A4 OR *5-httlpr* OR *STin2*). References from identified original studies and relevant review articles were carefully screened to extract studies not indexed in the electronic database.

Inclusion criteria of studies

Included studies had to meet all the following criteria: 1) used a case-control design; 2) compared the *STin2* or *5-httlpr* of serotonin transporter gene between patients with HD and control subjects; 3) reported sufficient original data for analysis; and 4) were independent from other studies. One study that included and reanalyzed a previously published dataset was not regarded as an independent study; in this situation, only the study consisting of a larger sample size was included in the meta-analysis.

Meta-analytic methods

Separate meta-analyses were conducted for examination of the association of HD with *5-httlpr* and with *STin2*. Hardy–Weinberg equilibrium was examined in all included studies. The strength of the association of HD with *5-httlpr* and with *STin2* was shown as the odds ratio (OR), whereby a greater value of OR indicates a direction of positive association of HD with *5-httlpr* S allele, or with the 10-repeat allele in *STin2*. The results of individual studies were pooled by a random effects model,²² by which ORs were pooled and a 95% confidence interval (CI) of OR was computed. The significance of the pooled OR was determined by the z-test.

A homogeneity test (Q statistics) was conducted to assess whether the group of effect sizes (ln[OR]) came from a homogeneous source.²³ A rejection of homogeneity suggests that there might be a systematic difference among included studies. If the pooled analysis showed significant association, a sensitivity test was performed to examine if any one study contributed significantly to the overall association. Publication bias was assessed by Egger's linear regression analysis²⁴ and funnel plots.

We performed meta-analysis by using Comprehensive Meta-Analysis, Version 2 (Biostat, Englewood, NJ, USA). Two-sided *P*-values <0.05 were considered statistically significant.

Results

Through computerized database search, studies from 11 papers were initially identified.^{20,21,25–33} Among them, 4 papers provided association data for both *5-httlpr* and *STin2* polymorphisms of 5-HTT gene.^{27–30} The studies by Saiz et al^{29,30} shared the same research subjects, hence only the latter was included in the current meta-analysis. The percentages of alleles and genotypes of control subjects in all included studies were consistent with Hardy–Weinberg equilibrium.

First, the percentage of the S allele of *5-httlpr* was compared between patients with HD and controls. Six studies,

Table 1 Association studies of heroin dependence and 44-bp repeats polymorphism in serotonin transporter gene promoter

Study	Ethnic groups	Diagnostic criteria	Subject category	N	Genotype frequency, N (%)		
					LL	LS	SS
Kotler et al ²⁵ (1999)	Non-Ashkenazi Jewish	DSM-IV	Patients	186	54 (29)	84 (45)	48 (26)
			Controls	217	53 (24)	114 (53)	50 (23)
Li et al ²⁷ (2002)	Chinese	DSM-IV	Patients	106	8 (8)	38 (36)	60 (57)
			Controls	190	17 (9)	60 (32)	113 (59)
Gerra et al ²¹ (2004)	Italian Caucasians	DSM-IV	Patients	101	27 (27)	44 (44)	30 (30)
			Controls	101	34 (34)	51 (51)	16 (16)
Szilagyi et al ²⁸ (2005)	Hungarian Caucasians	DSM-IV	Patients	52	15 (29)	25 (48)	12 (23)
			Controls	362	135 (37)	163 (45)	64 (18)
Saiz et al ³⁰ (2008)	Spanish Caucasians	DSM-IV	Patients	114	24 (21)	59 (52)	31 (27)
			Controls	420	124 (30)	203 (48)	93 (22)
Wang et al ³² (2016)	Chinese	DSM-IV	Patients	309	14 (5)	62 (20)	233 (75)
			Controls	301	8 (3)	99 (33)	194 (64)

Abbreviation: DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed.

with 2,459 subjects (868 patients and 1,591 controls), were included into the analysis (Table 1). While only two studies showed a significant association of the S allele with HD,^{21,32} other studies showed no association (Figure 1A). The homogeneity analysis showed a negative result ($\chi^2=4.72$,

$df=5$, $P=0.451$), which suggested that the effect sizes from individual studies were not statistically different and justified the use of fixed effects model. The pooled OR from these studies was 1.23 (95% CI=1.08–1.41, $P=0.002$) (Figure 1A), indicating a small but significant association between HD and

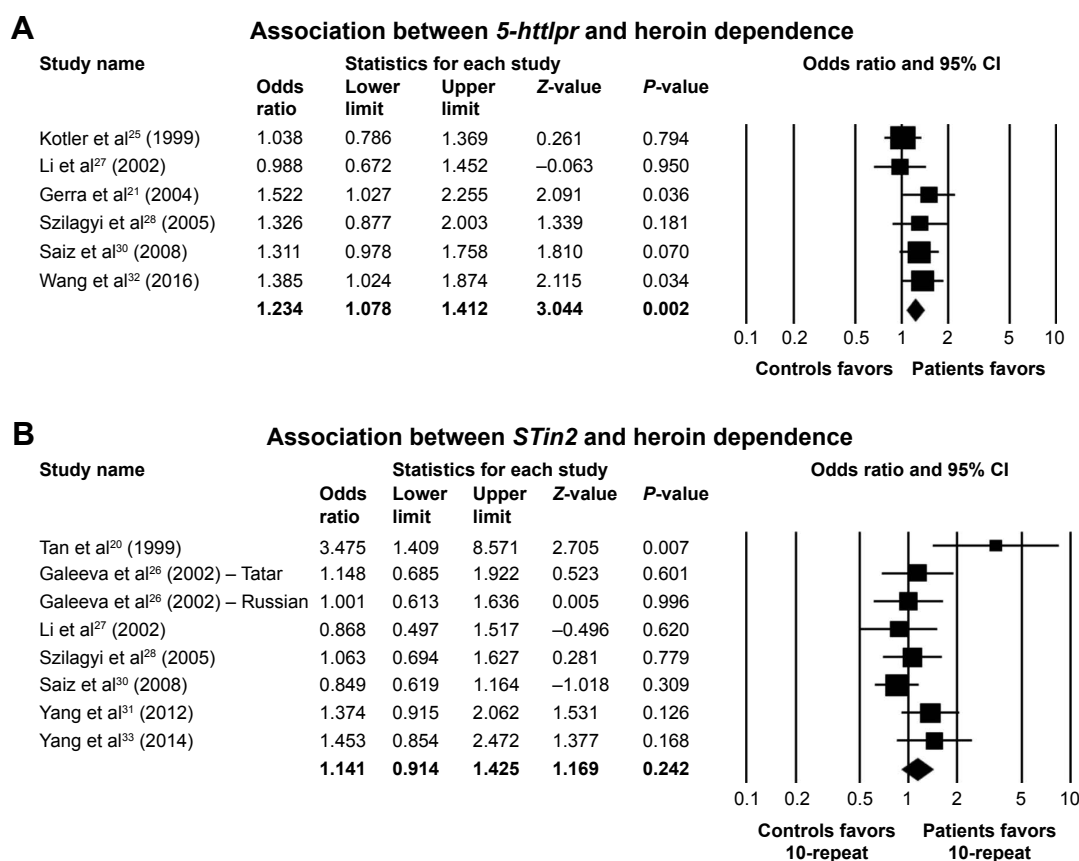


Figure 1 Odds ratios (ORs) and 95% confidence intervals (CIs) of individual studies and pooled data for all included association studies between heroin dependence and (A) the allelic distribution in serotonin transporter gene promoter polymorphism (5-HTTLPR), and (B) the allelic distribution in 17-bp variant number tandem repeats in intron 2 of 5-HTT gene (STin2).

Abbreviations: 5-HTTLPR, 5-hydroxytryptamine transporter-linked promoter region; STin2, serotonin transporter intron 2.

the S allele. In addition, sensitivity test found that the pooled OR remained significant after removing any one of the six included studies, indicating the significant association was not excessively influenced by any of them.

Although heterogeneity test of the included studies did not show significant difference in their effect sizes, ethnic difference may cause a differential distribution of genetic polymorphisms, evidenced by a significant increase in the L allele in the controls of three studies with Caucasian subjects^{21,28,29} than that in the others^{25,27,32} (56.8% vs 38.6%, $P<0.001$). So, the association of the *5-httlpr* polymorphism with HD was also examined separately in studies with Caucasian and non-Caucasian subjects. Analyses of Caucasian subjects showed HD was significantly associated with the S allele (OR = 1.37, 95% CI = 1.12–1.68, $P=0.003$). However, analyses of non-Caucasian subjects showed no association ($P=0.226$). These results indicated ethnic heterogeneity in genetic susceptibility of *5-httlpr* to HD.

Second, we compared allelic distribution of *STin2* polymorphism of serotonin transporter gene between HD patients and controls. Eight studies, with 2,731 subjects (1,329 patients and 1,402 controls), were included into the analysis (Table 2). The paper by Galeeva et al contained data from two distinct ethnic groups (Russians and Tatars),²⁶ which were regarded as two individual studies. Three different alleles, 9-repeat, 10-repeat, and 12-repeat, have been found among these studies. We omitted subjects carrying 9-repeat allele from our analysis because this allele was too rare (<1%) or there were none in individual studies. In our analysis, there was no association between HD and the 10-repeat allele (OR = 1.14,

95% CI = 0.91–1.42, $P=0.242$) (Figure 1B), nor was heterogeneity among the ORs of the studies ($\chi^2=11.91$, $df=7$, $P=0.104$). The result was still insignificant when limiting studies from either Caucasian or non-Caucasian subjects.

Finally, by using linear regression analysis, there is significant publication bias for the association studies of HD with *STin2* ($P=0.043$), but not with *5-httlpr* ($P=0.667$). The results were also shown in the funnel plots (*5-httlpr* in Figure 2A, *STin2* in Figure 2B).

Discussion

Current analysis showed association of HD with the S allele of *5-httlpr* polymorphism, whereas only two included reports showed such association (Figure 1).^{21,32} Expression of serotonin transporter protein was influenced by the *5-httlpr*, where the L allele produced the expression level much higher than the S allele.^{12,13} Moreover, 5-HTT binding sites and mRNA levels in the dorsal raphe, median raphe, and the substantia nigra of postmortem brains also varied by *5-httlpr* genotypes, with the highest levels from subjects with LL genotype rather than LS or SS genotype.³⁴ Hence, our result suggested a role of lower activity of 5-HTT protein in the pathogenesis of HD. This result is supported by recent studies suggesting a linkage between HD and markers on the long arm of chromosome 17,^{35,36} where the serotonin transporter gene resides. Similar association between the low-expression allele of *5-httlpr* and other addictive behaviors has been shown, such as alcohol dependence,³⁷ pathological gambling,³⁸ and excessive Internet use,³⁹ although not with cocaine dependence.⁴⁰

Table 2 Association studies of heroin dependence and 17-bp repeats polymorphism in intron 2 of serotonin transporter gene

Study	Ethnic groups	Diagnostic criteria	Subject category	N	Genotype frequency, N (%)		
					10/10	10/12	12/12
Tan et al ²⁰ (1999)	Chinese	DSM-IV	Patients	63	1 (2)	17 (27)	45 (71)
			Controls	72	0 (0)	7 (10)	65 (90)
Galeeva et al ²⁶ (2002)	Russians	Not stated	Patients	94	16 (17)	39 (41)	39 (41)
			Controls	53	7 (13)	26 (49)	20 (38)
Galeeva et al ²⁶ (2002)	Tatars	Not stated	Patients	81	13 (16)	32 (40)	36 (44)
			Controls	54	4 (7)	26 (48)	24 (44)
Li et al ²⁷ (2002)	Chinese	DSM-IV	Patients	115	1 (1)	19 (17)	95 (83)
			Controls	188	3 (2)	33 (18)	152 (81)
Szilagyi et al ²⁸ (2005)	Hungarian Caucasians	DSM-IV	Patients	52	5 (10)	29 (56)	18 (35)
			Controls	352	42 (12)	170 (48)	140 (40)
Saiz et al ²⁹ (2009)	Spanish Caucasians	DSM-IV	Patients	109	17 (16)	38 (35)	54 (50)
			Controls	415	64 (15)	177 (43)	174 (42)
Yang et al ³¹ (2012)	Chinese	DSM-IV	Patients	538	10 (2)	112 (21)	416 (77)
			Controls	173	2 (1)	27 (16)	144 (83)
Yang et al ³³ (2014)	Chinese	DSM-IV	Patients	277	10 (4)	57 (21)	210 (76)
			Controls	95	0 (0)	19 (20)	76 (80)

Abbreviation: DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed.

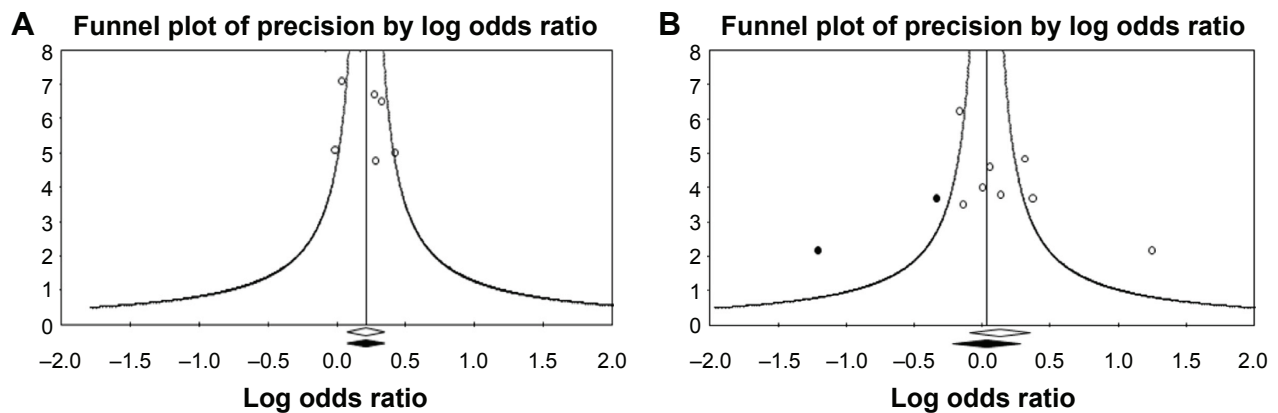


Figure 2 Funnel plots examining publication bias in studies examining association between heroin dependence and (A) the allelic distribution in serotonin transporter gene promoter polymorphism (*5-HTTLPR*), and (B) the allelic distribution in 17-bp variant number tandem repeats in intron 2 of 5-HTT gene (*STin2*). The plots describe the relationship between effect sizes (log odds ratio) of studies and their precisions (inverse of standard error). The empty dots and diamond represent included studies and pooled effect size, respectively. The black dots represent imputed studies meant to balance skewed distribution of included studies in the funnel plot. The black diamond represents pooled effect size when considering imputed studies.

Abbreviations: *5-HTTLPR*, 5-hydroxytryptamine transporter-linked promotor region; *STin2*, serotonin transporter intron 2.

However, this effect was complicated by the later finding that an A/G single nucleotide polymorphism in the L allele of *5-HTTLPR* contributed to the functional variation of the gene and was significantly associated with obsessive-compulsive disorder.⁴¹ Because L(G) and S alleles gave almost equivalent effect in gene expression, but lower than that of the L(A) allele. It provided functional triallelic variability that was previously unidentified. Subjects with LL or LS genotype in previous studies may carry the lower-expressing L(G) allele, thus may obscure a true effect of *5-HTTLPR* on gene expression.

Although this study supports the role of the *5-HTTLPR* polymorphism in the susceptibility to HD, caution needs to be taken to explain the results. HD is a highly heterogeneous disorder in its etiologies, clinical symptoms, and treatment response, which can be influenced by personality traits, or comorbid mental illnesses. Difference in these intermediate phenotypes may also result from genetic variability. Some studies have examined the genetic susceptibility to clinical characteristics and personality traits in heroin addicts. For example, Gerra et al found that SS genotype was significantly associated with violent offenders, but not with non-offenders with HD. Also, HD subjects with SS genotype showed higher levels of suspiciousness and negativism, compared to LL subjects.²¹ In addition, higher harm avoidance trait was found in HD patient groups, and was also associated with the interaction between *DRD2*, *5-HTTLPR*, and *ALDH2* genes.⁴² In the study of Galeeva et al, as a whole, no association between HD and *STin2* polymorphism was found, but they found heterozygous 10-/12-repeats genotype was protective from early-onset opiate abuse.²⁶ Moreover, a recent report showed a synergistic effect of a 5-HT_{2A} polymorphism and

both *5-HTTLPR* and *STin2* on the risk of HD.³⁰ Whether the gene variant is associated with only a part of HD patients or with certain personality traits that predispose individuals to substance abuse needs further clarification.

In addition, population stratification is one important bias of association studies, especially in those carried out using population-based design. To overcome this possible bias, we stratified the studies by the primary ethnicity of the study sample and found significant association only in Caucasian samples. Such ethnicity-specific association was also observed in a recent meta-analysis of genetic studies of obsessive-compulsive disorder.⁴³ Difference in allelic distribution in multicultural populations was supported in the association of the serotonin transporter gene with substance use disorder.⁴⁴ However, addictive behaviors, such as HD, were shaped by environmental risk factors, which can be different among races. Family-based association studies can be performed to decrease the confounding effect related to population stratification.

Conclusion

In summary, although revealed significant association between HD and the S allele, the interpretation of the results was limited by small amount of included studies. Also, the existence of prevalent psychiatric comorbidities of in patients with HD may complicate the genetic effects on this disorder. These polymorphisms may play a more significant role in some endophenotypes or a subpopulation of the patients. Larger and more carefully designed studies are required to validate the role of *5-HTTLPR* polymorphism in the susceptibility in HD.

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Author contributions

PY Lin designed the study, analyzed and interpreted data, wrote the initial draft, and finalized the manuscript. YS Wu wrote the initial draft and revised the manuscript. Both authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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