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The Serotonin Transporter Gene and Risk for Alcohol Dependence: A Meta-Analytic Review

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Abstract

Previous studies have implicated a relationship between particular allelic variations of the serotonin transporter gene (5HTTLPR) and alcohol dependence. To provide a current estimate of the strength of this association, particularly in light of inconsistent results for 5HTTLPR, we conducted a meta-analytic review of the association between 5HTTLPR and a clinical diagnosis of alcohol dependence. Of 145 studies initially identified, 22 (including 8,050 participants) met inclusion criteria. Results indicated that there was a significant albeit modest association between alcohol dependence diagnosis and the presence of at least 1 short allele (OR = 1.15, 95% CI = 1.01, 1.30, $p < .05$). Slightly more robust results were observed for participants who were homogeneous for the short allele (OR = 1.21, 95% CI = 1.02, 1.44, $p < .05$). These results were unrelated to sex and race/ethnicity of participants; however, the effect size was moderated by study sample size and publication year. Additionally, the fail-safe N analysis indicated potential publication bias. Therefore, although our review indicates that there is a significant association between 5HTTLPR and alcohol dependence diagnosis, this result should be interpreted with caution.

Keywords

Serotonin transporter gene; 5HTTLPR; Alcohol Dependence

1. Introduction

Despite the large body of research dedicated in recent years to identifying genetic risk factors for psychiatric disorders, results have been characterized by modest effect sizes and limited replication (e.g., Allen et al., 2008; Risch et al., 2009). For example, in a meta-analytic review of 14 studies capturing over 14,000 participants, Risch and colleagues (2009) failed to confirm the landmark Caspi and colleagues (2003) study identifying an interaction between the serotonin transporter gene (5HTTLPR) and life stress on the risk for depression. Instead, Risch et al. (2009) noted a replication failure among studies subsequent to Caspi et al. (2003); across studies, Risch et al. (2009) found no consistent evidence for either a direct relationship between 5HTTLPR and depression, or an interaction between the gene and life events on the risk for depression. This recent finding underscores the importance of quantitative analyses to evaluate the magnitude of effect sizes across studies. In the present study, we conducted an effect size analysis of the association between the serotonin transporter gene and alcohol dependence.

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In the search for potential genetic risk factors for substance dependence, much work has focused on genes involved in neurotransmitter regulation. For example, associations with alcohol dependence have been established for the dopamine transporter gene (Kohnke et al., 2005), the D2 dopamine receptor gene (Smith et al., 2008), and the monoamine oxidase A gene (Contini et al., 2006). Given the relevance of serotonin to alcohol use and abuse (see Tabakoff and Hoffman, 2004), the serotonin transporter gene has also received substantial research attention.

A common polymorphism at the promoter region of serotonin transporter gene influences the reuptake of serotonin, thereby regulating its concentration in the synaptic cleft. Among individuals with one or more copies of the short allele at this location, serotonin reuptake is attenuated, resulting in increased availability of serotonin in the synapse and downregulation of post-synaptic binding sites (see Lesch et al., 1996). Allelic variation at 5HTTLPR has been implicated in alcohol use disorders relative to several domains, such as alcohol craving (Bleich et al., 2007) and relapse (Pinto et al., 2008); however, results have been mixed, with studies also failing to find an association between such variables and 5HTTLPR (e.g., Kohnke et al., 2006; Rasmussen et al., 2009). A more consistent finding in the literature has been the link between 5HTTLPR and alcohol dependence diagnosis. A meta-analytic review of 17 studies (including 3,489 alcohol dependent and 2,325 control participants) found support for a significant association between this polymorphism and diagnosis, with alcohol dependent participants being 18% more likely to possess at least 1 short (s) allele relative to control participants (Feinn et al., 2005). Given these initial promising results for an association between 5HTTLPR and alcohol dependence, the number of studies in this area has almost doubled since the publication of the Feinn and colleagues (2005) review. The goal of the current study was to attempt to replicate the findings of Feinn and colleagues (2005), by updating their review with the studies published subsequent to their analysis, and to systematically assess for publication bias.

2. Methods

2.1. Search Strategy

The identification of articles began with selecting the published studies analyzed by Feinn et al. (2005). To capture studies published since that time, the search engines PubMed, PsychInfo, and the Cochrane library were examined through March 2009 using the following search terms in combination: *serotonin transporter gene*, *5HTTLPR*, *SCL6A4*, *alcohol dependence*, *alcohol use disorders*, and *alcoholism*. Finally, the reference section of each of the relevant publications identified through these literature searches was reviewed to identify any additional studies that would be informative to the review.

2.2. Study Selection and Data Abstraction

Studies identified through these methods were then selected based on the following criteria: (a) inclusion of individuals diagnosed with alcohol dependence according to *Diagnostic and Statistical Manual 3rd Edition, Revised (DSM-III-R)*; (American Psychiatric Association, 1987) or *DSM-IV* (American Psychiatric Association, 1994) criteria; (b) inclusion of a control group; and (c) results of genotyping did not violate Hardy-Weinberg equilibrium (HWE). Additionally, studies were included only if sufficient information to determine the number of participants with each genotype in both groups could be extracted from data presented in the article, or if such data was provided by study authors upon request. Data were abstracted from the articles by one of the authors (RKM) and independently checked for accuracy.

2.3. Study Characteristics

Only case-control studies were evaluated in order to maximize the consistency of studies and to facilitate comparison between groups. Several other variables were evaluated to determine whether they moderated the association between disorder status and presence of any s allele. These included study sample size, sex (expressed as % men in each study), and race/ethnicity (defined as % non-Caucasian).

2.4. Data Synthesis

The primary outcome measure identified for this analysis was the presence or absence of any s allele, consistent with past evaluations in this area (e.g., Feinn et al., 2005). An odds ratio (OR) was used as the effect size measure for this analysis because variables were dichotomous in nature. ORs were calculated for each study using the frequencies of s alleles in the alcohol

dependent and control groups, based on the following formula: $OR = \frac{p/(1-p)}{q/(1-q)}$, where p represents the proportion of alcohol dependent participants with at least 1 s allele and q represents the proportion of control participants with at least 1 s allele. Thus, the ORs reported reflect the ratio of the likelihood of possessing at least one s allele in the alcohol dependent group to the likelihood of possessing at least one s allele in the control group (i.e., an OR greater than 1 reflects a higher likelihood of possessing an s allele in the alcohol dependent group). Random-effects models were used for effect size estimates. The use of a random-effects model is appropriate when the aim is to draw inferences that may generalize to a population of studies larger than the sample of studies used in the analysis (Hedges and Vevea, 1998).

We evaluated publication bias in several ways. First, we utilized the “fail-safe N” method (Rosenthal, 1991; Rosenthal and Rubin, 1988) to determine the number of additional studies with a null result needed to reduce the overall effect size to non-significance. Rosenthal (1991) suggested that if the fail-safe N exceeds 5 multiplied by K (the number of studies in the meta-analysis) + 10, the results of the meta-analysis can be interpreted as robust. Second, we conducted a visual inspection of the funnel plot to evaluate symmetry relative to the mean effect size (with greater symmetry reflective of a lesser likelihood of publication bias). Finally, year of publication was evaluated as a potential moderator. Analyses were completed using the standard software program *Comprehensive Meta-Analysis* (Version 2; Borenstein et al., 2005).

3. Results

3.1. Trial Flow

Figure 1 details the study selection process. Our search methods yielded a total of 145 potential studies. Of these, 22 met our inclusion criteria (15 were included in the Feinn et al., 2005 paper). Two studies included in the Feinn and colleagues meta-analysis (Edenberg et al., 1998; Lichtermann et al., 2000) were not included in the analysis because they used the transmission disequilibrium test (TDT) methodology, which may compromise the ease of comparison to the majority of studies using case-control methods. In addition, two studies published since the Feinn et al. analysis were excluded because they also did not use the case-control method (i.e. Samochowiec et al., 2006, used the TDT, and Dick et al., 2007, used the Pedigree Disequilibrium Test). Notably, these studies reported mixed results, with Edenberg et al. (1998), Dick et al. (2007), and Samochowiec et al. (2006) reporting no association and Lichtermann et al. (2000) reporting a strong association between the presence of any s allele and alcohol dependence. One study (Schuckit et al., 1999) that was also included in the Feinn et al. paper, and a follow-up from this study (Hu et al., 2005), pre-selected all participants based on an estimation of these individuals being at high risk for the development of alcohol problems, and those who did develop alcohol dependence were compared to those who did

not. Given that the control group used in these studies was not a true healthy group, these two studies were excluded. Another study (Kweon et al., 2005) reported a violation of HWE in the alcohol dependent group and thus was excluded. Other studies were excluded because they lacked a healthy control group or did not evaluate alcohol dependence diagnosis. Of the remaining 22 identified studies, data was extracted as described above. In cases where insufficient data were available to conduct analyses, corresponding authors were contacted and the needed information was successfully acquired.

3.2. Quantitative Data Synthesis

The 22 studies included in the final analysis are described in Table 1. Odds ratios for the association between any s allele and alcohol dependence diagnosis across studies ranged from 0.67-2.23 (see Figure 2). Evaluation of the overall effect size indicated that there was a significant association between alcohol dependence diagnosis and the presence of at least 1 s allele (OR = 1.15, 95% CI = 1.01, 1.30, $p < .05$). Similar results of a slightly greater magnitude were noted for comparison of participants who were homozygous (s/s) for the s allele (OR = 1.21, 95% CI = 1.02, 1.44, $p < .05$).

Evaluation of publication bias suggested that only 9 studies reporting a null effect would be sufficient to shift the observed effect to a non-significant level. A fail-safe N of 9 is substantially lower than the number of studies needed for a robust effect ($n = 120$) according to Rosenthal (1991). The funnel plot is presented in Figure 3. The plot appears to be roughly symmetrical by visual inspection. Additionally, there was a significant moderating effect of year of publication ($\beta = -0.04$, $SE = 0.02$, $p < .05$), reflecting a greater number of studies showing null results published in recent years. Indeed, the effect size across studies published since the Feinn et al., (2005) meta-analysis did not reflect a significant association between 5HTTLPR and alcohol dependence (OR = 0.93, 95% CI = 0.76, 1.14, $p = .48$).

Moderation analyses identified no effect of sex as defined by percent of men in the study ($\beta = 0.00$, $SE = 0.00$, ns), and no effect of race/ethnicity as defined by percent of non-Caucasian participants ($\beta = 0.001$, $SE = 0.0$, ns). Study sample size did significantly moderate the effect ($\beta = -0.001$, $SE = 0.00$, $p < .05$), with larger studies demonstrating smaller effects relative to smaller studies.

4. Discussion

This study evaluated the magnitude of the association between allelic variation at 5HTTLPR and alcohol dependence in 22 case-control studies. Findings indicated a significant but modest association, characterized by a 15% greater likelihood of the presence of at least 1 s allele among individuals with alcohol dependence relative to control participants. This finding provides an estimate of the strength of results from a prior meta-analysis (Feinn et al., 2005) and extends these results to include 7 additional studies. However, evaluation of publication bias indicated that only 9 unpublished studies with null results would be necessary to reduce the magnitude of this result to non-significance. Visual inspection of the funnel plot did not indicate bias; however, a significant moderating effect of year of publication and study sample size suggest that publication bias may be an issue relative to this association. Thus, despite the presence of a significant effect across 22 studies, these results should be interpreted with caution.

The small magnitude of this finding is consistent with findings in the area of affective disorders, where evaluations of this association have yielded mixed or weak results when evaluating disorder status (e.g., presence of depression; Risch et al., 2009) or trait characteristics (e.g., trait anxiety) alone (Munafo et al., 2005). As noted, a recent meta-analysis suggested that the effect of the interaction between 5HTTLPR and stressful life events on the risk of depression

was not consistently replicated across studies and that evaluation of overall effect sizes did not support this interaction effect (Risch et al., 2009). However, studies have found far more robust associations with 5HTTLPR for more distinct or clearly defined affective variables, such as amygdala activation (Dannlowski et al., 2008; Furmark et al., 2004; Hariri et al., 2002; Heinz et al., 2005; Smolka et al., 2007), anxiety sensitivity (Stein et al., 2008), HPA axis activation (Gotlib et al., 2008), and attentional vigilance to threat (Beevers et al., 2007; Hayden et al., 2008). This pattern of results highlights the importance of evaluating more elemental characteristics (e.g., amygdala response to emotional stimuli) as modulators of the association between 5HTTLPR and disorder status. In short, there may be a variety of important pathways to alcohol dependence, and the 5HTTLPR gene may be linked with a risk factor for one of these pathways, such as greater affective intolerance (see Stein, Schork, & Gelernter, 2008). Indeed, Lesch (2005) argued that affective variables that are influenced by serotonin, such as reactivity to stress and poor emotion regulation, may be key components of the susceptibility for alcohol dependence.

Alternatively, specific comorbidities or markers of overall severity may moderate the strength of the relationship between 5HTTLPR and alcohol dependence. However, within the study of alcohol dependence, there has been inconsistency in findings of the role of comorbid depression reflected the overall literature (Reich et al., 2009), with an association between the s allele and comorbid depression in some (Gokturk et al., 2008; Marques et al., 2006; Nellissery et al., 2003) but not other studies of alcohol dependent samples (Gorwood et al., 2000). Such inconsistency may imply that diagnostic status is the wrong level of analysis for whatever risk the s allele may confer. Further evaluation of emotion regulation factors (e.g., amygdala activation, HPA axis activation, anxiety sensitivity, and attentional vigilance) may be a much more fruitful direction for future research.

There are several limitations to the present study. First, only published studies were included in the review and thus studies that have not been published due to null findings are not included. Given the low fail-safe N found in this study, the presence of a “file drawer” effect could substantially change the results of this analysis. In addition, differences in methodology precluded the combination of case-control and family-based studies and thus several studies examining the association between 5HTTLPR and alcohol dependence were excluded from the present study due to use of family-based designs (Dick et al., 2007; Edenberg et al., 1998; Lichtermann et al., 2000; Samochowiec et al., 2006).

In summary, this evaluation of effect size across studies of the association between 5HTTLPR and alcohol dependence diagnosis found that those with this diagnosis had a 15% greater likelihood of possessing at least 1 s allele relative to control participants. This effect should be interpreted with caution given the indication that a small number of negative findings could result in the reduction of this finding to non-significance. These results are similar to those found in a previous analysis (Feinn et al., 2005), in which alcohol dependent groups were 18% more likely to possess at least 1 s allele. Given the continued finding of a modest relationship between 5HTTLPR and alcohol dependence, future research on potential modulators of this association, such as affective variables, is of particular importance.

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Figure 1.
Study selection process

Figure 2.

Odds ratios of the association between 5-HTTLPR alleles and alcoholism

Figure 3.
Funnel plot of precision by Log odds ratio

Table 1
Sample Characteristics for Studies of the Association of 5-HTTLPR Alleles and Alcohol Dependence

Study	Year	Population	% Male (AD group)	Mean age of cases (S.D.)	Total Sample Size	s allele frequency (AD group)	s allele frequency (controls)
Choi et al.	2006	Korean	100	43.5 (7.5)	234	72	68
Foley et al.	2004	Caucasian			182	50	75
Gelernter et al.	1997	EA	77.8		290	75	42
Gokturk et al.	2008	Caucasian	0		741	65	418
Gorwood et al.	2000	French	100	43.6 (10.5)	171	77	37
Hallikainen et al.	1999	Finnish	100	30.1 (8.4)	105	36	28
Hammoumi et al.	1999	French	60	43.57 (1.43)	140	68	18
Ishiguro et al.	1999	Japanese	92.2	52.2 (9.4)	456	160	282
Johann et al.	2003	German	83	43.1	534	227	151
Kohnke et al.	2006	German			309	140	59
Konishi et al.	2004	MA	100	39 (10.8)	451	168	188
Kranzler et al.	2002	EA, AA	74.6		706	343	177
Lee et al.	2009	Korean	100	39.05 (10.65)	173	92	73
Marques et al.	2006	Brazilian	100		332	82	159
Matsushita et al.	2001	Japanese	100	50.5 (9.7)	967	671	262
Mokrovic et al.	2008	Croatian	100	32 (6)	341	32	180
Nelissery et al.	2003	Caucasian, AA	68	40.8 (9.3)	615	140	115
Philibert et al.	2008	Caucasian, AA	50		192	18	107
Preuss et al.	2001	German		41 (8.3)	280	112	76
Sander et al.	1998	German	86	42.2 (9)	531	216	135
Stoltenberg et al.	2002	Caucasian	100		44	24	8
Thompson et al.	2000	European			256	88	74