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The Cys Allele of the *DRD2* Ser311Cys Polymorphism has a Dominant Effect on Risk for Schizophrenia: Evidence from Fixed- and Random-Effects Meta-Analyses

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RUNNING HEAD: DRD2 and Schizophrenia Meta-Analyses

ABSTRACT

Previously we derived independent estimates of the effect of the dopamine D2 receptor (*DRD2*) Ser311Cys polymorphism on risk for schizophrenia using fixed- and random-effects meta-analyses. Both analyses identified a significant association between the Cys allele and schizophrenia, but neither included all available data. Furthermore, genotype data were not evaluated in either analysis, thus precluding any determination of the mode of inheritance. The present study was conducted to resolve discrepancies between the existing meta-analyses and provide more comprehensive and accurate estimates of the nature and magnitude of the influence of the Ser311Cys polymorphism on risk for schizophrenia. All discrepancies between the two sets of previously meta-analyzed studies were identified and resolved to the mutual satisfaction of the authors, and the final dataset was analyzed independently by fixed- and random-effects meta-analyses. A total of 27 samples, comprising 3707 schizophrenia patients and 5363 control subjects, were included in the analyses of allelic association, while smaller numbers of studies and subjects were included in each of the genotypic association analyses. A significant effect of the Cys allele was observed under both fixed-effects (odds ratio [OR] = 1.4; $p = 0.002$) and random-effects (OR = 1.4; $p = 0.007$) models. Cys/Ser heterozygotes were at elevated risk for schizophrenia when compared to Ser/Ser homozygotes (fixed- and random-effects ORs = 1.4, ps ≤ 0.005), but Cys/Cys homozygotes were at no elevated risk relative to heterozygotes (ORs = 1.0, ps ≥ 0.948). There was no evidence of heterogeneity, excessive influence of any single study, or publication bias in any of the analyses, suggesting that the effect of this DRD2 polymorphism on schizophrenia risk is reliable and uniform across populations, and that our estimates of its magnitude are robust and accurate.

KEYWORDS: association, dopamine D2 receptor, gene, meta-analysis, polymorphism

The dopamine neurotransmitter system in general, and the dopamine D2 receptor in particular, has been implicated repeatedly in the pathophysiology of schizophrenia by multiple lines of evidence over the course of several decades (Abi-Dargham 2004; Seeman 2002). As such, the gene coding for the dopamine D2 receptor (*DRD2*) was among the earliest functional candidate genes to be tested for allelic association with the illness. In an expanded sample of the subjects initially studied by Itokawa et al. (1993), Arinami et al. (1994) published the first significant evidence of an effect of the Cys allele of the *DRD2* Ser311Cys polymorphism on risk for schizophrenia. The magnitude of this effect was quite sizable (odds ratio [OR] = 3.1; 95% confidence interval [CI] = 1.4-6.7; $p = 0.004$) and the polymorphism also was shown to alter the physiology and function of the receptor (Itokawa and others 1993); thus, this promising association quickly became the object of widespread replication efforts, most of which failed. In fact, only two of the 23 subsequent association studies of schizophrenia and the *DRD2* Ser311Cys polymorphism found a significant relationship (Jonsson and others 2003; Serretti and others 2000). As a consequence, the initial finding of association became widely regarded as a type-I inferential error (Verga and others 1997); however, it remained unclear if these failed replication attempts were due to the low power of individual studies, etiologic heterogeneity across samples, or random error in the absence of a true effect.

In an attempt to resolve these uncertainties, we previously derived independent estimates of the effect of the *DRD2* Ser311Cys polymorphism on risk for schizophrenia using fixed- and random-effects meta-analyses (Glatt and others 2003; Jonsson and others 2003). Within the collective body of literature, both analyses identified a significant association between the Cys allele and schizophrenia that did not appear to be attributable to either publication bias or the effect of any single study [*e.g.*, the initial significant result obtained by Arinami et al. (1994)].

However, some uncertainties persisted, as the two meta-analyses differed slightly in their composition (Levinson 2005), and neither provided estimates of the nature and magnitude of genotypic associations between this polymorphism and schizophrenia. The present study was therefore conducted to reconcile discrepancies between the existing meta-analyses, and to provide more comprehensive and accurate estimates of the influence of the Ser311Cys polymorphism on risk for schizophrenia.

Detailed methods for literature searching, study identification, data extraction and coding, and statistical modeling are described elsewhere (Glatt and others 2003; Jonsson and others 2003). Briefly, MEDLINE citations (January, 1966-July, 2005) were surveyed with "schizophrenia" and "DRD2" as keywords. The retrieved abstracts were read to identify studies that examined the allelic association between a polymorphism within the *DRD2* gene and schizophrenia. Studies of this type were then read in their entirety to assess their appropriateness for inclusion in the meta-analysis. All references cited in these works were also reviewed to identify additional works not indexed by MEDLINE.

Several discrepancies were identified between the two independently retrieved sets of studies. These arose almost exclusively from differences in the handling of suspected non-independence of samples used in multiple publications; however, limited electronic or other access to selected articles also contributed to these discrepancies. Wherever possible, the authors of the original studies were contacted to clarify any uncertainties regarding potential overlap with other studies in the literature (and/or to obtain genotypic information when such was not provided within the published work). If the authors could not be contacted and the independence of studies could not be determined unambiguously, we conservatively included only one of the studies in question (*i.e.*, generally the latest and/or largest study). Ultimately, all discrepancies

between the two independently retrieved sets of studies were resolved to the mutual satisfaction of both authors (Table 1). Allele and genotype frequency data were then extracted from each study (Table 2), and fixed-effects and random-effects meta-analytic methods were conducted on these data using Stata SE (version 8.2; StataCorp.; College Station, TX; U.S.A.).

A total of 27 samples, comprising 3707 schizophrenia patients and 5363 control subjects, were included in the analyses of allelic association. A significant effect of the Cys allele on schizophrenia risk was observed under both fixed-effects (OR = 1.38, 95% CI = 1.13-1.68, z = 3.13, p = 0.002) and random-effects (OR = 1.36, 95% CI = 1.09-1.70, z = 2.72, p = 0.007) models. A test for heterogeneity within the dataset was not significant ($\chi^2_{(28)}$ = 28.28, p = 0.345), suggesting that the effect of the Cys allele was uniform across samples. To determine if the significant pooled ORs observed were excessively influenced by the results of any particularly influential study (*i.e.*, studies with large sample or effect sizes), each study was removed sequentially from the dataset and the pooled ORs were then recalculated without that study's data. Pooled ORs derived from fixed-effects meta-analyses varied only slightly (1.30-1.43) with the removal and subsequent replacement of each of the 27 studies, and all remained significant as none of the 95% CIs around these pooled ORs contained a value of 1.0. Similarly, removal and subsequent replacement of each study from the calculation of the random-effects pooled OR produced values between 1.30 and 1.41, and no 95% CIs that included 1.0.

To determine the mode of inheritance of the Cys allele and its effect on schizophrenia risk, we performed two sets of comparisons of genotype frequencies between schizophrenia cases and control subjects. The first was a contrast of the frequency of Cys/Ser heterozygotes and Ser/Ser homozygotes among 3461 schizophrenia patients and 5158 control subjects from 26 samples. Cys/Ser heterozygotes were at elevated risk for schizophrenia when compared to

Ser/Ser homozygotes within either a fixed-effects (OR = 1.38; 95% CI = 1.11-1.72; $z = 2.91$; $p = 0.004$) or random-effects (OR = 1.39, 95% CI = 1.11-1.74, $z = 2.84$, $p = 0.005$) framework. No significant evidence of heterogeneity was observed among the studies ($\chi^2_{(25)} = 22.81$, $p = 0.588$). As with the allelic association meta-analyses, sequential removal and replacement of each study from the calculation of the pooled OR had little effect on its value (which ranged from 1.33-1.45), and none of the 95% CIs around these pooled ORs contained a value of 1.0.

Due to the relatively low frequency of the Cys allele in the studied populations [range: 1-6% (Glatt and others 2003)], Cys/Cys homozygotes were rare. Thus, far fewer samples ($n = 7$) and subjects (schizophrenia patients: $n = 76$; control subjects: $n = 114$) were included in the second set of genotype-based meta-analyses, which compared the frequency of Cys/Ser heterozygotes and Cys/Cys homozygotes in the two groups. Cys/Cys homozygotes were not at any elevated risk relative to Cys/Ser heterozygotes under either the fixed-effects (OR = 1.03, 95% CI = 0.35-3.05, $z = 0.06$, $p = 0.950$) or random-effects (OR = 0.96, 95% CI = 0.28-3.34, $z = 0.06$, $p = 948$) models. No significant evidence of heterogeneity was observed among the studies ($\chi^2_{(6)} = 3.52$, $p = 0.742$), and no single study was solely responsible for the non-significance of the pooled OR (95% CIs computed after sequential removal and replacement of each study all included a value of 1.0). In combination with the finding of a significant difference in risk between Ser/Ser homozygotes and Cys/Ser heterozygotes, this result could indicate that the Cys allele has a dominant effect on risk for schizophrenia; however, the failure to detect a difference in risk between Cys/Ser heterozygotes and Cys/Cys homozygotes might also be a function of the lower power of this contrast due to the smaller sample size and number of studies.

In light of the widely recognized correlation between the statistical significance of a study's main result and its probability of acceptance into the peer-reviewed literature (Begg and

Berlin 1989; Colhoun and others 2003), we performed formal tests for "publication bias" within each meta-analyzed dataset using the method of Egger et al. (1997). Briefly, this method regresses the standard normal deviate (SND) of each observed OR (z) on its precision (POR, the inverse of the standard error of the OR). Since POR increases with sample size, the regression of z on POR should run through the origin in the absence of bias (*i.e.*, small samples with low precision have large standard errors and small SNDs, whereas large samples with high precision have small standard errors and large SNDs). The slope (b) of the regression line indicates the size and direction of association and, in the presence of bias, the intercept of the regression (a) will be significantly different from zero, as determined by the t test. Because the four samples assessed by Spurlock et al. (1998) were published simultaneously in the same report, those samples were pooled for the analyses of publication bias. Due to the relatively low power of this test and the high cost of failing to detect publication bias, we conservatively set $\alpha = 0.10$ for these analyses, per the authors' recommendation (Egger and others 1997). Despite this, no significant evidence of publication bias was observed in any of the datasets (all ps ≥ 0.214). A representative publication bias plot (that for the allele frequency dataset) is provided in Figure 1.

In summary, these results indicate that the Cys allele of the Ser311Cys polymorphism of DRD2 increases risk for schizophrenia, and appears to exert this influence in a dominant manner. Fixed- and random-effects models yielded very similar results, although the fixed-effects models predictably yielded smaller confidence intervals due to the assumption of a uniform effect across studies. In this collection of studies, where no evidence of between-study heterogeneity was detected, this assumption may be valid; however, caution must be used when selecting a model for meta-analyzing other datasets that are not as homogeneous. In addition to an absence of heterogeneity, there was also no evidence of excessive influence of any single study or

publication bias in any of the analyses. The possibility that the significant effects observed here are the result of publication bias is made even more remote by considering that 21 of these 24 studies (88%) were accepted into the peer-reviewed literature as negative reports presenting no significant evidence of an association between this DRD2 polymorphism and schizophrenia. These findings suggest that the effect of this DRD2 polymorphism on schizophreniarisk is reliable and uniform across populations, and that our estimates of its magnitude are robust and accurate. Whereas the current results likely could not have been identified in the past without meta-analysis due to the relatively small pooled effect size of the polymorphism and the restricted sample sizes of individual studies, these effects can be evaluated more powerfully in the near future in the much larger case-control datasets now being assembled by several groups. These efforts may then validate the Cys allele of this DRD2 polymorphism as a recognized risk factor for the illness.

Several limitations and potential pitfalls of meta-analysis are also illustrated by this study. In particular, this joint effort was made necessary due to existing ambiguities in the presentation of methods and results in the literature, which can severely threaten the validity of any meta-analysis. The most common problem encountered has been in regard to the independence of published studies. Many authors of genetic studies have adopted the practice of publishing their results incrementally, with a smaller pilot study being followed by a larger-scale study in the same population; however, the degree of overlap between the two studies is often not made explicit. For the present meta-analyses, whenever such overlap was suspected (most often due to similar authorship on multiple studies) and could not be disproved by contacting the authors or otherwise, we included only one of the studies in question; however, this is not the optimal resolution, since some potentially independent and eligible studies may have been unnecessarily

excluded. To avoid this situation, authors of new genetic association studies should be urged to acknowledge other related work that they have published, and explicitly state the degree of overlap with that prior work, if any. In addition, to facilitate the inclusion of their data in future meta-analyses, authors should be encouraged to present actual frequencies of each genotype and allele in both cases and controls or, if space is at a premium, to present genotype frequencies which can then be used to unambiguously determine allele frequencies. Advances in high-throughput genotyping, the establishment of genetic association databases [*e.g.*, the Genetic Association Database (Becker and others 2002)], and an increased capacity and propensity toward data-sharing in the psychiatric genetics community all ported an increase in the use of meta-analysis in the future. The establishment of such standards for presenting genetic association data will facilitate these efforts and thus make possible the identification of reliable risk genes for schizophrenia and many other psychiatric disorders.

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Table 1. Studies Differently Assessed in Three Different Meta-Analyses

Study	Jönsson et al., 2003	Glatt et al., 2003	Present study	Notes
Arinami et al., 1994	Included*	Included	Included	See footnote.
Arinami et al., 1996	Included*	Included	Included	Among patients, 258 Ser alleles were used in Jönsson et al. (2003) and the present study. Glatt et al. (2003) used 260 Ser alleles based on a typographic error in the
Fujiwara et al., 1997	Not included	Included	Included	Study was unavailable to Jönsson et al. (2003).
Gejman et al., 1994	Included	Included	Included	Among controls, 246 Ser alleles were used in Jönsson et al. (2003) and the present study. Glatt et al. (2003) used 222 Ser alleles.
Goldman et al., 1997	Included	Not included	Not included	Subjects had a primary diagnosis of alcohol abuse or dependence, not schizophrenia.
Harano, 1997	Included	Included	Included	Among patients, 132 Ser alleles were used in Glatt et al. (2003) and the present study. Jönsson et al. (2003) used 130 Ser alleles.
Itokawa et al., 1993	Not included	Included	Not included	Complete overlap with Arinami et al. (1994) was verified by the corresponding author.
Jönsson et al., 2003	Included	Not included	Included	Study was unavailable to Glatt et al. (2003).
Morimoto et al., 2002	Included	Not included	Included	Genotype frequencies were unavailable to Glatt et al. (2003).
Nanko et al., 1994	Not included	Included	Not included	Complete overlap with Hattori et al. (1994) was verified by the corresponding author.
Ohara et al., 1996	Not included	Included	Included	Study was unavailable to Jönsson et al. (2003).
Sasaki et al., 1996	Included	Included	Included	Among controls, 499 Ser and 11 Cys alleles were used in Glatt et al. (2003) and the present study. Jönsson et al. (2003) used 498 Ser and 10 Cys alleles.
Shaikh et al., 1994	Included	Included	Included	Among patients, 287 Ser alleles were used in Jönsson et al. (2003) and the present study. Glatt et al. (2003) used 273 Ser alleles.
Spurlock et al., 1998: Austria	Included*	Included*	Included	See footnote.
Spurlock et al., 1998: Ireland	Included*	Included*	Included	See footnote.
Spurlock et al., 1998: Italy	Not included	Included*	Not included	Overlap with Verga et al. (1997) was suspected, but could not be confirmed; thus, to be conservative, the Italian sample was excluded in the present study.
Spurlock et al., 1998: Sweden	Included*	Included*	Included	This sample was pooled with the Swedish subjects of Jönsson et al. (2003), while Glatt et al. (2003) pooled this sample with the other samples from Spurlock et al. (1998). The sample was included in the present meta-analysis as a separate study.
Spurlock et al., 1998: Wales	Included*	Included*	Included	See footnote.

**In Jönsson et al. (2003), subjects from the same research centers were pooled and considered as one study (e.g., the two studies of Arinami et al. (1994, 1996) were pooled), while Glatt et al. (2003) treated these as semi-independent reports with the overlapping samples excluded. In the collaborative study of Spurlock et al. (1998), samples from different centers were separated and each was treated as an independent study in Jönsson et al. (2003), while Glatt et al. (2003) treated all samples in Spurlock et al. (1998) as one study.*

Table 2. Allele and Genotype Frequencies of the DRD2 Ser311Cys Polymorphism in Schizophrenia Patients and Control Subjects

Study	Schizophrenia Patients					Control Subjects				
	Cys Alleles	Ser Alleles	Cys/Cys Genotypes	Cys/Ser Genotypes	Ser/Ser Genotypes	Cys Alleles	Ser Alleles	Cys/Cys Genotypes	Cys/Ser Genotypes	Ser/Ser Genotypes
Arinami et al., 1994	17	295	3	11	142	11	589	0	11	289
Arinami et al., 1996	12	258	0	12	123	14	544	1	12	266
Asherson et al., 1994	2	222	0	2	110	1	127	0	1	63
Chen et al., 1996	4	224	0	4	110	5	171	0	5	83
Crawford et al., 1996	7	161	1	5	78	3	159	0	3	78
Fujiwara et al., 1997	2	102	0	2	50	1	51	0	1	25
Gejman et al., 1994	3	209	0	3	103	4	246	0	4	121
Harano, 1997	8	132	0	8	62	8	194	0	8	93
Hattori et al., 1994	7	193	0	7	93	8	192	1	6	93
Himei et al, 2002	15	365	0	15	175	6	200	0	6	97
Hori et al., 2001	24	458	NA	NA	NA	16	386	NA	NA	NA
Jönsson et al., 2003	14	332	1	12	160	4	468	0	4	232
Kaneshima et al., 1997	4	152	0	4	74	7	217	0	7	105
Laurent et al., 1994	5	221	0	5	108	3	365	0	3	181
Morimoto et al., 2002	3	93	0	3	45	3	93	0	3	45
Nöthen et al., 1994	4	354	0	4	175	5	271	0	5	133
Ohara et al., 1996	1	305	0	1	152	3	239	0	3	118
Sasaki et al., 1996	12	534	0	12	261	11	499	1	9	245
Serretti et al., 2000	37	695	0	37	329	15	519	0	15	252
Shaikh et al., 1994	7	287	0	7	140	1	199	0	1	99
Sobell et al., 1994	12	664	0	12	326	67	3761	1	65	1848
Spurlock et al., 1998: Austria	1	143	0	1	71	4	110	0	4	53
Spurlock et al., 1998: Ireland	1	67	0	1	33	4	174	0	4	85
Spurlock et al., 1998: Sweden	0	134	0	0	67	2	128	0	2	63
Spurlock et al., 1998: Wales	1	193	0	1	96	2	210	0	2	104
Tanaka et al., 1996	9	203	0	9	97	8	204	0	8	98
Verga et al., 1997	11	195	0	11	92	5	189	0	5	92

NA: These data were not available in the published work or from the authors.

Figure 1. Publication Bias Plot of Allele Frequency Data from 24 Studies of the Association between the DRD2 Ser311Cys Polymorphism and Schizophrenia