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Association between Catechol-O-Methyltransferase (COMT) gene rs4680 SNP and rs165599 SNP and schizophrenia: A meta-analysis of case-control studies

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Abstract. The relationship between schizophrenia and single-nucleotide polymorphisms (SNPs) in the Catechol-O-MethylTransferase (COMT) gene has been investigated in numerous research, yielding varying conclusions. The investigation aimed to perform a meta-analysis for the purpose of determining the combined impact measure of the association of the COMT gene rs165599 SNP and ra4680 SNP with schizophrenia. The effect size used to assess the relationship between these two SNPs and schizophrenia was the odds ratio (OR). R studio was used to achieve the pooled ORs. Additionally, for the sake of assessing bias of publications, this paper utilize the Egger's test. Meta-analyses involving 19 independent studies have not revealed a statistically significant association between rs4680 and rs165599 SNPs and schizophrenia; however, the A versus A genetic model regarding rs4680 SNP has demonstrated a positive association with schizophrenia (OR=0.86,95% CI = 0.75-0.99, I^2= 42%,P= 0.04), which is dependent on two studies. According to this study, there may be no association between the COMT gene rs16599 SNP and rs4680 SNP and the risk of schizophrenia or its psychopathological symptoms.

Keywords: COMT, meta-analysis, odds ratio, schizophrenia, SNP.

1. Introduction

A severe mental illness characterized by growing functional impairment and recurring psychotic relapses is schizophrenia. It is the outcome of an unclear gene-environment interaction. In schizophrenia, the gene encoding catechol-O-methyltransferase (COMT) is probably involved. Its rs165599 (A/G) polymorphism has been linked to changes in the expression of the COMT gene. Additionally, the human COMT gene, which spans approximately 35 kb on chromosome 22q11.2, may result in reduced dopamine levels as well as more effective dopamine degradation [1]. Due to its functional significance, the COMT Val158/108Met (rs4680) polymorphism represents the gene variation that has been researched the most in the field of psychiatry. Studies on linkage and association suggested a connection between this locus and schizophrenia [2,3]. Apart from these deficiencies, individuals with VCFS also show a higher frequency of mental and behavioral issues, such as schizophrenia. The prevalence of schizophrenia in VCFS patients is approximately 24%, while it is only 1% in the general population [4]. Owing to its position on the genome and its role in dopamine catabolism, COMT is considered a promising prospect gene for schizophrenia [5].

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With the increasing of independent studies of the association of schizophrenia and the COMT, the results of these studies vary, which may cause confusion. For example, due to the different area of populations, the result may be opposite. Additionally, the small sample size was insufficient to mitigate its impact.

A technique for synthesizing the findings of several separate research done on a related subject is called meta-analysis. For the most extensively researched single-nucleotide polymorphism (SNP), rs4680, numerous meta-analyses have been carried out and updated [6-11]. A further SNP that is frequently researched is rs165599. Furthermore, rs4680 is also commonly researched. With the help of suitable meta-analytical techniques, we updated the pooled effect size calculation in this study by looking at the association of schizophrenia and the single-nucleotide polymorphisms rs165599 and rs4680 specifically in case-control research.

2. Methodology

2.1. Literature Review

To find papers from April 2024 on databases like Web of Science, PubMed, and so on, this paper uses Search terms for schizophrenia, COMT. We also looked through the key papers' references to locate further relevant research. When the data needed to be more precise, we made an attempt to get in touch with the authors directly. To find further pertinent research, we also looked through the reference lists of the publications that we had already identified and the most recent literature reviews. Figure 1 presents a detailed flow chart outlining the selection procedure used.

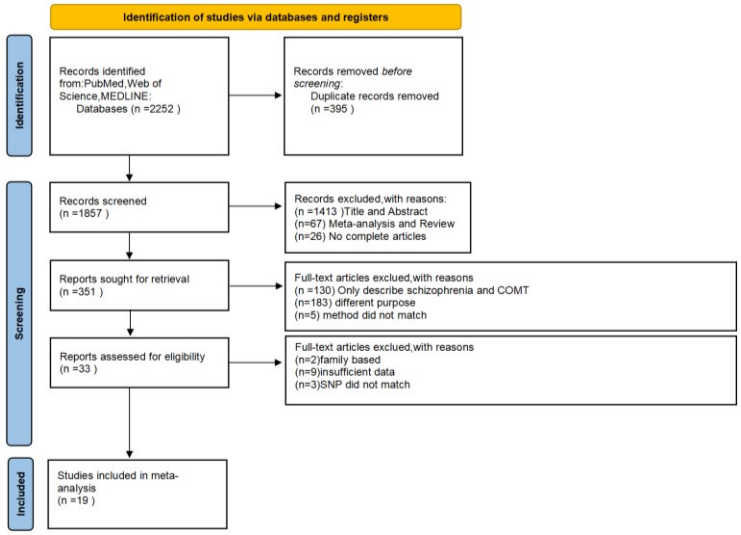

Figure 1. Diagram outlining the study selection procedure for inclusion in the meta-analysis

2.2. Inclusion And Exclusion Criteria

The studies included in meta-analysis examined the relationship between COMT SNPs and schizophrenia, using healthy people as controls in case-control research. They also ensured that the control population's genotype distribution followed Hardy-Weinberg equilibrium (HWE). All studies used DSM-IV diagnostic criteria for diagnosis. Studies published in languages other than English were excluded.

2.3. Meta-analysis

The odds ratio (OR) is a commonly used risk statistic in retrospective case-control studies. Retrospective analysis helps determine the level of exposure to the assumed risk factor [12]. An OR can be any non-negative number. Interpretation of the OR: for the desired result, exposure to the factor is not risky if OR = 1, risky if OR > 1, and risky if OR < 1 [13]. The odds was used to measure the correlation of allele

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distribution and schizophrenia. For the meta-analysis, the studies utilized three different genetic models—A versus A, A versus G, and G versus G. The pooled ORs were tested for significance using a z test, while Egger's test was applied to examine publication bias . Furthermore, because of the substantial heterogeneity among the studies in the meta-analyses, eight studies of rs16599 SNP and eighteen studies of rs4680 SNP were employed in the subgroup analyses. The studies conduct their analysis in R studio (version 1.6.0), applying a significance threshold of 0.05.

3. Results

3.1. Study Features

After conducting an extensive search through the internet database, we first discovered 2252 citations. After 395 duplicates were electronically eliminated, 1857 citations remained. After removing 1413 papers because their titles and abstracts did not match the qualifying requirements, we additionally eliminated 93 articles because they were reviews, which are not suitable for publication. Then, we eliminated 313 citations since they exclusively discussed schizophrenia and the COMT and had distinct goals. Nineteen studies were eliminated due to various reasons, such as inconsistencies in the method or SNPs, and insufficient data. Lastly, there were nineteen citations. In Figure 1, a PRISMA flowchart was presented. We created a total of 7053 cases and 8944 controls in 19 investigations. Furthermore, from 1998 to 2015, all of these research were case-control studies. Furthermore, a wide range of locations were chosen. Table 1 presents the attributes of the 19 studies that were chosen and subsequently included.

Table 1. Features of the studies incorporated into the meta-analysis

author	year	country	sample size		SNPs	Diagnostic System
			case	control		
cordeiro et al.	2012	Brazilian	245	834	rs165599	DSM-IV
voisey et al.	2012	Australia	201	266	rs4680	DSM-IV
Nonukawa et al.	2007	Japan	399	440	rs4680	DSM-IV
			398	440	rs165599	DSM-IV
Ho Jin Kang et al.	2010	Korea	348	360	rs165599	DSM-IV
			348	360	rs4680	DSM-IV
Tovilla-Zarate et al.	2013	Mexico	186	222	rs4680	DSM-IV
Galderisi et al.	2005	Italy	106	111	rs4680	DSM-IV
Lee,S.G. et al.	2005	Korea	320	379	rs4680	DSM-IV
Huang,C.C et al.	2012	China	434	442	rs165599	DSM-IV
			434	442	rs4680	DSM-IV
Lajin et al.	2011	Syria	71	102	rs4680	DSM-IV
Oomori,O. et al.	1998	Japan	150	150	rs4680	DSM-IV
Acar,Ceren et al.	2015	Turkey	96	100	rs165599	DSM-IV
			96	100	rs4680	DSM-IV
AI-Asmary,S et al.	2014	Saudi Arabia	172	177	rs4680	DSM-IV
Maria,Ktrotsou et al.	2012	Greece	108	97	rs165599	DSM-IV
			108	97	rs4680	DSM-IV
Altinyazar,Vesile et al.	2015	Turkey	181	368	rs165599	DSM-IV
			181	368	rs4680	DSM-IV
Zhang,Fuquan et al.	2012	China	768	1348	rs165599	DSM-IV
			963	992	rs4680	DSM-IV
Wan,Ching-Lee et al.	2011	Malaysia	317	417	rs4680	DSM-IV

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Table 1. (continued).

Wonodi,I et al.	2003	Maryland	96	79	rs4680	DSM-IV
Liou,Y.J et al.	2001	China	198	188	rs4680	DSM-IV
Herken,H et al.	2001	Turkey	129	65	rs4680	DSM-IV

3.2. Outcomes

3.2.1. rs1655599 SNP

There are 8 studies all shown the negative association(AA:OR=1.02,95% CI = 0.89-1.18, I^2= 0%,P= 0.76;AG:OR=1.04, 95% CI = 0.92-1.19, I^2= 57%,P= 0.51;GG:OR=1.03, 95% CI = 0.92-1.16, I^2= 0%,P= 0.62) between exposure and control. In our meta analyses, we also found the same result which a sample size of 3394 as shown in supplementary Figure 2. Through a leave-one-out influence analysis, we found the result does not rely on any study.

3.2.2. rs4680 SNP

For the rs4680 SNP, we included 18 studies with a 6956 sample size. Only two genetic models have shown insignificance association: A versus G(OR=1.02,95% CI = 0.85-1.23, I^2= 60%,P= 0.80) and G versus G(OR=1.00,95% CI = 0.91-1.10, I^2= 10%,P= 0.97). Nevertheless, the genetic model A versus A demonstrates a significant result(OR=0.86,95% CI = 0.75-0.99, I^2= 42%,P= 0.04) through sensitivity analysis which information can be acquired in Figure 3 A.The reason why we considered this may be attributed to the sample size and geographic location of the two experiments, which need to be further proven.

3.2.3. Publication bias

For rs4680 SNP, we have sufficient sympathy to analyze the publication bias which is listed in Figure 4. On the contrary, due to the insufficient studies of rs165599 SNP included in our studies we can not access the publication bias. Through the funnel graph to test the publication bias. The asymmetry of funnel graph showed it there may exist publication bias that triggers positive results.

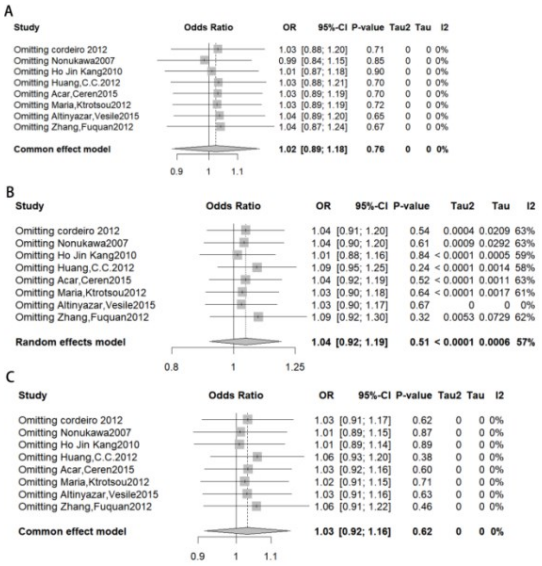

Figure 2. Forest graph for the correlation between rs165599 SNP and schizophrenia under (A) A versus A(B) A versus G (C) G versus G genetic model.

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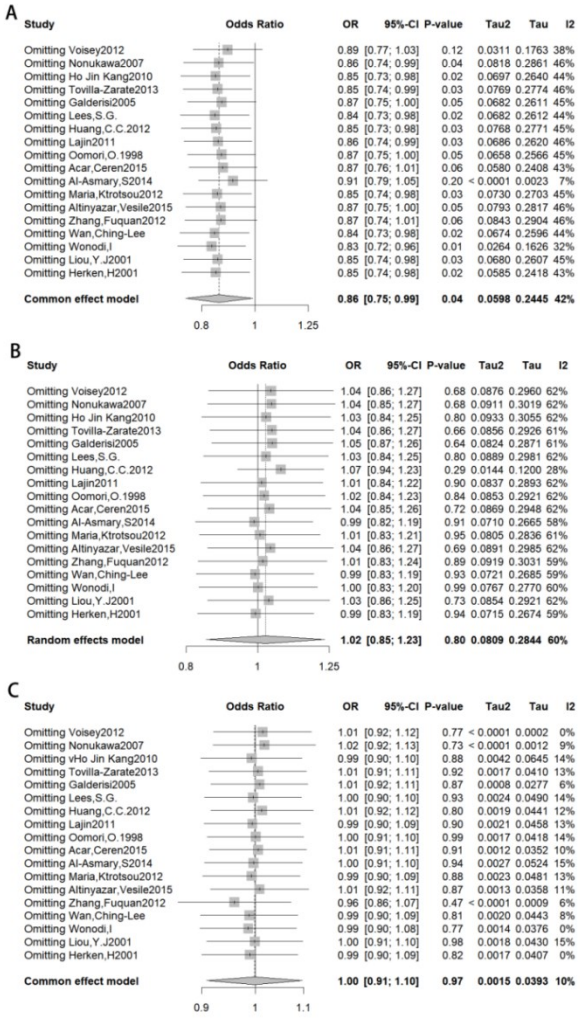

Figure 3. Forest graph for the correlation between rs4680 SNP and schizophrenia under (A) A versus A(B) A versus G (C) G versus G genetic model for all studies.

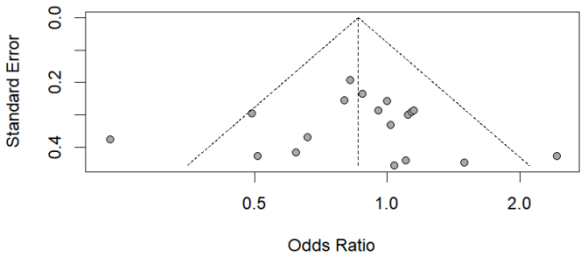

Figure 4. funnel plot for the correlation between rs4680 SNP and schizophrenia under genetic model.

4. Conclusion

Numerous investigations have looked into the relationship between schizophrenia and COMT gene polymorphisms. Eight of the 19 papers that address this looked into the connection between the rs165599 SNP and schizophrenia. Moreover, two studies revealed a substantial positive correlation between the rs4680 SNP and schizophrenia, and 18 of them were included in the description of the SNP. The remaining ones all have negligible correlations. Overall the meta-analyses we discovered an insignificant association. However, when leaving one out of influence analysis we found the result relied

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on two studies which are AI-Asmary, 2014 [14]and Voisey, 2012[15]. In other words, excluding these two studies the result becomes insignificant.

Through these studies the sample size was all less than 1000, in addition to a study Zhang, Fuquan et al.2012[16] which contained 2116 people in rs165599 SNP and 1955 people in rs4680 SNP. Moreover, the case-control study as a method was used in inclusive studies. From this paper, these studies may need a bigger sample to reduce bias. Our meta-analyses which are based on these studies also showed a negative result that COMT and schizophrenia did not have a significant association.

The results of the prior investigation indicated that there was no correlation between schizophrenia and the SNPs rs4680 and rs165599. Additionally, a negative correlation was shown by our meta-analyses. However, there is insufficient data to demonstrate a negligible connection between schizophrenia and COMT. It is said that differences in linkage disequilibrium (LD) across populations may result in distinct haplotypes, rather than single-nucleotide polymorphism, being associated with schizophrenia in various populations. Also, in this meta anaylsis, we just include two SNPs rarely, and the relevant SNPs are still existing numerous numbers. Thus, in future research endeavors, all of these SNPs should be involved and pay more attention to the relationship among different SNPs. Finally, there is a significant potential for the utilization of various other methods in future research studies.

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