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Meta-analysis of Odds Ratios for the COMT Gene rs737865 SNP for Schizophrenia

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Meta-analysis

History

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ABSTRACT

Objective: The collection of methods that enable combining the findings of several independent studies on the topic of interest with appropriate statistical methods is called meta-analysis.
Schizophrenia is a complex psychiatric disease linked to many environmental and genetic factors and affects up to 1% of the world's population.
A candidate gene for schizophrenia susceptibility is the catechol-O-methyltransferase (COMT) gene.
This study aimed to combine the odds ratios obtained from different studies according to the rs737865 SNP (single nucleotide polymorphism) of the COMT gene for schizophrenia by meta-analysis.

Material and Method:
Publications written in English were scanned with the keywords "COMT and schizophrenia" in Web of Science, Pubmed, and Google Scholar databases until October 2024. Common odds ratio estimates were obtained with the help of appropriate meta-analytic methods under different genetic models for 17 studies that met the inclusion criteria, as well as 8 and 4 studies for Asians and Caucasians, respectively, by race. STATA 14 program was used for all analyses.

Results: Under different genetic models applied to seventeen studies, only carriers of the CC genotype were found to have a higher risk for schizophrenia than carriers of the T (TT+CT) allele [OR=1.133 (95% CI=1.008 - 1.273)]. In subgroup analyses according to race, no risk was found for Asians. In contrast, for Caucasians, it was found that carriers of the C (CC+CT) allele had an increased risk of schizophrenia compared to those with TT genotype [OR=1.586 (95% CI=1.349 - 1.865)].

Conclusion: With the help of applied meta-analytic methods, overall estimates were obtained for odds ratios (OR) obtained from independent studies under different genetic models. However, it is thought that the association between COMT gene rs737865 SNP and schizophrenia should be examined with studies conducted in larger groups homogeneous in terms of ethnicity.

Keywords: Meta-analysis, COMT, odds ratio, schizophrenia

Şizofreni İçin COMT Geni rs737865 SNP Odds Oranlarının Meta Analizi

Meta Analiz

Süreç

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ÖZET

Amaç: İlgilenilen konuda yapılan birden çok bağımsız çalışmanın bulgularını uygun istatistiksel metotlarla birleştirmeyi sağlayan metotlar topluluğuna meta analizi adı verilir.
Şizofreni, birçok çevresel ve genetik faktörle bağlantılı karmaşık bir psikiyatrik hastalıktır ve dünya nüfusunun %1'ini etkilemektedir. Katekol-O-Metiltransferaz (COMT) geni şizofreniye yatkınlık için aday bir gen olarak görülmektedir. Bu çalışmada, şizofreni için COMT geninin rs737865 SNP'ne (tek nükleotit polimorfizmi) göre farklı çalışmalardan elde edilen odds oranlarının meta analizi ile birleştirilmesi amaçlanmıştır.

Yöntem: Yazım dili İngilizce olan yayınlar "COMT ve şizofreni" anahtar kelimeleri ile Ekim 2024 tarihine kadar Web of Science, Pubmed ve Google Akademik veri tabanlarında ile taranmıştır. Dâhil olma kriterlerini sağlayan 17 çalışma ve ayrıca ırka göre Asyalı ve Beyaz ırklar için sırasıyla 8 ve 4 çalışma için farklı genetik modeller altında, uygun meta analitik yöntemler yardımıyla ortak odds oranı kestirimleri elde edilmiştir. Tüm analizlerde STATA 14.0 programı kullanılmıştır.

Bulgular: On yedi çalışmaya uygulanan farklı genetik modeller altında, sadece CC genotipine sahip olanların T (TT+CT) alleli taşıyıcılarına göre şizofreni için risk taşıdığı bulunmuştur [OR=1,133 (%95 G.A.=1,008 – 1,273)]. Irka göre yapılan alt grup analizlerinde ise Asyalı ırk için bir riskten söz edemezken Beyaz ırk için C (CC+CT) alleli taşıyıcılarının TT genotipine sahip olanlara göre şizofreni riskini arttırdığı bulunmuştur [OR=1,586 (%95 G.A.=1,349 – 1,865)].

Sonuç: Uygulanan meta-analitik yöntemler yardımıyla bağımsız çalışmalardan elde edilen odds oranları (OR) için farklı genetik modeller altında tümel kestirimler elde edilmiştir. Bununla birlikte, etnik köken açısından homojen daha büyük gruplarda yapılan çalışmalar ile COMT geni rs737865 SNP'i ile şizofreni arasındaki bağın incelenmesi gerektiği düşünülmektedir.

Anahtar Kelimeler: Meta analiz, COMT, odds oranı, şizofreni

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Introduction

Today, most diseases are known to be related to genetic factors. Schizophrenia affects 1% of the world's population and is approximately 80% inherited. Due to its function and location, the catechol-o-methyltransferase gene is a strong candidate gene for schizophrenia.[1]

Numerous case-control studies have been conducted to determine the association between the COMT gene rs737865 polymorphism and schizophrenia, but the results have been inconstant; some studies have concluded that there is a significant association between the polymorphism and schizophrenia, while others have concluded that there is no association. In the majority of studies, no significant association was found.

In this case, the researcher needs research synthesis to make a decision. Meta-analysis, one of the most effective research synthesis methods, helps us now. Meta-analysis is one of the most frequently used research syntheses.[2,3] Meta-analysis is a statistical method that combines the results of several independent studies on a particular question, explains the differences in those results, and makes the results more reliable.[4] This study aimed to determine the association between COMT gene rs737865 SNP and schizophrenia using the meta-analysis method.

Materials and Methods

Literature search

Publications written in English were scanned with the keywords “COMT” or “catechol-O-methyltransferase” and “schizophrenia" in Web of Science, Pubmed, and Google Scholar databases until October 2024.

We also checked the bibliographies of key studies to find further relevant studies. As there was no detailed information on how effect sizes were calculated, we attempted to contact the authors.

The flowchart in Figure 1 describes the process used to select the studies that were included in the meta-analysis.

Inclusion-Exclusion Criteria

Case-control studies including patients diagnosed according to DSM-IV diagnostic criteria were considered as inclusion criteria. Studies including family (family-based, trio, sibling) data, patients with additional mental illness or any comorbidity, head trauma, violent tendencies, Alcohol and/or drug abuse were excluded. We found 17 studies examining the association between the r737865 SNP for the COMT gene and schizophrenia that met our criteria. In the first application, the results of 17 studies shown in Table 1 were combined by meta-analysis.

In the second application, the results of 8 and 4 studies were combined for Asian and Caucasian races, respectively, among the studies examining the association between rs737865 SNP for COMT gene and schizophrenia.

Meta-Analysis

In this study, to examine the association between COMT gene rs737865 SNP and schizophrenia, as an effect size the odds ratio (OR) was used. OR can only take positive values and indicates the risk of a factor on an outcome. An exposure to the factor is not risky if OR=1, it increases the risk if OR>1, and it decreases the risk for the outcome of interest if OR<1.

When calculating the ORs, we used each study's genotype and allele frequencies. In some studies (C and T) allele frequencies were also given, for studies in which only genotype distributions were presented (CC, CT, TT), we calculated the allele frequencies. Following the purpose of the study, odds ratios obtained based on genotype frequencies and allele frequencies were combined with appropriate meta-analytical methods.

To decide whether to use the fixed or random effect model for combining the study results, the heterogeneity of the effect sizes between the studies was evaluated. For this purpose, Q statistic and I^2 values were utilized. If the Q statistic resulted as $p<0.05$, it was regarded as statistically significant.[30] When I^2 is greater than 50%, it is classified as large heterogeneity.[30] If there was the absence of heterogeneity or moderate heterogeneity between studies; the common OR was calculated with the Mantel-Haenszel fixed-effects model (MH). Otherwise, the DerSimonian-Laird random-effects model method (DSL) was used.

For the 17 studies considered for the first application, the Der Simonian-Laird method was used under the random effect model since the effect sizes were heterogeneous among the studies.

In the 8 and 4 studies considered in the second application, it was found appropriate to use fixed effect models since homogeneity between studies was provided for both Asian and Caucasian races.

For both applications, the odds ratio point estimate and 95% confidence interval of each study and the common estimation obtained as a result of meta-analysis are presented with a forest plot. A funnel plot, in which the logarithm of the point estimates is plotted against their standard errors, was used to visualize publication bias. In addition, Egger's test was implemented to

evaluate the publication bias. Trim and fill analysis was performed to eliminate publication bias. For all analyses, the significance level was considered 0.05. Statistical analyses and graphical representations were performed using the STATA 14.0 software (Stata Corporation, College Station, Texas, USA).

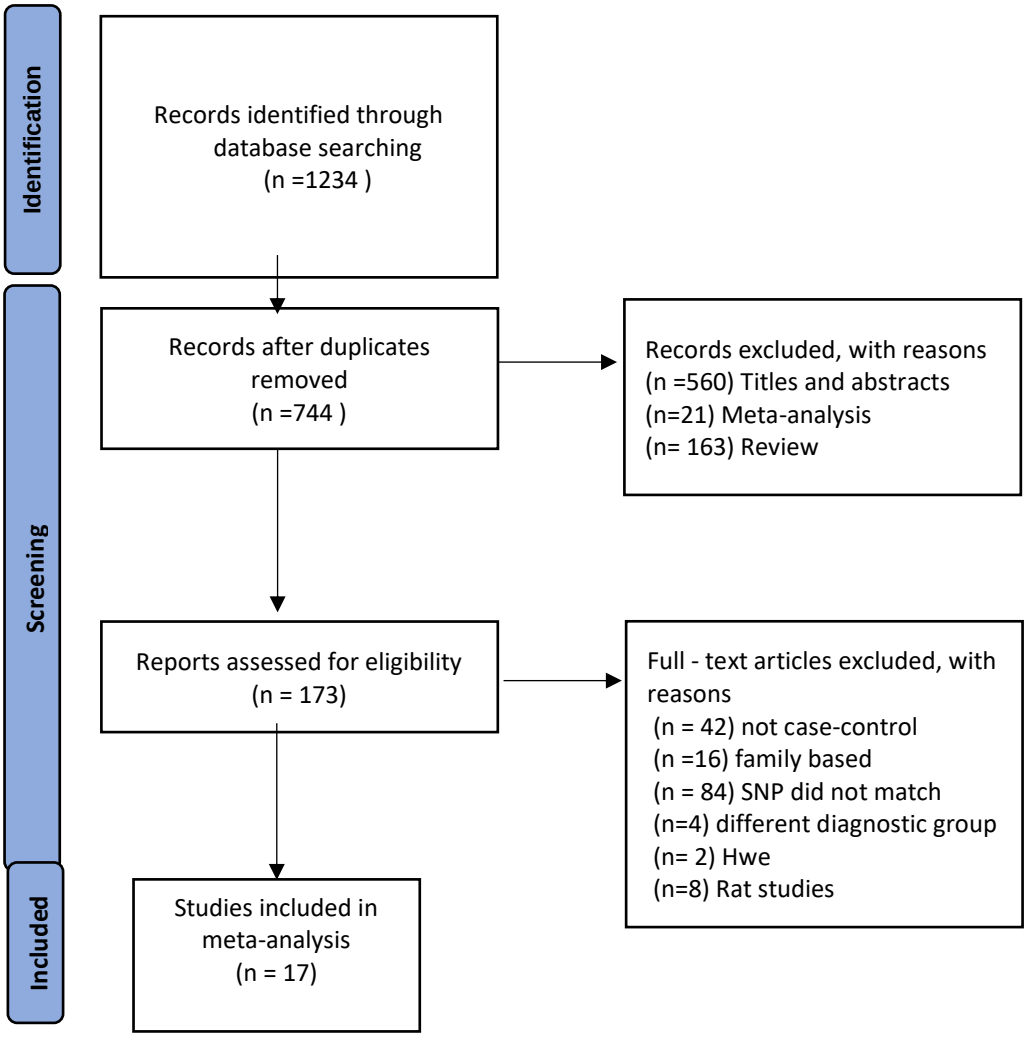

Figure 1. Flow chart of the selection process of the studies included in the meta-analysis

The literature search identified 17 case-control studies that met the inclusion criteria, enrolling 7664 cases and 10235 controls. Of the 17 studies, 8 involved Asian populations and 4 Caucasian populations. The OR estimates for these studies were pooled using appropriate meta-analytic methods. Table 1 gives the characteristics of the included studies.

Table 1. Characteristics of the populations from studies included in the meta-analysis

First Author	Study Year	Population	n		
			Case	Control	Total
Shifman	2002	Israil	714	2849	2965
Lee	2005	Korean	320	379	641
Funke	2005	Caucasion-Usa	394	467	597
Yu	2007	Han Chinese	241	290	484
Nunokawa	2007	Japanese	399	440	779
Martorell	2008	Caucasion-Spain	585	615	1070
Okochi	2009	Japanese	1118	1100	2031
Gupta	2009	Southern Indian	398	241	591
Chien	2009	Taiwanese	124	112	221
Park	2009	Korean	354	396	682
Chen	2011	Han Chinese	434	442	819
Wright	2012	South Africa	238	240	461
Maria	2012	Greek	108	97	189
Acar	2015	Turkish	96	100	172
Higashiyama	2016	Japanese	1854	2137	1101
Dean	2016	European Han Chinese	75	73	172
Matsuzaka	2017	Mixed	212	257	396

Table 2. The findings of meta-analyses performing different genetic models for all studies

Genetic model	I^2	p_Q	Method	OR (95% C.I.)	p_Z	p_E
T versus C [17]	43.2	0.030	DSL	1.007 (0.934 – 1.087)	0.854	0.236
TT versus (CC+CT) [17]	41.6	0.037	DSL	1.002 (0.909 – 1.104)	0.972	0.855
(TT+CT) versus CC [17]	**22.4**	**0.194**	**MH**	**1.133 (1.008 – 1.273)**	**0.036**	**TF**
TT versus CC [17]	26.6	0.150	MH	1.133 (1.000 – 1.283)	0.050	**TF**

Note: The numbers in parentheses indicate the number of studies included in the meta-analysis. p_Q: p-value for Q test; p_z: p-value for Z test; p_E: p-value of Egger's test; TF: Trim and Fill analysis

When the Egger test was carried out to assess the bias in the publications, if the test result showed publication bias, a trim and fill analysis was performed (Table 2).

The pooled odds ratios with 95% CIs did not show a statistical association between the COMT gene rs737865 SNP and the risk of schizophrenia except for the (TT+CT) vs CC genetic model (Table 2). It was found that carriers of the CC genotype have a higher risk for schizophrenia than carriers of the T (TT+CT) allele [OR=1.133 (95% CI=1.008 - 1.273)].

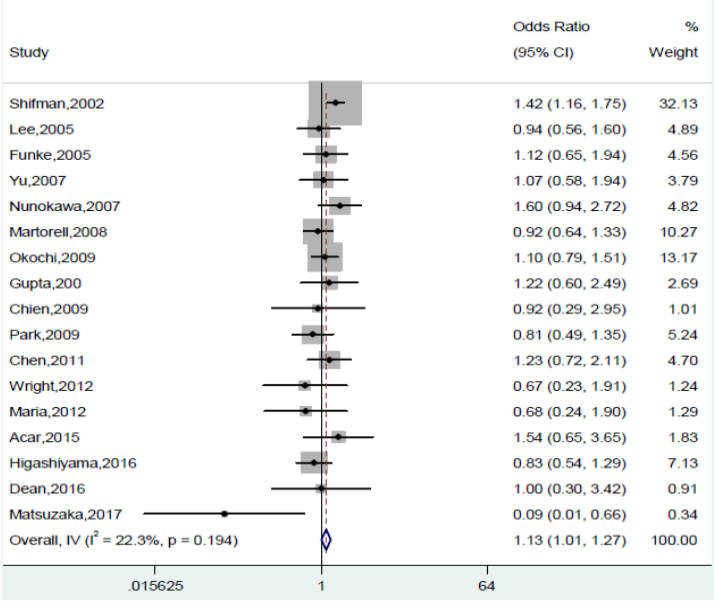

Figure 2. Forest plot for rs737865 (TT+CT) versus CC genetic model for all studies

In forest plots (Figure 2 and 3), the squares and horizontal lines indicate study-specific OR and 95% CI. The area of the squares corresponds to the study-specific weight of the study. The diamond shows the pooled OR and 95% CI.

In the stratified analysis according to race (Table 3), there was no heterogeneity between studies for Asian and Caucasian subgroups under any genetic model (I^2=0, p>0.05). While no risk was found for Asians, for Caucasians it was found that carriers of the C (CC+CT) allele had an increased risk of schizophrenia compared to those with TT genotype [OR=1.586 (95% CI=1.349 - 1.865)] (Figure 3).

Table 3. Results of meta-analyses for race subgroups based on different genetic models.

	Genetic model	I^2	p_Q	Method	OR (95% C.I.)	p_Z
Asian	T versus C [8]	0	0.890	MH	0.997 (0.927 – 1.073)	0.946
	TT versus (CC+CT) [8]	0	0.701	MH	0.984 (0.898 – 1.079)	0.735
	(TT+CT) versus CC [8]	0	0.654	MH	1.043 (0.877 – 1.241)	0.633
	TT versus CC [8]	0	0.797	MH	1.035 (0.866 – 1.238)	0.705
Caucasian	T versus C [4]	0	0.679	MH	0.989 (0.871 – 1.123)	0.864
	TT versus **(CC+CT)** [4]	0	0.804	MH	**1.586 (1.349 – 1.865)**	**<0.001**
	(TT+CT) versus CC [4]	0	0.600	MH	0.999 (0.758 – 1.315)	0.992
	TT versus CC [4]	0	0.577	MH	0.985 (0.737 – 1.317)	0.920

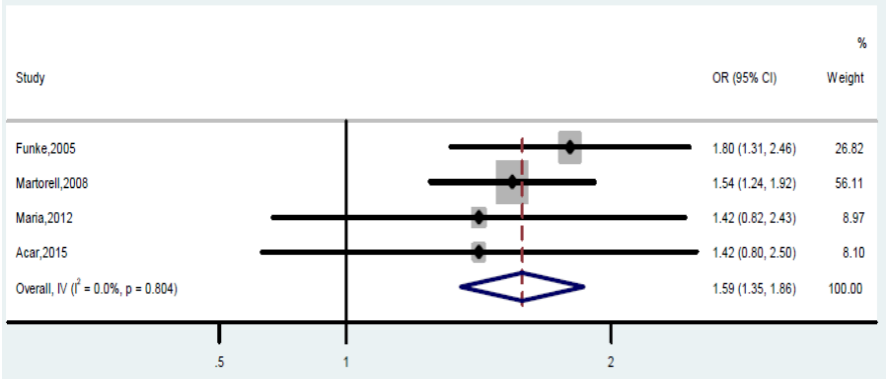

Figure 3. Forest plot for rs737865 TT versus (CC+CT) genetic model for Caucasians.

Discussion

The COMT gene is a strong candidate for schizophrenia susceptibility. It is a likely candidate gene because of the enzyme's role in dopamine metabolism and the chromosomal location of 22q11. Many studies in different populations around the world have produced conflicting results regarding the COMT gene and schizophrenia. This study aims to investigate the association between COMT gene rs737865 SNP and schizophrenia. We examine this relationship by performing a meta-analysis that includes case-control studies.

We found that having CC genotype have a higher risk for schizophrenia than T (TT+CT) allele carriers (OR=1.133, 95% C.I=1.008 – 1.273). Similarly, a meta-analysis included 10 studies conducted by Okochi et al. found having CC genotype increases the risk of schizophrenia (OR=1.155, 95% C.I=1.025 – 1.303).[16]

Also, in our meta-analysis based on four studies which were carried out on Caucasians, the pooled OR (1.586, 95% C.I=1.349 – 1.865) estimation indicated that having a C (CC+CT) allele increases the risk of having schizophrenia compared to TT homozygous genotype. These results suggest that T allele might have a protective effect. However, when we compared T allele carriers with C allele carriers, we found no statistically significant association between allele frequencies and schizophrenia.

Oppositely, in Wright et.al's study they found that the C allele is protective against schizophrenia in an African population.[6]

In the study by Shifman et al., rs737865 SNP was found to be highly associated with schizophrenia in Ashkenazi

Jews and affects both sexes but in different ways. They reported that the CC genotype is associated with susceptibility to schizophrenia in males and the TT genotype is protective in females.[4]

Another case-control study reported no association between COMT haplotype (rs4680, rs6267, rs737865, rs4633, rs6269) and schizophrenia risk in the Korean population.[8] Also, no significant association was found between COMT polymorphisms including six SNPs (rs737865, rs740603, rs4633, rs6267, rs4680, rs165599) and schizophrenia in the Korean population.[19]

A case-control study of five functional polymorphisms (rs2075507, rs737865, rs6267, rs4680, and rs165599) in the Japanese population was carried out by Nunokawa et al. (399 schizophrenia patients and 440 controls). Neither COMT haplotypes nor polymorphisms were shown to be significantly linked to schizophrenia.[5] Another research of eight SNPs in the Japanese population, including rs737865, rs6267, rs4680, and rs165599, found no evidence of a significant association between schizophrenia and COMT polymorphisms or haplotypes.[11]

In the Chinese population studies by Yu et al. and Chien et al., no association was found between haplotype (rs737865, rs4680, rs165599) and risk of case and control groups. Similarly, Chen et al. concluded that the COMT gene haplotype (rs2075507 - rs737865 - rs933271) would not cause schizophrenia risk and psychopathological symptoms in a Chinese population study.[12,18] In an additional Chinese population study Dean et al. did not find an association between COMT genotype SNPs (rs4680 or rs4818, as well as rs165519 and rs737865) and schizophrenia in a case-control study. [17]

In a case-control study in a Turkish population, no association was found between COMT gene rs737865, rs4680, and rs165599 polymorphisms, and schizophrenia.[14] However, Maria et al. demonstrated an association between the COMT gene and schizophrenia in a Greek population. Although no significant results were obtained individually, haplotype analysis showed that haplotypes 2 (rs737865 - rs165599) and 3 (rs737865, rs4680 and rs165599) were highly associated with schizophrenia.[25]

According to Funke et al., the rs737865 SNP is not associated with schizophrenia, bipolar disorder, schizoaffective disorder, or major depressive disorder in the population of the United States. For all included psychiatric diseases, however, haplotype analysis produced statistically significant results (278A/G; rs737865; Val108/158Met; rs165599).[9]

Martorell et al. found no evidence for an association between the COMT gene and schizophrenia.[7] Their study included the 3 most commonly studied SNPs, rs737865, rs4680 (Val/Met), and rs165599, which are highly related to schizophrenia in Ashkenazi Jews.[4]

There is no evidence that the COMT gene is linked to schizophrenia, according to Martorell et al.[7] The three most often researched SNPs that are strongly linked to schizophrenia in Ashkenazi Jews (rs4680, rs737865, rs165599) were included in their analysis.[4]

In a case-control study, Gupta et al. constructed a haplotype analysis containing seven SNPs (rs3788319, rs737865, rs6269, rs4818, rs4633, rs4680, rs165599) of the COMT gene were found to be associated with schizophrenia in the Indian population.[20] According to Shifman et al., COMT haplotype of three SNPs (rs737865, rs4680, and rs165599) and schizophrenia were significantly associated. Similarly, Gupta et al. reported that their investigation revealed a strong association between schizophrenia and this three-marker haplotype.[20]

A study of an African population by Wright et al, which investigated 14 SNPs (including rs737865, rs165599, and rs4680, etc.) in the COMT gene, a significant association was found between schizophrenia and rs737865 and rs2020917 polymorphisms.[6]

However, in a mixed population, Matsuzaka et al. assessed the contribution of three COMT SNPs (rs737865, rs165599, and rs4680) to schizophrenia and discovered a strong association between the rs737865 genotype and schizophrenia. They concluded that the CC genotype had a protective effect and CT had a risk effect.[24]

Conclusion

In conclusion, some of the studies with different populations and different sample sizes found a significant association between SNP rs737865 and schizophrenia, while others found nonsignificant results. In our meta-analysis, the pooled OR obtained from 17 independent studies led us to conclude generally CC genotype is associated with the disease. However, according to ethnicity the risky allele or genotype can be changed. So, we think it would be better to investigate the association between the SNPs and the disease for different ethnicities separately. Because, when we constructed the meta-analysis for population subgroups, the heterogeneity between studies disappeared. Also, differences in linkage disequilibrium (LD) between populations suggest that different haplotypes, rather than SNPs, are associated with schizophrenia in different populations.[28,30]

Nevertheless, the association between schizophrenia and the COMT gene rs737865 single-nucleotide

polymorphism or haplotype analysis needs to be confirmed by appropriately designed researches with larger sample sizes.

Ethics Committee Approval

It is a meta-analysis study and the data of the studies included in the research are open access.

Author Contributions

Concept – HGB, GH Design HGB, GH ; Supervision HGB.; Materials -HGB,GH ; Data Collection and/or Processing - GH; Analysis and/or Interpretation -GH; Literature Review - GH.; Writing – GH,HGB; Critical Review – GH.

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Compliance with ethical standards

Conflict of interest: The authors declare no conflict of interest.

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