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The association of serotonin transporter gene polymorphism and geriatric depression: A meta-analysis

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HIGHLIGHTS

- 5-HTTLPR polymorphism is associated with the risk of geriatric depression.
- The susceptibility to geriatric depression is higher for S carrier vs L/L genotype.
- Subjects with S/S genotype have a higher risk for geriatric depression.

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ABSTRACT

Serotonin-transporter-linked promoter region (5-HTTLPR) polymorphism is the genetic variant coding for the serotonin transporter and may play an important role in the etiology of depression. However, genetic studies examining the relationship between 5-HTTLPR polymorphism and geriatric depression have produced inconsistent results. We conducted a meta-analysis to compare the frequency of 5-HTTLPR variants in geriatric depression cases and non-depressed controls in the elderly. A total of 5 studies involving 579 geriatric cases and 1372 non-depressed controls met the inclusion criteria. With strong statistical power, pooled odds ratios (ORs) and 95% confidence intervals (CIs) for genotypic analyses (S carrier versus L/L, S/S versus L/L) were provided. The results of our analysis indicate statistically significant association between S allele and the risk of geriatric depression ($OR_{S\ carrier\ vs\ S/S} = 1.29$, 95% CI 1.01–1.66; $OR_{S/S\ vs\ L/L} = 1.68$, 95% CI 1.20–2.35). Our findings suggest that 5-HTTLPR polymorphism is of importance in the development of geriatric depression.

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1. Introduction

Depression is a complex and multi-factorial mental illness with important genetic and non-genetic factors [1]. The elderly are particularly at risk for depression, which cause burden on both patients and their families. Among the genetic factors, a functional polymorphism in serotonin transporter-linked promoter region (5-HTTLPR) has shown to be associated with geriatric depression.

5-HTTLPR consists of two major alleles, a short (S allele) and a long (L allele) genetic variant [2]. Previous studies indicated that 5-HTTLPR is responsible for serotonin reuptake into presynaptic neurons and regulates the level of serotonin concentration in the synaptic cleft [3]. The S allele shows a lower level of both transcriptional efficiency of 5-HTT gene promoter and serotonin reuptake than L allele. Serotonin is a key neurotransmitter in the central and peripheral nervous systems, and lack of serotonin may contribute to the pathophysiology of depression [4]. Moreover, aging is generally associated with decreased levels of the serotonin and its postsynaptic receptor, which may contribute to an increased risk of geriatric depression.

Accumulating evidences have shown that depressed individuals generally have a higher frequency of S alleles than non-depressed controls. Recent studies have linked this locus to suicidality and the response to antidepressants [5]. In addition, S allele is highly related to several other mood disorders, such as neuroticism and anxiety symptoms [6]. This meta-analysis aims to investigate the association between 5-HTTLPR polymorphism and geriatric depression. In our study, we hypothesize that S allele is a risky factor for geriatric depression.

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2. Materials and methods

2.1. Search Strategy

Data were collected from PubMed, Medline, EmBase and PsychINFO. The keywords 5-HTTLPR and (depress* or major depress*), and geriatric (depress* or major depress*) were used to search the studies.

Published studies to examine the association between 5-HTTLPR polymorphism and geriatric depression were carefully selected by two independent investigators (Z Gao and MH Sun). Studies published in English language before the 1st of January 2014 were considered.

2.2. Inclusion criteria

Case-control studies of 5-HTTLPR genotype frequencies in geriatric depression cases and age-matched healthy controls were included for further selection. Studies were selected with strict inclusion criteria to exclude non-geriatric depression cases. In our study, only cases with clear diagnosis of geriatric depression were included. The diagnosis was based on DSM-III, DSM-III-R, DSM-IV and DSM-IV-R, or patients with significant depressive symptoms defined by other depression rating scales.

2.3. Data extraction

Two investigators (Z Gao and HY Yuan) independently extracted data to avoid potential mistakes, using a standardized data extraction form. In each study, the following data were coded: the first author and year of publication, sample sizes, depression measure and sample characteristics such as gender ratio, mean age, genotype and allele frequencies of 5-HTTLPR polymorphism. Genotype frequencies are required to be in Hardy-Weinberg equilibrium (HWE) in healthy controls ($p > 0.01$).

2.4. Meta-analysis methods

The meta-analysis examined the relationship between the frequency of S allele and risk of geriatric depression. In addition, odds ratios (ORs) and its 95% confidence interval (95% CI) were estimated for both S carrier versus L/L and S/S versus L/L.

To combine individual study results, we conducted the meta-analysis using RevMan (version 5.2.6). The heterogeneity between studies was tested using a chi-squared-based Q-statistic test, which is to assess between-study heterogeneity. $P < 0.1$ indicates the presence of statistically significant heterogeneity. Inconsistency across studies was calculated with the I^2 metric, which can be interpreted as the percentage of total variation across several studies due to heterogeneity. Besides, Galbraith and L'Abbe tests were also conducted to check the consistency of included studies and evaluate between-study heterogeneity. We also performed sensitivity analysis to assess the deviations of pooled OR that individual sample may bring to the whole case pool.

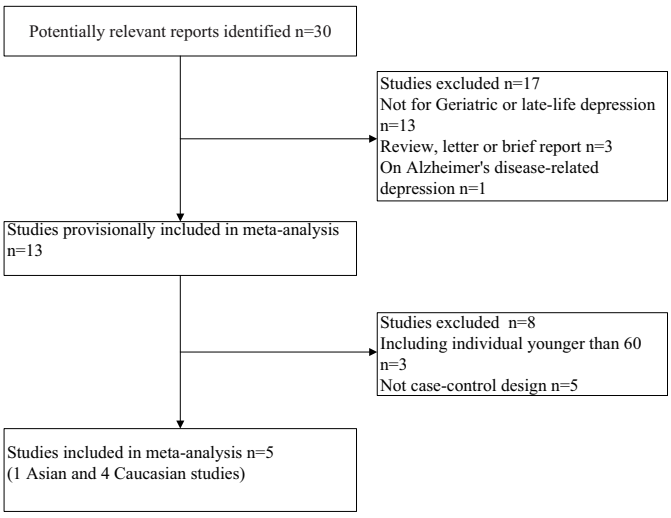

Fig. 1. Flow diagram of the study selection process.

2.5. Evaluation of publication bias

Publication bias is the preferential publication of a study with positive findings. In our meta-analysis, STATA (version 12, Stata Corp LP, TX) was used to detect the presence of potential publication bias. Both Begg's and Egger's tests were used to statistically assess publication bias.

3. Results

3.1. Description of studies identified in meta-analysis

We identified 30 potentially relevant research papers using our search strategies, while 25 did not meet the inclusion criteria after reviewing the abstracts or papers (Fig. 1). In our study, we only included cases that followed all the inclusion requirements, and cases with any deviation from our criteria were excluded. The excluded papers included 13 studies that were not for geriatric depression [7–19], 3 brief reports or reviews [20–22] and 1 that is on Alzheimer's disease related depression [23]. We also excluded 3 studies that contained cases of unclear diagnosis of depression [24–26]. In addition, studies without case-control design were also excluded. Five case-control datasets were included in this meta-analysis (Table 1) [27–31], which included 579 cases and 1372 psychiatrically healthy controls in total.

3.2. Effect of 5-HTTLPR on geriatric depression

We tested the association between 5-HTTLPR polymorphism and geriatric depression by estimating the ORs for S carrier versus L/L and S/S versus L/L. The pooled analysis was carried out with a fixed-effects model and no significant heterogeneity was found in both studies ($OR_{S\ carrier\ vs\ L/L}$ $I^2 = 16\%$, $p > 0.1$; $OR_{S/S\ vs\ L/L}$ $I^2 = 7\%$,

Table 1
Characteristics of the studies included in the meta-analysis of 5-HTTLPR polymorphism and geriatric depression.

Study (author, year)	Ethnic	Depression Measure	Case			Control		
			L/L	L/S	S/S	L/L	L/S	S/S
Taylor et al., 2005 [31]	Caucasian	DDES	47	67	21	29	41	13
Grünblatt et al., 2006 [27]	Caucasian	DSM-IV	25	38	20	144	164	52
Kim et al., 2007 [28]	Asian	GMS	7	41	53	89	209	333
Steffens et al., 2008 [30]	Caucasian	DSM-IV	78	98	41	50	70	21
Mendes et al., 2013 [29]	Caucasian	GDS	11	17	15	56	73	28

S, short allele; L, long allele; DDES, Duke Depression Evaluation Schedule; GMS, Geriatric Mental State diagnostic schedule; GDS, Geriatric Depression Scale.

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