Journal of Clinical Neuroscience 30 (2016) 1–7

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Review

The -141C Ins/Del and Taq1A polymorphism in the dopamine D2 receptor gene may confer susceptibility to schizophrenia in Asian populations

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ARTICLE INFO

Article history:
Received 2 June 2015
Accepted 31 October 2015

Keywords:
DRD2
Meta-analysis
Schizophrenia
Taq1A
-141C Ins/Del

ABSTRACT

It has been reported that two single nucleotide polymorphisms (SNP) Taq1A and -141C Ins/Del in the *DRD2* gene may be associated with susceptibility to schizophrenia. Due to inconclusive and mixed results, a meta-analysis was conducted to further clarify the relationship between the two SNP and schizophrenia susceptibility. A systematic literature search for the association of these two SNP with schizophrenia susceptibility was conducted using PubMed, ScienceDirect, Chinese Biomedical Literature Database, and Chinese National Knowledge Infrastructure. Odds ratios (OR) with 95% confidence intervals (CI) were used to assess the strength of the associations reported. A total of 5558 schizophrenic patients and 6792 healthy controls from 31 articles were included in this study. Evidence regarding the association between -141C Ins/Del polymorphism and schizophrenia was found in the allele frequency comparison (Ins *versus* Del: OR 1.29, 95% CI 1.06–1.57; $p = 0.01$, $P_{raw} = 0.1$, $P_{False\ Discovery\ Rate} = 0.023$). In ethnic subgroup analysis, the result revealed that the 141C Ins/Del polymorphism was associated with schizophrenia in all genetic models in Asians, but not in Caucasians. For Taq1A polymorphism, a significant association was found in the allele frequency (A1 *versus* A2: OR 0.71, 95% CI 0.52–0.98, $p = 0.03$). Stratification by ethnicity indicated an association between the Taq1A polymorphism and schizophrenia in Asians, but not Caucasians. The present study suggests that the -141C Ins/Del polymorphism carries a significantly increased risk of schizophrenia, while the Taq1A polymorphism carries a significantly decreased risk of schizophrenia susceptibility in Asians.

1. Introduction

Schizophrenia is a disabling brain disorder with a median lifetime prevalence of 4 per 1000 people, characterized by positive symptoms such as hallucinations and delusions and negative symptoms such as disorganized communication, reduced motivation, poor planning, and blunted affect [1,2]. Although the biological basis of schizophrenia remains obscure, the importance of genetic factors in schizophrenia has consistently been demonstrated in epidemiological [2], twin [3] and family studies [4]. The dopamine D2 receptor (*DRD2*) gene has been recognized as one of the most pertinent candidate genes for schizophrenia.

Biochemistry and pharmacology studies have also strongly suggested that schizophrenia may be a result of dysfunction of the dopaminergic system [5]. Dopamine is the most abundant catecholaminergic neurotransmitter in the brain, and is involved in the regulation of emotions, motivation, reward and reinforcement behavior through the mesocorticolimbic pathway [6]. *DRD2* is most densely expressed in the basal ganglia, an area of the central nervous system that regulates movement [7]. Dopamine is a major target of antipsychotic drugs used to treat schizophrenia and their effect appears to be related to their capacity to block dopamine receptors [8]. Moreover, *DRD2* mRNA levels in peripheral blood leukocytes have been correlated with positive symptoms in acute schizophrenic patients [9]. Collectively, accumulating evidence has implied that *DRD2* is associated with schizophrenia.

The *DRD2* gene is located within 270 kilobases of chromosome 11q22-23 [10], with several polymorphisms in *DRD2* identified in the past few decades. Recently, these polymorphisms have attracted widespread attention, including a polymorphism 3′ to the *DRD2* gene which is actually an amino acid change in the *ANKK1* gene, referred to as Taq1A (rs1800497). A large number of studies have been conducted to investigate the relationship between Taq1A

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http://dx.doi.org/10.1016/j.jocn.2015.10.052
0967-5868/

polymorphism and the risk of schizophrenia. However, findings of these studies have been inconsistent. Several studies have shown that the Taq1A polymorphism of *DRD2* increases susceptibility to schizophrenia [11,12], but other papers have shown contrary results [13,14]. The -141C Ins/Del (rs1799732) polymorphism of *DRD2* has also been reported to be involved in schizophrenia risk [15,16], but again results have been inconsistent.

Meta-analysis is a statistical method to effectively combine the results of several studies to produce a single estimate of the major effect with enhanced precision [17]. Previous meta-analyses have suggested that *DRD2* Taq1A and -141C Ins/Del may not be genetic risk factors for schizophrenia [18,19], but many new studies of the role of those two single nucleotide polymorphisms (SNP) in schizophrenia have been published recently [12,20,21]. Therefore, to further explore the association between *DRD2* SNP and schizophrenia risk in populations, two SNP of *DRD2* gene were eligible for this update meta-analysis: Taq1A (rs1800497) and -141C Ins/Del (rs1799732).

2. Materials and methods

2.1. Literature search

To obtain relevant articles a systematic literature review was conducted using PubMed, ScienceDirect, Chinese National Knowledge Infrastructure, and Chinese Biomedical Literature Database up to 4 August 2014. The following combined terms were employed: "schizophrenia", "SCZ", "polymorphism", "dopamine receptor D2" and "*DRD2*". Studies published in English and Chinese were considered. References cited in retrieved articles and prior meta-analyses were examined to obtain additional eligible studies. Only full length published papers were considered, meaning all meeting or conference abstracts were discarded. When one patient was included in several publications, only the most recent or most complete study was included in the meta-analysis. The inclusion criteria were as follows: (1) study evaluates the relationship between the Taq1A and/or -141C Ins/Del polymorphism of the *DRD2* gene and schizophrenia; (2) case–control study design; (3) sufficient data about both cases and controls to calculate an odds ratio (OR) with 95% confidence interval (CI); and (4) available allele frequency or genotype distribution data for comparison. The exclusion criteria were: (1) studies with insufficient data; (2) studies that contained overlapping data; (3) studies reporting family members, and (4) genotype distribution of the control population that did not conform to the Hardy–Weinberg equilibrium (HWE).

2.2. Data extraction

All potential relevant studies were assessed independently by two researchers (Y.W. and L.L.) according to the inclusion and exclusion criteria. Disagreements about eligibility were resolved by discussion with a third researcher (L.X.). The following characteristics were extracted: first author, year of publication, original country, ethnicity, diagnostic criteria for patients, number of patients and controls, allele frequencies and genotype distribution of patients and controls.

2.3. Qualitative assessment

The quality of included studies was evaluated by two independent reviewers using the modified Newcastle–Ottawa Scale [22]. Selection, comparability and exposure were used to judge quality, consisting of four, two and three items each, respectively. Each item had a maximum score of 1 point, meaning scores ranged from 0 to 9. Studies with a score $\geqslant 6$ were considered high quality (Table 1).

2.4. Statistical analysis

In this study, the χ^2-test was used to calculate the HWE if the enrolled articles did not report this test themselves. The OR with 95% CI was used to estimate the strength of the association between DRD2 Taq1A and -141C Ins/Del polymorphisms and schizophrenia risk. The significance of the pooled OR was determined using the Z-test with a p value less than 0.05 considered statistically significant. Cochran's Q statistic [23] was performed to investigate the degree of heterogeneity across the included studies, while the I^2 test also measured the effect of heterogeneity ($I^2 = 100\% \times [Q - \text{degrees of freedom}]/Q$) [24]. I^2 values of 25%, 50% and 75% were defined as low, moderate and high estimates of heterogeneity, respectively. When a p value less than 0.10 for the Q-test or I^2 >50% indicated heterogeneity across studies, a random-effects (Dersimonian and Laird) model [25] was used to summarize the pooled OR; otherwise, the fixed-effects (Mantel–Haenszel) model [26] was used. To adjust for multiple comparisons, step-down Bonferroni method [27] and Benjamini–Hochberg method [28] were used to control the familywise error rate and false discovery rate (FDR), respectively. Begg's rank regression and Egger's weighted regression were used to estimate potential publication bias. All statistical analyses were carried out using STATA version 11.0 (StataCorp, College Station, TX, USA).

3. Results

3.1. Characteristics of eligible studies

A total of 695 relevant articles were initially identified from the search. After titles and abstracts were screened, 46 were retrieved for more detailed evaluation. After reviewing the full text, 15 studies were excluded as six were reviews [18,19,29–32], two were in Russian [33,34], one was in Polish [35], one was based on family members [36], two observed HWE disequilibrium in the control group [37,38] and three had overlapping data [39–41]. Thus, a total of 31 articles [8,11–16,20,21,42–63] were included in this meta-analysis. The detailed retrieval process is shown in Figure 1. Among these articles, one [58] included two independent investigations into Taq1A and -141C Ins/Del in schizophrenia, but the HWE was not found when investigating the Taq1A polymorphism, so we extracted the data only for -141C Ins/Del. One study included subjects from two different ethnic groups so we extracted the data separately and used it as two studies [46]. Finally, the present review contained 5558 schizophrenia patients and 6792 healthy controls, with 13 studies concerning Taq1A and 22 for -141C Ins/Del. Characteristics of the included studies is summarized in Table 1. All included studies were high quality with Newcastle–Ottawa Scale scores $\geqslant 6$.

3.2. Meta-analysis

Table 2 demonstrates the present meta-analysis for the *DRD2* (Taq1A and -141C Ins/Del) polymorphisms with genetic susceptibility to schizophrenia.

3.2.1. Analysis for DRD2 gene -141C Ins/Del polymorphism

Our meta-analysis showed a significant association between *DRD2* -141C Ins/Del polymorphism and schizophrenia risk in the allele frequency comparison (Ins *versus* Del: OR 1.29, 95% CI 1.06–1.57, $p = 0.01$, $P_{raw} = 0.1$, $P_{FDR} = 0.023$; Fig. 2). However, no significant association was found in the dominant model (Ins/Ins + Ins/Del *versus* Del/Del: OR 1.36, 95% CI 0.92–2.01, $p = 0.13$, $P_{raw} = 0.65$, $P_{FDR} = 0.173$), recessive model (Ins/Ins *versus* Ins/Del + Del/Del: OR 1.26, 95% CI 1.02–1.57, $p = 0.04$, $P_{raw} = 0.36$, $P_{FDR} = 0.08$) or homozygote comparison (Ins/Ins *versus* Del/Del: