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Research article

Association between *ANKK1* (rs1800497) polymorphism of *DRD2* gene and attention deficit hyperactivity disorder: A meta-analysis

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HIGHLIGHTS

- The association between *ANKK1* polymorphisms and ADHD was analyzed using meta-analysis.
- Rs1800497 locus was associated with the risk of ADHD in the dominant model.
- Meta-regression was performed to explore sources of significant heterogeneity.

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ABSTRACT

The role of dopamine neurotransmitter in attention deficit hyperactivity disorder (ADHD) remains controversial. Many molecular studies focusing on dopamine receptors have attempted to analyze the gene polymorphisms involved in dopaminergic transmission. Of these, rs1800497 (*Taq*IA) single nucleotide polymorphism (SNP) of the dopamine D2 receptor (*DRD2*) gene has been focused on by the most attention. However, this locus has recently been identified within the exon 8 of ankyrin repeat and kinase domain containing 1 (*ANKK1*), giving rise to a Glu713-to-Lys substitution in the putative *ANKK1* protein. Thus, we performed a meta-analysis to determine whether *ANKK1* polymorphism influences the risk of ADHD and examined the relationship between rs1800497 genetic variant and the etiology of ADHD. Relevant case-control studies were retrieved by database searches and selected according to established inclusion criteria. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of the associations. Meta-regression, subgroup analysis, sensitivity analysis and cumulative meta-analysis were performed. A total of 11 studies with 1645 cases and 1641 controls were included. In the dominant model, the rs1800497 locus was associated with ADHD, with a pooled OR of 1.785 (95% CI = 1.068–2.984, $p = 0.027$). Subgroup analysis for ethnicity indicated that the polymorphism was associated with ADHD in Africans (OR = 3.286, 95% CI = 1.434–7.527, $p = 0.005$), but not in East Asians (OR = 1.513, 95% CI = 0.817–2.805, $p = 0.188$) and Caucasians (OR = 1.740, 95% CI = 0.928–3.263, $p = 0.084$). However, the results of meta-regression indicated that publication date ($p = 0.601$), source of controls ($p = 0.685$), ethnicity ($p = 0.755$) and diagnostic criteria ($p = 0.104$) could not explain the potential sources of heterogeneity. This meta-analysis indicates that the rs1800497 locus may be associated with ADHD. These data provide possible references for future case-control studies in childhood disorders.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common childhood psychiatric disorders, which affects around 1–3% of children, and can persist into the adulthood with significant social, academic and occupational influences [1,2]. Recent investigations support a model in which multiple genetic and environmental factors interact to create a neurobiological susceptibility to develop ADHD [3]. Its heritability ranges from 60% to 90% [4,5] and family, twin and adoption studies have identified the impact of genetic variation on the risk of the disorder [6]. However, the definite etiology of ADHD is difficult to determine and remains inconclusive [7,8]. Molecular genetics research has been attempting to ascertain the inherited susceptible genes of ADHD. Consistent with the dopamine deficit hypothesis of ADHD etiology [9], dysregulation of dopaminergic neurotransmission has been implicated in the pathogenesis of ADHD [10,11].

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Dopamine is an important neurotransmitter which plays a significant role in modulating cognitive, mood and motor functions of the brain [12]. It plays a regulatory function by binding to the dopamine receptors of the postsynaptic membrane. Several molecular studies focusing on dopamine receptors in ADHD patients have attempted to analyze the polymorphisms involved in dopaminergic transmission. Of these, rs1800497 (*Taq*IA) single nucleotide polymorphism (SNP) of the dopamine D2 receptor (*DRD2*) gene has attracted the most attention. This locus lies 10,541 bp downstream of the termination codon of the *DRD2* gene, where it makes a presence of a restriction fragment length polymorphism [13]. The two alleles are referred to as C (cytosine/A2) and T (thymine/A1). However, this polymorphism has recently been identified within the exon 8 of ankyrin repeat and kinase domain containing 1 (*ANKK1*), giving rise to a Glu713-to-Lys substitution in the putative *ANKK1* protein [14]. Thus, rs1800497 locus localization within a protein-coding region of *ANKK1* summons the straightforward explanation between this variant and *DRD2*.

Rs1800497 is located in a putative substrate binding domain of the *ANNK1* gene, which results in a Glu713Lys substitution and may alter substrate-binding specificity [14]. *ANKK1* gene may affect phosphorylation of amino acid residues within key proteins involved in dopaminergic activity [15] and is associated with susceptibility to second generation antipsychotic-induced akathisia [16]. Additionally, it was also considered to modulate the function and expression of *DRD2* for its vicinity to *DRD2* [17]. Among the five dopamine receptor subtypes, *DRD2* seems to be the cardinal type that regulate the firing rate, synthesis and release of dopamine in presynaptic membrane [18]. Signal transduction through *DRD2* controls substance abuse, locomotor behavior and antipsychiatric drug treatment response in ADHD patients [19–21]. Thus, it is not unexpected that rs1800497 variance is associated with the occurrence of ADHD.

In recent years, numerous molecular epidemiological studies have been conducted to investigate the putative association between rs1800497 SNP and ADHD in different samples. The T allele was found to be significantly more prevalent in patients with ADHD than in controls [22,23]. Moreover, studies in Czech population conducted in hyperkinetic boys and control boys supported the positive association [24,25]. A positive association was found between this polymorphism and ADHD in male African–Caribbean patients [26]. However, no relationship with rs1800497 locus has been observed in American [27] and Taiwanese patients [28]. Family studies found no significant difference in transmission rate between rs1800497 T and C alleles and did not support this variance playing a major role in the etiology of ADHD [29,30]. The above results were conflicting or inconclusive, presumably due to various genetic backgrounds, small sample size and potential confounding bias. Meta-analysis is a widely used statistical method in medical studies, particularly for a topic that are being extensively studied with controversial results [31]. Thus, we performed a meta-analysis to provide a more comprehensive assessment of the association between this polymorphism and ADHD.

2. Materials and methods

2.1. Identification and eligibility of relevant studies

To identify studies eligible for inclusion in this meta-analysis, three online electronic databases (PubMed, Embase, and Web of Science) were searched (the last search update was 2014 October), and the following keywords were used in the literature search: *DRD2* – dopamine receptor 2; ankyrin repeat and kinase domain containing 1 – *ANKK1*; attention deficit hyperactivity disorder – ADHD; rs1800497; polymorphism. Reference lists from identified articles and potentially relevant review articles were also screened to identify additional studies. Studies met the following inclusion criteria: (1) case-control design; (2) included patients with ADHD; and (3) stated available allele or genotype frequencies. For the studies with the same or overlapping data published by the same authors, the most recent articles were selected. Major reasons for exclusion were: (1) no control population; (2) duplicate of an earlier publication; and (3) lack of usable genotype frequency data. Study authors were contacted for additional details (e.g., allele or genotype frequencies or sample characteristics) if we needed to retrieve additional data that was not contained in the original report.

2.2. Data extraction

Based on the inclusion criteria, two reviewers (Yu-qing Pan and Lin Qiao) independently extracted information from all eligible publications. Disagreements were resolved by discussion until the two reviewers reached an agreement. The following data were included from each study: first author's last name, publication year, sample size, region, and number of genotypes between cases and controls. To delineate potential moderating influences on the effects obtained from the case-control studies under consideration, we also included the following variables: (1) ethnicity of the sample population; (2) diagnostic criteria; (3) mean age of the case group; and (4) proportion of males in the ADHD sample.

2.3. Quality assessment

Two authors (Yu-qing Pan and Xin-dong Xue) independently assessed the quality of the included studies according to the Newcastle Ottawa Scale (NOS) (www.ohri.ca/programs/clinical_epidemiology/oxfprd.asp). This scale consists of three components related to sample selection, comparability and ascertainment of exposure. A score of five or more (maximum of nine) was regarded as "high quality"; studies with scores from zero to four were considered "low quality" [32].

2.4. Statistical analysis

All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. The meta-analysis was performed using Stata version 10.0 (Stata Corp., College Station, TX). Hardy–Weinberg equilibrium (HWE) in the genotype distribution of controls was calculated. The chi-square goodness of fit was used to test deviation from HWE. Pooled frequency analysis was performed according to Thakkinstian's method [33]. The strength of the association between the target locus and ADHD was measured by odds ratios (ORs) with 95% confidence intervals (CIs). Pooled effect sizes across studies were performed by a random effects model. The degree of heterogeneity between studies was determined by Q-statistic [34,35]. Subgroup analysis was performed by ethnicity (East Asian, Caucasian, and Africans), source of controls (hospital-based and population-based), diagnostic criteria (DSM-III, DSM-III-R and DSM-IV) and study quality (high and low). Meta-regression was used to measure the potential sources of heterogeneity including publication date, source of controls, ethnicity and diagnostic criteria. To explore dynamic trends as studies accumulated over time, a cumulative meta-analysis was carried out by publication date [36]. The detail description was supplied in Supplementary material.

3. Results

After the removal of overlapping articles and those that did not meet the inclusion criteria, a total of 11 articles [22–26,37–42] including 11 studies with 1645 cases and 1614 controls were finally

Table 1
Distribution of genotype and allele frequencies of the *ANKK1* rs1800497 locus.

	Genotype distribution							Allele frequency					
	Cases, *n*			Controls, *n*				Cases, %		Controls, %		Sample size	
Author	CC	CT	TT	CC	CT	TT	P_{HWE}	C	T	C	T	Case	Control
Ballon	10	25	5	46	37	5	0.4872	56.25	43.8	73.3	26.7	40	88
Comings	56	42	6	84	24	0	0.1939	74.04	26.0	88.9	11.1	104	108
Comings	80	68	15	40	56	20	0.9579	69.94	30.1	58.6	41.4	163	116
Drtilkova	65	46	8	111	39	3	0.8422	73.95	26.1	85.3	14.7	119	153
Kopeckova	24	40	36	73	25	2	0.9341	44.00	56.0	85.5	14.5	100	100
Nyman	45	68	5	22	54	15	0.0644	66.95	33.1	53.8	46.2	118	91
Paclt	120	104	45	230	81	6	0.7126	63.94	36.1	85.3	14.7	269	317
Park	14	36	8	37	53	20	0.8933	55.17	44.8	57.7	42.3	58	110
Qian	9	96	232	4	31	80	0.6461	16.91	83.1	17.0	83.0	337	115
Sery	65	45	8	110	40	3	0.7721	74.15	25.8	85.0	15.0	118	153
Waldman	154	59	6	173	81	9	0.8983	83.79	16.2	81.2	18.8	219	263

Note: P_{HWE} reprents the *P* value of Hardy-Weinberg equilibrium test in the genotype distribution of controls.

included in our meta-analysis. The key characteristics of the studies and NOS scale information are described in Table S1. Based on results of the NOS scale, 8 studies were considered high quality, and 3 studies were considered low quality. Genotype and allele frequencies, HWE and sample size are described in Table 1. Of the total 11 studies, no studies were observed to present the significant deviation from HWE.

3.1. Frequency of risk allele in the control population

We calculated the pooled frequencies of the rs1800497 locus in controls stratified by ethnicity. The allele frequencies of this variance varied among ethnicities: the pooled T allele frequency was highest among East Asians (55.3%, 95% CI = 22.3–88.4%), followed by Caucasians (19.2%, 95% CI = 16.0–22.3%), and the overall pooled T allele frequency was 25.8% (95% CI = 21.0–30.6%).

3.2. Quantitative synthesis and heterogeneity analysis

We analyzed 11 studies that included 1645 cases and 1641 controls regarding the association between rs1800497 and ADHD. We summarized the pooled ORs and corresponding 95% CIs for the rs1800497 locus in homozygous codominant, heterozygous codominant, dominant, recessive, and allele contrast genetic models (Table S2 and Figs. S1–S5). The dominant model was determined according to the principle of genetic model selection [43,44]. Summary results indicate that there was an association between the rs1800497 locus and the occurrence of ADHD and the pooled OR using random effects model was 1.785 (95% CI = 1.068–2.984, $p = 0.027$). Subgroup analysis for ethnicity indicated that the polymorphism was associated with ADHD in Africans (OR = 3.286, 95% CI = 1.434–7.527, $p = 0.005$), but not in East Asians (OR = 1.513, 95% CI = 0.817–2.805, $p = 0.188$) and Caucasians (OR = 1.740, 95% CI = 0.928–3.263, $p = 0.084$) (Table S3). Moreover, no association between rs1800497 locus and ADHD was observed when subgroup analysis for source of controls was conducted (hospital-based: OR = 1.535, 95% CI = 0.679–3.473, $p = 0.303$; population-based: OR = 1.940, 95% CI = 0.978–3.849, $p = 0.058$). When subgroup analysis was performed by diagnostic criteria, the relationships were observed between rs1800497 locus and ADHD according to three different diagnostic criteria (DSM-III: OR = 3.000, 95% CI = 1.654–5.441, $p < 0.001$; DSM-III-R: OR = 0.546, 95% CI = 0.334–0.892, $p = 0.016$; DSM-IV: OR = 1.936, 95% CI = 1.117–3.356, $p = 0.019$). In addition, subgroup analysis for study quality showed that the variance was associated with ADHD in high quality studies (OR = 2.062, 95% CI = 1.102–3.858, $p = 0.024$), but not in low quality studies (OR = 1.228, 95% CI = 0.491–3.070, $p = 0.660$).

Meta-regression was performed to explore sources of significant heterogeneity. Results of the meta-regression indicated that publication date ($p = 0.601$), source of controls ($p = 0.685$), ethnicity ($p = 0.755$) and diagnostic criteria ($p = 0.104$) had no statistical significance.

3.3. Cumulative meta-analysis

Cumulative meta-analysis was performed using a dominant model for rs1800497 locus. No continuous trend toward a significant association with a more narrowing 95% CI was presented as studies published by year (Fig. S6).

3.4. Sensitivity analysis

Sensitivity analysis was performed for each meta-analysis to assess the influence of every single study. Corresponding pooled ORs showed no significant change when one study was removed at a time from each meta-analysis, indicating that these results are stable and reliable.

3.5. Publication bias

A funnel plot was generated to assess potential publication bias (Fig. S7). Egger's test was used to supply statistical evidence for funnel plot symmetry and the result did not show any evidence of publication bias ($p = 0.874$).

4. Discussion

Overall, our meta-analytical results provided evidences that rs1800497 locus was associated with ADHD. Subgroup analysis stratified by source of controls, ethnicity, diagnostic criteria, and study quality were performed to further explore the distribution disequilibrium of cases and controls. Additionally, cumulative meta-analysis and sensitivity analysis strengthened the validity of the results.

Previously, two meta-analyses investigated the association between the rs1800497 polymorphisms and ADHD [10,45]. Our results were largely consistent with Wu's results (OR = 1.65, 95% CI = 0.89–3.06, $p = 0.110$) [10], but opposite to Gizer's (OR = 1.65, 95% CI = 1.05–2.58, $p < 0.0001$) [45]. Although Wu's study observed a significant association, partly due to the excessive heterogeneity, this positive relationship should be explained cautiously and the source of heterogeneity need to be sought. Though our meta-analysis may seem superfluous, to some extent, it still possessed several advantages over previous studies with respect to the following points. First, we included the recent published studies concerned

with the association between *ANKK1* polymorphism and the occurrence of ADHD. Second, due to the excessive heterogeneity, besides stratified analyses, we further preformed meta-regression and cumulative meta-analysis to assess potential sources of heterogeneity and study stability respectively. To some degree, our study could provide a more precise assessment of the relationship between the *ANKK1* gene and ADHD.

Associations between *ANKK1* loci and ADHD varied with different ethnicities. *ANKK1* polymorphism was associated with ADHD in Africans, while this association disappeared in East Asians and Caucasians. However, the relationship between the target locus and ADHD is just based on a single study including 40 cases and 88 controls [26]. Thus, the association should be cautiously interpreted. This phenomenon may result from two factors. Different genetic backgrounds may contribute to divergence, because the distribution of rs1800497 allele frequencies varies among Africans, East Asians and Caucasians. Apparently, genetic liability is a high risk factor for ADHD [46]. Gene polymorphisms vary among different ethnicities and may affect disease outcome by acting synergistically or antagonistically and thus, their combined effect becomes an important aspect to study in the disease etiology [6]. Furthermore, parents of children with ADHD differed by ethnicity in their utilization of certain parenting strategies. Additionally, different populations have diverse life-styles and are affected by the varied environmental factors [47]. Epigenetic risk mechanisms in ADHD may respond to environmental risk factors or trans-regulatory and the gene × environment effects in the development of child psychopathology might play a potential consequential role in the etiology of ADHD [48]. When stratifying by the source of controls, neither of the associations between hospital-based and population-based control studies was not observed, the pooled result solely containing the population-based control studies presented a margin relationship trend. Hospital-based studies are more likely to generate unreliable results in that control patients from hospitals do not completely represent the general population, particularly when the target polymorphisms in question might be related to the disorders that afflict hospital-based control patients [49]. In addition, the subtypes of ADHD represent distinct clinical entities and may have the different genetic backgrounds [50].

There are several potential limitations to the present study. First, we did not perform the subgroup of sources of cases for the reason that there was not sufficient data of the proportion between population and hospital patients. However, this analysis should be done, considering that the same symptoms of participants may have the diverse characteristic of the etiology and there are differences not only in the clinical manifestations but also in the effect of environmental and genetic influences on the family aggregation in population and hospital patients [51]. Second, there was significant heterogeneity in overall and subgroup analyses. Clinical subtypes of ADHD (combined presentation, predominantly inattentive presentation and predominantly hyperactive/impulsive presentation), gene-gene interaction and epigenetics were not examined in this study due to insufficient information. Although we performed meta-regression, including publication date, source of controls, ethnicity and diagnostic criteria, to investigate potential sources of heterogeneity, none of the factors completely accounted for the heterogeneity. These results suggest that other aspects might partially contribute to heterogeneity. Finally, the sample size of the rs1800497 locus was not large enough to draw meaningful conclusions. Small samples with limited participants are usually accompanied by selection biases. These studies lack sufficient power to uphold or deny an association [52].

In summary, our findings suggest that the *ANKK1* gene rs1800497 polymorphism is associated with ADHD and that the T allele is a risk factor. Large sample studies, particularly in different ethnicities, will be necessary to confirm the results of this meta-analysis and to investigate epigenetic mechanisms and environmental influences on the occurrence of ADHD.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neulet.2015.01.076.

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