Journal of Psychiatric Research 81 (2016) 56–62

Contents lists available at ScienceDirect

Journal of Psychiatric Research

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

Two SNAP-25 genetic variants in the binding site of multiple microRNAs and susceptibility of ADHD: A meta-analysis

Chuanzhong Ye [a, *, 1], Zhijian Hu [b, 1], Evan Wu [c], Xiaolu Yang [b], Ushimbra J. Buford [a], Zhihong Guo [a], Radu V. Saveanu [a]

[a] Department of Psychiatry & Behavioral Sciences, University of Miami Miller School of Medicine/Jackson Health System, 1695 NW 9th Ave, 33136, United States
[b] Department of Epidemiology and Health Statistics, Fujian Medical University, 1 Xue Yuan Road University Town, Fujian, 350108, China
[c] Department of Health Sciences, University of Miami Miller School of Medicine, 1120 NW 14th St, Miami, FL, 33136, United States

ARTICLE INFO

Article history:
Received 24 March 2016
Received in revised form
23 May 2016
Accepted 10 June 2016

Keywords:
SNP
rs3746544
rs1051312
ADHD
microRNAs

ABSTRACT

The aim of this meta-analysis is to assess the associations between two most widely investigated polymorphisms (rs3746544 and rs1051312) in the 3′UTR of the SNAP-25 gene and susceptibility of ADHD. Two investigators selected related studies and assessed methodological quality independently. Six studies were included in this meta-analysis for a total of 715 cases and 655 controls. There is no apparent association between rs3746544 polymorphisms and risk of ADHD. However, subgroup analysis based on ethnicity demonstrated a strong association between rs3746544 polymorphism and ADHD in the subset of Asian participants, but not among Caucasians. Compared to the T allele, the allele G was associated with a significantly decreased risk of developing ADHD in the Asian population (odds ratio (OR) = 0.70, 95% confidence interval (CI) = 0.52–0.95, $p = 0.02$). The association between the TT genotype and ADHD risk was also significantly increased as compared to G/T (OR = 1.56, 95% CI = 1.00–2.44, $p = 0.05$) and the dominant genetic model (GG + GT vs. TT: OR = 1.51, 95% CI = 1.07–2.13, $p = 0.02$). For the rs1051312 SNP, being homozygous for the minor allele (C/C) was associated with a 3.66 higher odds of ADHD as compared to cases homozygous for the major allele (T/T) (95% CI = 1.64–8.13, $p = 0.001$), and 3.57 higher odds as compared to heterozygous (C/T) carriers (95% CI = 2.01–12.90, $p < 0.001$). Our results suggest that the polymorphisms rs3746544 and rs1051312 may increase the odds of developing ADHD. Additional studies are needed to confirm these findings.

ADHD is a multifactorial disorder with heritability estimates around 76%, suggesting an important role for genetic factors (Fonseca et al., 2015). Previous molecular genetics studies have proposed multiple genes that exert moderate effects on the development of ADHD (Faraone et al., 2005; Zhang et al., 2011). The genome-wide association (GWA) study is a useful tool for discovering novel risk variants as it allows a hypothesis-free interrogation of the entire genome. Several GWA analyses have been performed to identify ADHD risk loci using either case-control or family-based designs. However, there has yet to be discovered a single nucleotide polymorphism (SNP) reaching the stringent genome-wide significance threshold ($p < 5.00E-08$). Nonetheless, the results from GWA studies suggest that genes playing a role in ADHD are related to the processes that enhance neuronal plasticity, including neuronal migration, cell adhesion, cell division, and signaling via the potassium channel-system (Zayats et al., 2015; Gatt et al., 2015; Gao et al., 2014).

Although the case-control study SNP-GWAS has had limited success in identifying common genetic variants for ADHD that surpass critical significance thresholds, several candidate genes have been proposed to have promising associations, including the SNAP-25 gene (Lasky-Su et al., 2008; Hawi et al., 2015). SNAP-25 is a member of the soluble N-ethylmaleimide-sensitive factor attachment receptor (SNARE) protein complex, which plays essential roles in the modulation of different voltage-gated calcium channels and neurotransmitter release (Wang and Tang, 2006).

* Corresponding author. Department of Psychiatry & Behavioral Sciences, University of Miami Miller School of Medicine/Jackson Health System, 1695 NW 9th Ave, Suite 3100, D29, Miami, 33136, United States.
E-mail address: Chuanzhong.ye@jhsmiami.org (C. Ye).
[1] Chuanzhong Ye and Zhijian Hu have contributed to the work equally.

http://dx.doi.org/10.1016/j.jpsychires.2016.06.007
0022-3956/

Polymorphisms in the SNAP-25 gene, as well as altered expression of the protein, have been associated with abnormal behavioral phenotypes in both animal models and humans (Wilson, 2000; Braida et al., 2015). For example, the Coloboma mouse mutant, which is homozygous for a deletion spanning the SNAP-25 gene, has been shown to display spontaneous hyperactivity (Wilson, 2000).

MicroRNAs are approximately 19–23 nucleotide (nt) noncoding RNA molecules that can regulate target gene expression at the posttranscriptional level (He and Hannon, 2004). They bind to a region of mRNA (3′-UTR) that result in physiologic and pathologic changes. Single nucleotide polymorphisms (SNPs) is a mutation in a single nucleotide, the most common type of human genetic variation associated with disease susceptibility and population diversity (Shastry, 2002). SNPs in the 3′-UTR targeted by miRNAs can either abolish existing binding sites or create illegitimate binding sites, which result in the regulation of target genes that can affect the expression of target genes (Chen et al., 2008). Many studies have suggested that SNPs in miRNA target sites (miRSNP) are associated with the risk and the prognosis of various diseases (Hong et al., 2016; Sery et al., 2015; Wang et al., 2016; Ryan et al., 2015). There are two SNPs – rs1051312 (1069T > C) and rs3746544 (1065T > G) – of the SNAP-25 gene of particular interest in the development of ADHD (Nemeth et al., 2013; Barr et al., 2000). The relationship between the genetic differences and development of ADHD could be related to how the signaling pathways arranged by the miRNAs impact CNS development in children. Thus far, four family-based studies have shown that these two SNPs are associated with increased risk of ADHD (Barr et al., 2000; Brophy et al., 2002; Kustanovich et al., 2003; Mill et al., 2004). However, the findings from subsequent case-control studies have been inconsistent, and this discrepancy may be due to inadequate statistical power, ethnic differences and publication bias (Barr et al., 2000; Pazvantoglu et al., 2013; Sarkar et al., 2012; Galvez et al., 2014; Choi et al., 2007; Zhao et al., 2007; Herken et al., 2014).

Meta-analyses can enhance the power by combining data from different individual studies and draw a more integrated conclusion than a single study. We applied meta-analytic strategies to data from available association studies and considered possible factors that could account for heterogeneity between studies. The aim of this meta-analysis was to assess the associations between the rs3746544 and the rs1051312 polymorphisms and risk for development of ADHD.

1. Materials and methods

1.1. Publication search

We searched for studies in the PubMed, EMBASE, Cochrane Library, CINAHL, PsycINFO, and CNKI (China National Knowledge Infrastructure) electronic databases to include in this meta-analysis, using the terms “SNAP-25,” “polymorphism,” and “attention-deficit hyperactivity disorder(ADHD).” An upper date limit of Jul 5, 2000 was applied; no lower date limit was used. The search was restricted to English and Chinese language publications and studies conducted in humans. Reference lists in retrieved articles were also screened. Eligible studies should meet the following criteria: (a) case-control studies, (b) evaluated SNAP-25 (rs3746544 and rs1051312) gene polymorphisms and ADHD, (c) detailed genotype data for estimating OR and 95% CI, (d) supplied the number of individual genotypes for the SNAP-25 (rs3746544 and rs1051312) polymorphisms in ADHD cases and controls. If multiple studies had overlapping or duplicate data, only those with complete data were included.

1.2. Data extraction

Information was extracted from all eligible publications independently by two authors based on the inclusion criteria above. Disagreements were resolved through a discussion between the two authors.

The following data were collected from each study: first author’s surname, year of publication, country, ethnicity, study design, genotyping method, and the genotype distribution of SNAP-25 (rs3746544 and rs1051312) in cases and controls. The frequencies of the alleles in each study were then extracted. All data were extracted from published articles, and we did not contact individual authors for further information.

1.3. Statistical analysis

We calculated the OR and corresponding 95% CI to evaluate the associations between the SNAP-25 (rs3746544 and rs1051312) polymorphisms and ADHD. We applied either of two meta-analysis models for dichotomous outcomes, depending upon the heterogeneity test statistic across individual studies. Heterogeneity between studies was assessed using the Chi-square-based Q statistic test, and a Q statistic test was considered significant at $p < 0.10$. A fixed effects model (Mantel–Haenszel) was used to summarize the combined OR if $p \geq 0.10$, and a random-effects model (DerSimonian and Laird) if $p < 0.10$.

The significance of the pooled OR was determined by the Z-test. A p-value < 0.05 was considered significant. Publication bias was investigated with the funnel plot, where the standard error (SE) of log (OR) for each study was plotted against the respective log (OR). An asymmetric plot suggests a possible publication bias. Funnel plot asymmetry was assessed further using Egger’s linear regression method. The significance of the intercept was determined by the t-test, and a p-value < 0.05 was considered significant. The X^2 goodness-of-fit test was used to evaluate whether genotypes within the control subjects conformed to the Hardy–Weinberg equilibrium (HWE). All above analyses were performed using the software Stata 12.0 (Stata Corp., College Station, Texas) and all p-values were two-sided. In addition, we also used a macro (%metapower) developed by Guy Gafri et al. in the software SAS 9.2 to assess the statistical power of a meta-analysis (SAS, Cary, NC) (Cafri et al., 2009).

2. Results

2.1. Characteristics of studies

Using our search criterion, 21 potentially relevant publications were found. After excluding 15 records based on previously outlined exclusion criteria, six full-text publications were preliminarily identified for further review. According to the selection criteria, the six full-text publications yielded 715 cases and 655 controls eligible for inclusion in this meta-analysis (Supplemental Fig. 1). There were five English language articles and one Chinese language manuscript. All studies were case-control studies. Three of the studies had primarily Caucasian study participants, and three had primarily Asian participants. The distribution of SNAP-25 single nucleotide polymorphisms in controls was in agreement with HWE ($p > 0.05$) (Table 1).

2.2. Meta-analysis results

Table 2 showed the main results of the association between SNAP-25 polymorphisms (rs3746544 and rs1051312) and ADHD. For the rs3746544, the pooled OR of comprehensive studies by the