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Association between variants of zinc finger genes and psychiatric disorders: Systematic review and meta-analysis

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ABSTRACT

Psychiatric disorders have a negative impact on society and human lives. Genetic factors are involved in the occurrence and development of psychiatric diseases. *ZNF804A* has been identified as one of the most compelling risk genes associated with broad phenotypes related to psychosis. We conducted a systematic meta-analysis and reviewed *ZNF804A* variants in psychosis-related disorders, including schizophrenia, bipolar disorder, and attention-deficit hyperactivity disorder. We also summarized the association between other zinc finger protein genes (*ZNFs*) and psychiatric diseases. The meta-analysis included a total of six variants of *ZNF804A* and three variants of other *ZNFs* (*ZDHHC8* and *ZKSCAN4*), and the effects of *ZNF* variants on neurocognition and neuroimaging phenotypes were reviewed. The biological functions of these variants are also presented. We verified that *ZNF804A* was significantly related to psychiatric diseases, and the association between *ZNF804A* rs1344706 and psychosis (schizophrenia and bipolar disorder) did not vary with disease or ethnicity. The main brain area regulated by *ZNF804A* rs1344706 was the dorsolateral prefrontal cortex. The effect of *ZNF804A* variants on cognition did not display consistency with different diseases or methodologies. These findings suggest that *ZNF804A* might play an important role in common pathogenesis of psychiatric diseases, and its variants are likely involved in regulating the expression of psychosis-related genes, especially the dopamine pathway genes. Further research should focus on the molecular mechanisms by which *ZNF804A* variants act in psychiatric diseases and related phenotypes.

1. Introduction

Mental disorders cause an enormous burden on individuals, families, and society. They are the leading cause of disability worldwide and result in physical illness and premature mortality (Whiteford et al., 2013). Major psychiatric disorders include schizophrenia, bipolar disorder, major depressive disorder (MDD), attention-deficit hyperactivity disorder (ADHD), and others (Phillips et al., 2003). Many psychiatric illnesses are heritable. For example, the heritability estimates of schizophrenia are approximately 80% (Sullivan et al., 2003). One of the best analytical methods for discovering susceptibility genes is an unbiased genome-wide association study (GWAS), which compares the allele frequencies of all available polymorphic markers for a specific symptom or disease condition (Al-Chalabi, 2009). Zinc finger 804a (*ZNF804A*) was the first gene to achieve genome-wide significance for psychosis. It is a member of the zinc finger protein genes (*ZNFs*) family and has been the subject of intense research (O'Donovan et al., 2008). Many follow-up replication studies have also confirmed the results from the GWAS ((Zhang et al.,2011a; Steinberg et al., 2011; Schanze et al., 2011).

The ZNF family has motifs in DNA- and RNA-binding proteins in which amino acids are folded into a single structural unit around a zinc atom to stabilize the fold (el-Baradi and Pieler, 1991). Generally, *ZNFs* coordinate zinc ions through a combination of cysteine and histidine residues. Originally, the number and order of these residues were used to classify zinc fingers (e.g., Cys_2His_2, Cys_4, and Cys_6). Their functions are extraordinarily diverse, including DNA recognition, RNA packaging, transcriptional activation, apoptosis regulation, protein folding and integration, and lipid binding (Laity et al., 2001). Proteins that contain the classic Cys2His2 ZNF are among the most abundant in eukaryotic genomes. Most of them are transcription factors that function by binding to specific DNA sequences and mediating protein–protein interactions (Wolfe et al., 2000).

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Consisting of four exons and encoding a 1210-amino-acid protein, *ZNF804A* is known to be widely expressed in the brain and contains a C2H2-type domain that belongs to the ZNF family (Riley et al., 2010). Upstream, one study reported that *ZNF804A* is a target for hsa-miR-137 (el-Baradi and Pieler, 1991), which has been reported to be strongly associated with schizophrenia (Schizophrenia Psychiatric Genome-Wide Association Study [GWAS] Consortium, 2011). Downstream, *ZNF804A* is involved in encoding transcription regulators of the *SMARCA2* gene, the down regulation of which generates abnormal dendritic spine morphology that is an intermediate phenotype of schizophrenia (Loe-Mie et al., 2010). Other reports show that *ZNF804A* directly contributes to transcriptional control by regulating the expression of several schizophrenia-associated genes, such as *PRSS16* and *COMT* (Girgenti et al., 2012). *ZNF804A* knockdown also affects the expression of genes involved in cell adhesion, suggesting its role in such processes as neural migration, neurite outgrowth, and synapse formation (Hill et al., 2012). Furthermore, *ZNF804A* has been shown to be linked to neuroanatomical phenotypes of psychosis, such as gray matter volume (GMV; Alami et al., 1999) and white matter (WM) integrity (Lei et al., 2005). *ZNF804A* also influences cognitive performance that is related to psychopathic personality traits (Hill et al., 2012).

Increasing evidence suggests that genetic variants of *ZNFs* influence the susceptibility to psychiatric diseases, including schizophrenia and bipolar disorder. For example, zinc finger with KRAB and SCAN domains 4 (*ZKSCAN4*) and zinc finger DHHC domain-containing protein 8 (*ZDHHC8*) have been found to be associated with susceptibility to schizophrenia (Chen et al., 2004; Yue et al., 2011). However, most *ZNF804A* variants related meta-analyses and reviews published to date did not include studies on all related diseases or the other *ZNFs*. No consensus has been reached on the effect of other *ZNF*s on psychiatric disorders. In the present meta-analysis, we summarize genetic evidence that implicates polymorphisms of *ZNF804A* and other *ZNFs* as genetic risk factors for related psychiatric disorders and discuss their roles in these diseases. We first performed a meta-analysis of studies on *ZNF804A* and other *ZNF*s in all types of psychiatric diseases. We then separately analyzed the studies by individual diseases if data were available to determine whether the risk allele had the same effect in different psychiatric diseases. We also separately analyzed studies by ethnicity and gender if possible. At last, we summarized and discussed the function and potential mechanisms of these variants in the pathogenesis of psychiatric diseases.

2. Materials and methods

2.1. Search strategy

We first searched the following terms in PubMed, Embase, Proquest, and Google Scholar: ZNF ("ZNF" or "zinc finger"), gene ("gene" or "genetics" or "genetic" or "SNP" or "polymorphism" or "variants" or "variation"), and psychiatric disorders ("psychiatry disorders" or "mental illness" or "mental disorders" or "psychosis"). We found that most studies focused on *ZNF804A*, and some studies assessed other *ZNF*s, such as *ZDHHC8* and *ZKSCAN4*. The associations between *ZNF* variants and the susceptibility to psychiatric disorders, including schizophrenia, bipolar disorder, ADHD, autism, and MDD, were studied. To ensure that we missed as few studies as possible, we further searched these databases using these gene terms and major psychiatric disorders, including "schizophrenia," "bipolar disorder," "autism," "ADHD," "depression," "addiction," and so on. Studies published before July 2014 were included in this analysis. We then selected relevant studies and read their bibliographies for additional references.

2.2. Study selection

Eligible studies in the meta-analysis had to meet the following criteria: (1) they compared a sample of formally diagnosed subjects with a group of unrelated healthy control subjects; (2) case status was defined as having a diagnosis of a psychiatric disorder according to DSM-IV criteria, with control subjects who had no history of psychiatric disorders or other neurological disorders, (3) the studies had samples with no overlap with the other identified studies, and (4) the distribution of single-nucleotide polymorphisms (SNPs) was in Hardy–Weinberg equilibrium in both the case and control samples. Family-based association studies (Xu et al., 2013; Anitha et al., 2014) were excluded because no unrelated healthy controls were recruited or the controls were the family members of the patients. The samples of the study by Williams et al. (2011) had some overlap with the study by O'Donovan et al. (2008), so we only chose the data from the functional and tagSNP study stage 1 part in Williams' study that did not contain overlap.

2.3. Data extraction

The data were extracted independently by two authors and cross-checked to reach a consensus. The following variables were extracted: (1) the name of first author, year of publication, disease, methods, results, ethnicity, number of cases/controls and males/females, mean age, and risk allele frequency. For some of the subgroup analyses, allele frequencies and the number of samples were calculated from the available data.

2.4. Meta-analysis

We explored the possibility to perform a meta-analysis of all of the eligible papers. We conducted meta-analytical calculations using Review Manager 5.0 if at least two papers focused on the same genetic association. Heterogeneity between individual studies was tested using the Cochran's (Q) χ^2 test. The odds ratio (OR) and associated 95% confidence intervals (CIs) were also calculated. We included the results in a random-effect model when significant heterogeneity was found (defined as $p < 0.05$); otherwise, a fixed-effect model was used. We graphically present the pooled ORs and the 95% CIs by forest plot. Sensitivity analysis was conducted to assess the potential influence of any single study on the pooled ORs. The included studies were removed one at a time to check for significant alterations of the pooled ORs and associated p values. We found that removing any sample did not significantly change the p values for the heterogeneity tests or overall effects. The publication bias was analyzed according to the method of Egger et al. (1997) by using STATA 11.0 software and the funnel plots are presented.

3. Meta-analysis results and review

3.1. Included papers

We found 272 unduplicated association studies. The search strategy is shown in Fig. 1. After this preliminary literature search, 24 studies (49 data) were chosen for the meta-analysis of *ZNF804A* SNPs (Table 1), and 9 studies (10 data) were chosen for the meta-analysis of *ZKSCAN4* and *ZDHHC8* (Table 2). A total of six variants of *ZNF804A* and three variants of other *ZNF*s (*ZKSCAN4* and *ZDHHC8*) were meta-analyzed. Other reported variants and the effects on neurocognition and neuroimaging phenotypes were reviewed, and the biological functions of these variants are summarized.

3.2. ZNF804A SNPs and psychiatric disorders

3.2.1. rs1344706

3.2.1.1. Function. The rs1344706 SNP at chromosome 2q32.1 is located in the intron 2 region of *ZNF804A* (Riley et al., 2010) and is the first risk factor that was identified through the GWAS and follow-up studies with