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Lack of association between dendritic cell nuclear protein-1 gene and major depressive disorder in the Han Chinese population

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ABSTRACT

Objectives: Dendritic cell nuclear protein-1 (DCNP1) has been associated with major depressive disorder (MDD) based on analysis of a population of patients in the United Kingdom. In the present study we have investigated a possible role of DCNP in MDD in the Han Chinese population, including a meta-analysis of different ethnic populations.
Methods: Eight single nucleotide polymorphisms (SNPs) spanning the entire DCNP1 were carefully selected, genotyped and used for the SNP and haplotype analyses in 574 patients with MDD and 642 healthy controls. Considering the potential genetic association difference across different ethnic populations, we further conducted a meta-analysis for Chinese and European populations.
Results: rs10061623 showed initial association with MDD in females in the allele analysis (p-value: 0.043). However, this association did not remain significant after Bonferroni correction to adjust for multiple comparisons (corrected p-value: 0.344). Other single-marker and haplotype analyses did not reveal any significant differences between patients and controls. The SNP (rs12520799), positive in the original UK study, gave negative results in all our analyses. The meta-analysis results of rs12520799 also suggested possible negative association between this SNP and MDD in the Han Chinese population.
Conclusions: In the Han Chinese population, common DCNP1 polymorphisms are unlikely to be important in the genetic susceptibility to MDD.

1. Introduction

Major depressive disorder (MDD), characterized by dysphoria or anhedonia plus several additional symptoms for diagnosis, is a heterogeneous disorder with a highly variable course (Cassano and Fava, 2002). The lifetime incidence of depression is more than 12% in men and 20% in women. The heritability of depression is estimated to be about 30% to 40% (Fava and Kendler, 2000; Malhi et al., 2000; Wray and Gottesman, 2012). To identify genes underlying susceptibility to MDD is an accepted approach to get a better understanding of possible pathophysiological mechanisms underlying this serious disease.

Dendritic cell nuclear protein-1 (DCNP1) is a recently discovered protein specifically localized on the nuclear membranes of dendritic cells and expressed mainly in the human brain and skeletal muscle (Masuda et al., 2002). DCNP1 gene is also named as C5orf20, since it is located on chromosome 5 open reading frame 20. It has been shown that DCNP1 is co-localized with corticotropin-releasing hormone in paraventricular nucleus neurons and that both are up-regulated in depressed patients (Zhou et al., 2010). Interestingly, DCNP1 single nucleotide polymorphism (SNP) (rs12520799; $p = 0.003$) has been proposed as a novel candidate gene for MDD in a United Kingdom (UK) population. Thus, homozygous carriers of the T allele of DCNP1, which encodes a premature termination of translation at codon number 117 on chromosome 5, were reported to have an increased risk for major depression (Willis-Owen et al., 2006). Genome-wide association (GWAS) data of a study based on a European cohort further confirmed that DCNP1 is one of the few replicated candidate genes associated with MDD (Bosker et al., 2011). However, so far no results on DCNP1 and depression in other ethnicities has been reported. In the present study, we examined DCNP1 in the Han Chinese population to determine a possible association with MDD in conjunction with clinical variables. Besides the single marker analyses used in the

Abbreviations: DCNP1, Dendritic cell nuclear protein-1; MDD, Major depressive disorder; SNP, single nucleotide polymorphism; UK, United Kingdom; GWAS, Genome-wide association; SCID-D-CV, DSM-IV Axis I disorders-Clinical Version; HDRS, Hamilton's depression Rating Scale; HWE, Hardy-Weinberg equilibrium; LD, linkage disequilibrium; SCID-D-CV, DSM-IV Axis I disorders-Clinical Version; NESDA-NTR, The Netherlands Study of Depression and Anxietyand the Netherlands Twin Registry.

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previous study for a UK population (Willis-Owen et al., 2006), haplotype analysis was also employed in our research to achieve more reliable results. Subsequently, a meta-analysis was performed to thoroughly dissect DCNP1's role in MDD in different ethnic populations.

2. Subjects and methods

2.1. Subjects

In this study, 574 patients with MDD (248 males and 326 females; mean age ± SD, 38.1 ± 13.7, 39.4 ± 13.7 years) and 642 healthy controls (291 males and 351 females; 44.8 ± 14.8, 43.5 ± 13.9 years) were enrolled for the association analyses. The age and sex of the patients with MDD did not differ from those of the control subjects. All subjects were unrelated to each other. The patients were diagnosed according to Structured Clinical Interview for DSM-IV (American-Psychiatric-Association, 1994). All patients were interviewed by two trained psychiatrists using the DSM-IV Axis I disorders-Clinical Version (SCID-D-CV) and Hamilton's depression Rating Scale (HDRS; Hamilton, 1967). Patients with severe organic disorders or comorbidity for other psychiatric disturbances (e.g. substance/alcohol dependence, personality disorders, anxiety disorders and others) were excluded. All subjects were fully informed about the study and written informed consent from each subject had been obtained by the original investigators. This study was approved by the Ethics Committee of the Beijing Anding Hospital, Capital Medical University.

2.2. Genotyping

Genomic DNA was extracted from peripheral blood using a commercial DNA extraction and purification kit (Macherey-Nagel, GER) following the manufacturer's instructions. All SNPs were genotyped by TaqMan assay (Applied Biosystems, Foster City, CA). The plates were heated for 95 °C at 15 min, followed by 35 cycles of 94 °C for 30s, 56 °C for 90s and 72 °C for 60s. Detailed information is available upon request.

2.3. SNP selection and LD evaluation

Eight SNPs (rs4976298, rs10061623, rs17168357, rs12518053, rs12520809, rs12520799, rs13154143 and rs17168361) located in the DCNP1 were investigated to cover most of the common variation in the locus in this study. The selection of those SNPs was based on a public database (National Center for Biotechnology Information, dbSNP, http://www.ncbi.nlm.nih.gov/SNP/) and information of previous studies (Willis-Owen et al., 2006). The HapMap based on http://www.hapmap.org/ was consulted.

2.4. Statistical analysis

All statistical analyses were performed using PLINK software version 1.06 (http://pngu.mgh.harvard.edu/~purcell/plink/). Hardy–Weinberg equilibrium (HWE) was tested for controls and MDD cases separately by chi-square test, or Fisher's exact test, if necessary for each SNP. For haplotype analysis, the pairwise linkage disequilibrium (LD) between polymorphisms was evaluated by Haploview 4.1 software, and the solid spine algorithm with default values (spine was extended if $D0 > 0.80$) to define the haplotype block boundaries (Barrett et al., 2005). Based on this information a haplotype block was constructed, and each haplotype frequency was inferred to identify differences between groups. The association of haplotypes with MDD was calculated with a chi-square test using one degree of freedom.

2.5. Meta analysis

Considering the potential genetic association difference across different ethnicity populations, we further conducted a meta-analysis for those of different association loci between Chinese and European populations.

2.5.1. Literature selection

In this meta-analysis, we performed a systematic literature search in PubMed and EMBASE database, using terms such as follows: "polymorphism", "major depressive disorders", "genetic association", "dendritic cell nuclear protein-1" and "DCNP1". No restrictions were placed on language, race, ethnicity or geographic region. Eligible studies included in this meta-analysis had to fulfill the following criteria: (i) association studies using an unrelated case–control design, (ii) cases with MDD were confirmed by clinical diagnosis. In this process, two authors independently assessed trial eligibility and quality, and they reached a consensus on all items. For each study, that met our criteria, the following information was collected: year of publication, population, number of genotypes in cases and controls respectively.

2.5.2. Statistical analysis

Because we couldn't acquire the original genotype data of the UK study, we used the pooling weighted z-scores method to perform the meta-analysis, which is described as follows:

$$Z = \frac{\sum_{i=1}^{k} z_i \sqrt{n_i}}{\sqrt{\sum_{i=1}^{k} n_i}},$$

where n_i is the sample size of the i-th study, $z_i = \Phi^{-1}(1 - p_i)$ if the corresponding odds ratio value (T vs. A) is less than one, $z_i = \Phi^{-1}(p_i)$ if the corresponding odds ratio value is larger than one, p_i is the p-value of the i-th study, and $\Phi(.)$ is the standard normal cumulative distribution function.

We also used the original genotype data of the Chinese population and The Netherlands Study of Depression and Anxietyand the Netherlands Twin Registry (NESDA-NTR) population to investigate the association between rs12520799 and MDD risk in an allelic model (T vs. A). The inconsistency was measured with I^2 and the heterogeneity was tested with chi-square test. The I^2 is ranged from 0 to 100% (I^2 = 0–25%, no heterogeneity; I^2 = 25–50%, moderate heterogeneity; I^2 = 50–75%, large heterogeneity; I^2 = 5–100%, extreme heterogeneity). According to the heterogeneity, we selected random effect model or fixed effect model to perform meta-analysis. The significance of the pooled OR was determined by the z-test ($p < 0.05$ suggests a significant association). We applied RevMan software (http://ims.cochrane.org/revman) to implement this analysis.

3. Results

3.1. SNP analysis

There were no differences in age and gender distributions between the patient and control groups. The minor allele frequency (MAF) of 8 tag SNPs were all greater than 0.1. Except rs10061623 showing the deviation from Hardy–Weinberg equilibrium in the male MDD group ($p = 0.026$) and in the female control group ($p = 0.027$), genotype frequencies of all SNPs were in HWE for other groups ($p > 0.05$). We did not detect any associations between DCNP1and MDD in the allele/genotype or all marker haplotype analyses. To further assess the potential association, we performed single marker analyses of subjects divided by sex. We found rs10061623 was associated in females with MDD in the genotype analysis ($p = 0.043$). However, this significance did not remain after the p-value was adjusted following the Bonferroni correction (Table 1).