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Association of *APC* and *REEP5* gene polymorphisms with major depression disorder and treatment response to antidepressants in a Han Chinese population☆

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Abstract

Objective: Despite the high prevalence of depression and its considerable impact on the population, knowledge about the pathogenesis of the illness and the antidepressant treatment response is still unknown.
Methods: A total of 397 patients with major depression disorder (MDD) and 473 normal controls were employed in the present research. Twelve single nucleotide polymorphisms (SNPs) within the *adenomatous polyposis coli* (*APC*) and *receptor accessory protein* (*REEP5*) genes were selected for genotyping using the GoldenGate genotyping assay. A total of 165 MDD patients completed a 6-week antidepressant treatment. Responders were defined as patients with at least a 50% reduction in Hamilton Rating Scale for Depression total scores posttreatment.
Results: Two SNPs (rs2464805 and rs563556) within the *APC* gene exhibited a statistically significant association with MDD when analyzed by genotype and allele frequencies. Three SNPs (rs495794, rs153549 and rs153560) in the *REEP5* gene showed significant statistical differences between the responders and nonresponders.
Conclusions: The *APC* gene may be one of the susceptibility genes for MDD as well as a genetic link between psychiatric disease and cancer. *REEP5* gene polymorphisms may influence antidepressant treatment response in MDD.

Keywords: Depression; Treatment response; Pharmacogenetics; *APC* gene; *REEP5* gene

1. Background

Major depression disorder (MDD), one of the most common psychiatric disorders, contributes substantially to the global burden of disease and disability because of its chronicity and high comorbidity associated with other medical conditions. MDD is a multifactorial disease, signifying an interaction of environmental risk factors and genetic predisposition. Despite the high prevalence of depression and its considerable impact on the population, the current understanding of the pathogenesis of MDD is still rudimentary. Both candidate gene and genomewide association studies have failed to recover strong and consistent genetic risk modifiers [1,2], probably because of the clinical and genetic heterogeneity of depressive syndromes [3,4]. In recent years, the pathogenesis of cancer combined with depression has increasingly attracted the attention of researchers [5,6]. One out of two cancer patients may be diagnosed with psychiatric disorders, especially with MDD [7–10]. Depression is highly associated with oropharyngeal (22% to 57%), pancreatic (33% to 50%), breast (1.5% to 46%) and lung (11% to 44%) cancers. A lesser but notable

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prevalence of depression is reported in patients with other cancers, such as colon (13% to 25%), gynecological (12% to 23%) and lymphoma (8% to 19%) [11]. A number of factors, such as social support, satisfaction with consultation and information, behavioral factors (alcohol and tobacco usage), personality and family history of depressive symptoms, have been considered as possible causes of depression in cancer patients [12]. Although these factors may influence the pathogenesis of depressive symptoms in cancer patients, the potential link between depression and cancer remains an important but unsolved issue, especially whether these two types of diseases share a common genetic predisposition.

Working on the hypothesis that reduced incidence of cancer in schizophrenic patients may be related to differences in genetic background, Cui et al. [13] found a genetic association between schizophrenia and the *adenomatous polyposis coli* (*APC*) gene. The *APC* gene is a tumor suppressor that has been associated with both familial and sporadic colon cancer. This gene is a key component of the Wnt/Wingless signaling transduction pathway, which plays an important role in tumorigenesis [14]. This signaling pathway also plays an important role in neural development [15], indicating that an abnormal Wnt/Wingless signaling pathway may have a significant influence on the pathogenesis of depression disorder [16–18]. This is not surprising considering the phenomena of high comorbidity of depression and various cancers (e.g., colon cancer) [11].

The *receptor accessory protein* (*REEP5*) gene, located near the *APC* gene in chromosome 5q21-22, is a member of the DP1/Yop1p protein family involved in the endoplasmic reticulum (ER) tubule formation [19]. Previous genome association studies have indicated a genetic association between adult attention-deficit/hyperactivity disorder (ADHD) and the *REEP5* gene [20]. ADHD is defined as a clinically heterogeneous neurodevelopmental syndrome comprising the triad of inattention, hyperactivity and increased impulsivity. This condition represents the most common psychiatric disorder in childhood and adolescence, with similar prevalence rates throughout different cultural settings [20,21]. Moreover, the syndromal dimensions of hyperactivity and increased impulsivity are increasingly being recognized as highly persistent into adulthood. These conditions are associated with considerable risk for comorbidity of psychiatric disorders, such as depression and substance use disorder, as well as failure in psychosocial adaptation [22].

In the present study, we hypothesized that the genetic variants in the *APC* and *REEP5* genes may influence the susceptibility and/or clinical response after antidepressant treatment in patients with depression. We analyzed the association of polymorphisms in *APC* and *REEP5* genes with MDD and explored the influence of the single nucleotide polymorphisms (SNPs) in both genes with time in a 6-week study on a Han Chinese population.

2. Materials and methods

2.1. Samples

A total of 397 patients with major depression, consecutively admitted to the Mental Health Center of West China Hospital, Sichuan University, were recruited from 2008 to 2010. All patients were assessed by trained psychiatrists using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Axis I Disorders [23].

Diagnosis of MDD was assigned according to the DSM-IV. All patients were scored according to the 17-item Hamilton [24] Rating Scale for Depression (HAMD-17) to assess the severity of depressive symptoms. Subjects with scores of ≥ 18 on HAMD-17 were included in the study.

A total of 473 community volunteers were recruited as normal controls using the Structured Clinical Interview for DSM-IV-Text Revision Axis I Disorders-Nonpatient Edition to screen for a lifetime absence of psychiatric illnesses [23]. Subjects with significant physical illnesses, pregnancies or psychiatric disorders other than major depression were excluded.

All participants were Han Chinese. After the participants were fully informed of the procedure, informed consent was obtained from all subjects. Approval for the study was granted by the Ethics Committee of the West China Hospital of Sichuan University.

2.2. Antidepressant treatment

Patients received antidepressant treatment (mainly selective serotonin reuptake inhibitors [SSRIs]) for 6 weeks. Citalopram, paroxetine, fluoxetine and sertraline were used as antidepressants. All patients were evaluated at baseline and weekly after treatment using HAMD-17. The project was designed as a naturalistic pharmacogenetic study in which all patients were treated with antidepressants according to the choice of the psychiatrists. The daily drug doses were decided by clinicians based on clinical guidelines for depression [25] and patient responses. No other psychotropic medications were permitted, but benzodiazepines were allowed for insomnia. The HAMD scores of each participant were evaluated by a trained psychiatrist, who was blind to patient genotype, to assess treatment efficacy at baseline and at each week during the 6-week treatment. Responders were defined as patients with at least a 50% reduction in HAMD total score posttreatment.

2.3. Genotyping

Peripheral blood (2 ml) was collected from all participants, and genomic DNA was extracted according to a standard phenol–chloroform procedure. Twelve SNPs (rs2439591, rs2464805, rs563556, rs2229992, rs42427, rs465899, rs495794, rs818427, rs153549, rs6864403, rs149192 and rs153560) within the *APC* and *REEP5* genes were selected based on SNP tagging of Han Chinese in