Association Between the SLC1A1 Glutamate Transporter Gene and Obsessive-Compulsive Disorder in the Chinese Han Population

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Background: Obsessive-compulsive disorder (OCD) is a common, serious and genetically related mental illness; the etiology of OCD has not yet reached a definitive conclusion. Multiple evidence suggests that the glutamatergic system plays a major role in the pathophysiology of OCD. However, subsequent studies on the glutamate transporter gene are not consistent. OCD is a heterogeneous disease. To resolve the complex genetic basis of OCD, division the disorder into different subphenotypes is an effective method for studying the pathogenesis of OCD.

Methods: We recruited 438 OCD patients and 465 age- and sex-matched controls from a Chinese Han population. rs10491734, rs3780412, rs301434 and rs3087879 SNPs were genotyped by real-time TaqMan polymerase chain reaction, and the chi-squared test was used to compare allele and genotype frequencies of variants between the two groups.

Results: The genotype of rs301434 was statistically significant in total patients with OCD and the controls. After grouping by age and gender, the genotype of rs301434 was statistically significant in early-onset OCD, late-onset OCD as well as male OCD, the allele and genotype of rs3780412 was associated with late-onset OCD. Haplotype analysis showed that four loci haplotypes (G-A-A-G and G-G-A-G) were associated with total OCD, (G-G-A-G) was associated with female OCD, (G-A-G-G) was associated with male OCD, (G-A-A-G and G-G-A-G) were associated with late-onset OCD.

Conclusion: This study provides suggestive evidence that SLC1A1 may be involved in the development of OCD in the Han population. However, these findings require further replication.

Keywords: obsessive-compulsive disorder, glutamate transporter gene, haplotype

Introduction

Obsessive-compulsive disorder (OCD) is a common mental illness with complicated clinical symptoms. The disease is characterized by intrusive unwanted thoughts and repetitive behavior. The lifetime prevalence of patients is between 1% and 3%, and it is listed as one of the ten most disabling diseases in the world by the World Health Organization (WHO).1,2 OCD is often accompanied by other mental illnesses, such as Tourette’s syndrome or eating disorders, which makes treatment more difficult.3,4

More and more evidences show that the glutamatergic system plays an important role in the etiology and subsequent treatment of OCD.5 Imaging and biological studies have shown that glutamate dysregulated neurotransmission in special parts
of the brain leads to the appearance of OCD symptoms.\(^6\) According to multiple independent family-based association studies and a case-control analysis, the SLC1A1 gene is closely related to the occurrence of OCD.\(^7\)\(^-\)\(^9\) Studies have pointed out that compared with the control group, the concentration of glutamate in the cerebrospinal fluid of OCD patients is higher.\(^10\) And the abnormal glutamatergic transmission in the cortex-striatum-thalamus-cortex (CSTC) circuit plays a certain role in the pathogenesis of OCD.\(^11\) In addition, it has been observed that children with OCD exhibit a decreased amount of glutamate in the anterior cingulate cortex. In the brain regions of patients with OCD, the level of glutamate receptors is also modified. It has been reported that serotonin can affect dopaminergic activity indirectly through the glutamatergic and GABAergic systems.\(^12\) It has been reported that serotonin can influence dopaminergic activity indirectly through the glutamatergic and GABA-ergic systems.\(^13\)

SLC1A1 is located on chromosome 9p24, which is expressed in brain regions related to OCD,\(^14\) including the cerebral cortex, striatum, and thalamus.\(^15\) As research into the hereditary pattern of OCD increases, the role of the glutamate transporter gene SLC1A1 in the pathogenesis of the disease has attracted attention.\(^9\)\(^-\)\(^1\)\(^6\)\(^-\)\(^1\)\(^8\) The glutamate transporter EAAC1 (EAAT3) is a crucial transporter for mammals. Approximately 30-40% of synapses in the mammalian brain are affected by EAAC1, which is encoded by SLC1A1 gene.\(^19\) Bellini et al found that mice lacking EAAC1 showed increased anxiety-like and disrupted grooming behaviors, and then they identify new molecular mechanisms by which EAAC1 can shape glutamatergic and dopaminergic signals and control repeated movement execution.\(^20\) An important function of EAAC1 is to stop the postsynaptic effects of glutamate as well as to regulate extrasynaptic glutamate levels, thus limiting the activation of extra-synaptic neurotransmitter receptors by rapidly removing released glutamate from the synaptic cleft and so alleviating subsequent excitotoxicity. EAAC1 enables excitatory transmission between synapses to function correctly. The SLC1A1 gene polymorphisms may be factors that contribute to glutamate dysfunction in cases of OCD.

It has been speculated that genetic variation within or near the SLC1A1 gene is associated with OCD in the Chinese Han population. OCD is a complex disease, in which patients with early-onset OCD and patients with late-onset OCD have different genetic foundations and clinical symptoms, which makes their treatment results often different. We classified the onset-age <18 as early-onset and the onset-age ≥18 as late-onset in the present study. We aimed to provide basic evidence for SLC1A1 as a candidate gene for the etiology of OCD in this population. A total of 438 OCD patients and 465 healthy controls were genotyped, and four SNPs (rs10491734, rs3780412, rs301434 and rs3087879) were selected to validate our hypothesis.

### Materials and Methods

#### Case Control Sample

A total of 438 OCD patients (mean age, 29.27±13.96 years) and 465 controls (mean age, 28.77±9.25 years) from the Affiliated Hospital of Medical College Qingdao University participated in this study. All subjects provided written informed consent, children in the present study were written and provided by their guardians. The OCD patient group included 260 male patients and 178 female patients, while the control group comprised 276 male subjects and 189 female subjects. We diagnosed patients according to the criteria of the Diagnostic and Statistical Manual of mental disorders (DSM-IV) and Obsessive compulsive symptoms of participants were assessed through the Yale–Brown Obsessive Compulsive Scale Checklist (YBOCS-CL),\(^21\) indicating that all patients were severely affected (26.72±4.43). YBOCS severity scale scores range from 0 to 40, with a score ≥16, indicating clinically significant symptoms. A score of ≥16 on the YBOCS severity scale was required for inclusion in this study. Subjects with a diagnosis, according to DSM-IV, of schizophrenia, recurrent major depression, bipolar disorder, mental retardation, alcohol or other substance abuse within the last 6 months or a history of psychosurgery, encephalitis, or significant head trauma were excluded. Subjects showing slight OCD symptoms with serious comorbidity symptoms, such as anxiety, depression and tic, were also excluded. Subjects refusing to participate or permit the extraction of venous blood were excluded.

Healthy control (n=465) subjects were recruited from the Center of Health Examination of the Affiliated Hospital of Qingdao University Medical College. All controls were included after being interviewed using the Diagnostic Interview for Genetic Studies\(^22\) and Family Interview for Genetic Studies (assessing first-degree relatives of control families according to the
reports of controls) to confirm the absence of both personal and familial history of OCD and other psychiatric disorders. Two experienced psychiatrists conducted a MINI for each member of the control samples to ensure that none of the controls suffered from any psychiatric disorders before beginning the current study.

The protocol of this study conformed to the ethical guidelines of the 1975 Declaration of Helsinki. This study was approved through the Ethics Committees of Affiliated Hospital of Qingdao University Medical College. All subjects provided written informed consent. In particular, the informed consent for children in the present study was written and provided by their guardians.

**DNA Analysis and Statistical Analysis**

Genomic DNA was extracted from leukocytes in the peripheral blood using standard methods. DNA amplification was conducted using polymerase chain reaction (PCR). The following PCR primer sequences were used: rs301434 forward, 5-ACGTTGATGGCCCCTGAAAAATCCCTTGAC-3, and rs301434 reverse, 5-ACGTTGATGCAAGGGCAAGGCGAACAGACTTGCTC-3; rs3780412 forward, 5-ACGTTGGA TGAGCCCCACAAAATACTCTG-3, and rs3780412 reverse, 5-ACGTTGATGGAAGGTTTTATGTTTG TC-3; rs10491734 forward, 5-ACGTTGATGGAGA CTTTGACTTGGCCAC-3, and rs10491734 reverse, 5-ACGTTGATGCTTGTGTCTGAAATGCC-3; rs3087879 forward, 5-ACGTTGATGTGCCAGGT AAATCCCCACGAC-3, and rs3087879 reverse, 5-ACGTTGATGGAGGAAGACAGAAGTCATAG-3. PCR was performed in a final volume of 5 μL containing 1 μL of genomic DNA, 0.95 μL of H$_2$O, 0.625 μL of PCR Buffer (10×), 0.325 μL of MgCl$_2$ (25 mM), 1 μL of dNTP (2.5 mM each), 1 μL of primer, and 0.1 μL of HotStarTaq DNA Polymerase (5 U/μL). The following cycling conditions were used: initial denaturation at 94°C for 15 min, followed by 45 cycles at 94°C for 20 s, 56°C for 30 s, and 72°C for 1 min, with a final extension at 72°C for 3 min and storage at 4°C. Subsequently, we added the SAP reaction mix (final volume of 2 μL), containing 1.53 μL of H$_2$O, 0.17 μL of SAP Buffer (10×), and 0.3 μL of SAP enzyme (1 U/μL), to the PCR product. The reaction was initiated at 37°C for 40 min, followed by incubation at 85°C for 5 min. The reaction was maintained at 4°C. iPlex reagent (Sequenom, San Diego, CA) (final volume of 2 μL, containing 0.755 μL of H$_2$O, 0.2 μL of iPlex Buffer (10×), 0.2 μL of iPlex Termination mix, and 0.041 μL of iPlex enzyme) was then added to the reaction product. The following cycling conditions were used: 94°C for 30 s, followed by 40 cycles at 94°C for 5 s, five cycles at 52°C for 5 s, and 80°C for 5 s, with a final extension at 72°C for 3 min and storage at 4°C.

Following purification, the reaction product was analyzed using MassARRAY SpectroCHIP (Sequenom, San Diego, CA). SNPs were detected with a MassARRAY Compact Analyzer (Sequenom, San Diego, CA). Results were analyzed using TYPHER software (Sequenom, San Diego, CA) and genotyping data were obtained. Detection accuracy was 99.6%. SNP genotyping was performed at Shanghai Benegene Biotechnologies Co., Ltd., and data analysis was conducted using SPSS software (version 17.0 for Windows; SPSS, Inc., Chicago, IL, USA). Age comparisons between the OCD and control groups were made with a t-test. Allelic, genotypic, and haplotype frequencies between OCD participants and controls, as well as to estimate the Hardy-Weinberg equilibrium were established by SHEsis software (http://analysis.bio-x.cn).

**Results**

No deviation of the Hardy-Weinberg equilibrium was found in the distribution of the four SNPs among OCD and control groups (P>0.05). We found significant differences in genotype frequencies of rs301434 between all OCD and control groups, while there were significant differences in genotype frequency of rs301434 between early-onset OCD and control groups, late-onset OCD and control groups as well as male OCD and control groups (total χ²=9.948, P=0.007; male χ²=8.766, P=0.013; female χ²=2.331, P=0.311; early-onset χ²=8.982, P=0.011; late-onset χ²=8.839, P=0.012).

We also found that genotype and allele frequencies of rs3780412 were statistically significant for the late-onset OCD and control groups (genotype χ²=7.196, P=0.027; allele χ²=5.575, P=0.018). However, we found that genotype and allele frequencies of rs10491734 and rs3087879 were not statistically significant for OCD or control groups.

Four loci haplotypes (rs10491734-rs3780412-rs301434-rs3087879) were found to be associated with OCD. Haplotypes G-A-A-G and G-G-A-G were statistically significant for all OCD and control groups (P=0.033 and 0.030, respectively). Haplotype
G-A-G-G was associated with the male OCD group (P=0.010), while G-G-A-G was associated with the female OCD group (P=0.039). Finally, we found that G-A-A-G, G-G-A-G were associated with the late-onset OCD groups (P=0.019 and 0.050, respectively). In addition, our use of haplotype analysis showed that G-A-G-G is a risk factor for male OCD (OR = 1.737, 95% CI: 1.134–2.660), while G-G-A-G is a risk factor for total (OR = 1.412, 95% CI: 1.033–1.930), female (OR = 1.670, 95% CI: 1.021–2.730) and late-onset OCD (OR = 1.469, 95% CI: 0.997–2.166).

Discussion

Obsessive-compulsive disorder is a complex multifactorial disease, which seems to be affected by environmental and genetic factors. Recent reports indicate that glutamate transporter gene mutations play a role in the etiology of OCD. Our study found significant differences in genotype frequencies of rs301434 between total OCD group and control group. After grouping by gender and age, the results indicate a significant difference in the genotype frequency of rs301434 between early-onset OCD and control groups, late-onset OCD and control groups as well as male OCD and control groups (See Table 2). Arnold et al found that two variants located within a single haplotype block, rs301434 and rs301435, were associated with the transmission of OCD, while de Salles Andrade and colleagues found that the A-A-G (rs301434-rs3780412-rs301443) haplotype was twice as common for people with OCD than for controls. Regarding clinical characteristics, the G-A-G (rs301434-rs3780412-rs301443) haplotype in patients with OCD seems to be related to the symptoms of hoarding. This finding implicated that rs301434 may be an important SNP to OCD in the Han Chinese population. Rs301434 may influence the development of OCD through expression of the neuronal glutamate transporter.

Dickel et al found a positive relationship between rs3780412, rs301430 and OCD, where the association is limited to males in rs3780412. Wendland et al found three highly significant synthetic markers in haplotype analysis, where rs3087879, rs301430 and rs3858819 were significant in the OCD haplotype test. When we tested rs3780412 and rs3087879 in the Han population, we found a significant difference in allele and genotype frequency of rs3780412 between late-onset OCD and control groups. However, genotypes and alleles of rs3087879 were not statistically significant between OCD patients and control groups, nor between the stratified groups (See Tables 1 and 2).

The further research significance of dividing OCD into early and late subtypes lies in exploring the genetic and neurobiological determinants of OCD and predicting the best treatment plan. The symptoms of OCD are heterogeneous and are thought to emerge from complex genetic, environmental, and epigenetic interactions. Compared with late-onset OCD, early-onset OCD are more likely to be associated with Tourette syndrome, have greater heritability, and have more difficult treatment. We speculate that late-onset OCD may be related to rs3780412, which may have connection with the influence of psychosocial factors on patients. Certain social factors may have an impact on this SNP, which is expressed in patients with late-onset OCD. We will make further analysis of related influencing factors in future research.

Some authors have found that 3-SNP haplotype rs4740788-rs10491734-rs10491733 was associated with a total sample of OCD patients as well as with male OCD. Wu and colleagues found that rs10491734 was significantly associated with early-onset OCD. However, we did not reach this conclusion for the Han population (See Tables 1 and 2). This may be due to the polymorphism of the locus.

Although we only found positive results in the two SNPs rs301434 and rs3780412, haplotypes studies found more positive results, which may be due to polymorphisms at multiple loci alleles affect different subtypes of OCD and clinical symptoms (See Table 1). We found that haplotypes of the four SNPs (rs10491734-rs3780412-rs301434-rs3087879) showed significant differences between the OCD and control groups as a whole. After classifying OCD participants on the basis of sex and age, we found significant differences between male OCD and controls, female OCD and controls as well as late-onset OCD and controls. The haplotype G-A-A-G was associated with both total OCD and late-onset OCD. Haplotype G-A-G-G was associated with male OCD and is a risk factor for male OCD. Haplotype G-G-A-G was associated with total OCD, female OCD and late-onset OCD, and is a risk factor for these groups (See Table 3).
In conclusion, we found that the genotype of SLC1A1 rs301434 is significantly associated with all OCD and control groups, early-onset OCD and control groups, late-onset OCD and control groups as well as male OCD and control groups. The genotype and allele of rs3780412 is significantly associated with late-onset...
## Table 2: The Results of Single-Site Genotype Association Analysis for the Overall, Male, Female, Early-Onset, and Late-Onset OCD Samples

| SNP     | Group                  | No  | Genotype       | X²       | P       |
|---------|------------------------|-----|----------------|----------|---------|
| rs10491734 | overall OCD          | 438 | AA(0.046)      | 1.057    | 0.589   |
|         | control               | 465 | 0.058          | 0.346    | 0.596   |
|         | male OCD              | 260 | AA(0.050)      | 1.898    | 0.387   |
|         | male control          | 276 | 0.072          | 0.355    | 0.572   |
|         | female OCD            | 178 | AA(0.039)      | 0.053    | 0.973   |
|         | female control        | 189 | 0.037          | 0.328    | 0.635   |
|         | early onset OCD       | 252 | AA(0.048)      | 0.334    | 0.846   |
|         | control               | 465 | 0.058          | 0.344    | 0.598   |
|         | late onset OCD        | 186 | AA(0.043)      | 1.459    | 0.482   |
|         | control               | 465 | 0.058          | 0.344    | 0.598   |
| rs3780412 | overall OCD          | 438 | AA(0.555)      | 4.128    | 0.127   |
|         | control               | 465 | 0.606          | 0.329    | 0.65    |
|         | male OCD              | 260 | AA(0.565)      | 1.903    | 0.386   |
|         | male control          | 276 | 0.598          | 0.326    | 0.076   |
|         | female OCD            | 178 | AA(0.539)      | 3.052    | 0.217   |
|         | female control        | 189 | 0.624          | 0.328    | 0.048   |
|         | early onset OCD       | 252 | AA(0.599)      | 3.217    | 0.200   |
|         | control               | 465 | 0.609          | 0.327    | 0.065   |
|         | late onset OCD        | 186 | AA(0.495)      | 7.196    | 0.027*  |
|         | control               | 465 | 0.609          | 0.327    | 0.065   |
| rs301434 | overall OCD          | 438 | AA(0.735)      | 9.948    | 0.007*  |
|         | control               | 465 | 0.761          | 0.234    | 0.004   |
|         | male OCD              | 260 | AA(0.731)      | 8.766    | 0.013*  |
|         | male control          | 276 | 0.768          | 0.232    | 0.000   |
|         | female OCD            | 178 | AA(0.742)      | 2.331    | 0.312   |
|         | female control        | 189 | 0.751          | 0.238    | 0.011   |
|         | early onset OCD       | 252 | AA(0.746)      | 8.982    | 0.011*  |
|         | control               | 465 | 0.761          | 0.234    | 0.004   |
|         | late onset OCD        | 186 | AA(0.720)      | 8.839    | 0.012*  |
|         | Control               | 465 | 0.761          | 0.234    | 0.004   |
| rs3087879 | overall OCD          | 438 | CC(0.007)      | 1.391    | 0.499   |
|         | control               | 465 | 0.015          | 0.209    | 0.776   |
|         | male OCD              | 260 | CC(0.012)      | 0.621    | 0.733   |
|         | male control          | 276 | 0.011          | 0.192    | 0.797   |
|         | female OCD            | 178 | CC(0.000)      | 4.294    | 0.117   |
|         | female control        | 189 | 0.021          | 0.228    | 0.751   |
|         | early onset OCD       | 252 | CC(0.004)      | 2.159    | 0.339   |
|         | control               | 465 | 0.015          | 0.206    | 0.778   |
|         | late onset OCD        | 186 | CC(0.011)      | 1.118    | 0.572   |
|         | Control               | 465 | 0.015          | 0.206    | 0.778   |

Note: *p-value < 0.05 indicated significant statistical differences.

OCD and control groups. The haplotypes (G-A-A-G, G-G-A-G) are associated with total OCD and control groups. Haplotype (G-G-A-G) is associated with female OCD, haplotype (G-A-G-G) is associated with male OCD, and haplotype (G-A-A-G, G-G-A-G) is associated with late-onset OCD. Our findings support the idea that SLC1A1 is a susceptibility gene for OCD, but this study also has limitations, due to the limited sample size, our results need to further increase the sample data for verification.
Table 3: The Results of the Haplotype Analysis for SNP rs10491734-rs3780412-rs301434-rs3087879 in OCD Patients and Controls

| Haplotype* | Group              | Case (Frequency, %) | Control (Frequency, %) | \(\chi^2\) | P       | OR (95%CI) |
|------------|--------------------|---------------------|------------------------|------------|---------|------------|
| GGAG       | All OCD            | 100.59(0.115)       | 77.22(0.083)           | 4.707      | 0.030   | 1.412 [1.033–1.930] |
|            | Late-onset OCD     | 46.64(0.125)        | 77.03(0.083)           | 5.040      | 0.024   | 1.552 [1.055–2.283] |
|            | Female OCD         | 44.69(0.126)        | 29.39(0.078)           | 4.243      | 0.039   | 1.670 [1.021–2.730] |
| GAGG       | Male OCD           | 59.52(0.115)        | 38.21(0.069)           | 6.378      | 0.010   | 1.737 [1.134–2.660] |
| GAAG       | All OCD            | 403.99(0.462)       | 468.24(0.503)          | 4.536      | 0.033   | 0.815 [0.675–0.984] |
|            | Late-onset OCD     | 165.67(0.445)       | 469.92(0.505)          | 5.439      | 0.019   | 0.748 [0.585–0.955] |

Note: Haplotypes with frequency<0.03 are ignored in analysis.

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Disclosure
All authors declare no conflicts of interest for this work.

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