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# GRIN2B Gene Polymorphism in Chronic Ketamine Users

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**Background and Objectives:** We examined the allelic variants of *N*-methyl-D-aspartate receptor 2B (GRIN2B) and analyzed the associations between GRIN2B gene polymorphism with ketamine use conditions and psychopathological symptoms in chronic ketamine users.
**Methods:** A total of 231 subjects were recruited. Four single nucleotide polymorphisms of GRIN2B, rs1805502, rs7301328, rs890, and rs1806201 were examined in 151 male chronic ketamine users and 80 controls. Psychopathological symptoms in chronic ketamine users were evaluated using the Positive and Negative Syndrome Scale, the Beck Depression Inventory, and the Beck Anxiety Inventory.
**Results:** The genotype CC of rs1806201 had a lower frequency in ketamine users than that in control subjects ($\chi^2 = 8.167$, $P = .004$) and the T allele frequency of rs1806201 in ketamine users was higher than that in the control subjects ($P = .009$, odds ratio = 2.019 [1.196-3.410]). Ketamine users of genotype TT and CC of rs1806201 had an earlier onset of ketamine use than subjects of genotype TC ($P = .038$, $P = .049$, respectively). The dose of ketamine consumption per day of use was higher in genotype GG of rs7301328 than that in those with CG in ketamine users ($P = .026$). There were no significant differences of the severity of psychopathologic symptoms among different genotypes tested.
**Conclusion and Scientific Significance:** GRIN2B gene polymorphism may play a role in ketamine abuse. (Am J Addict 2020;00:00–00)

## BACKGROUND

Ketamine is a phencyclidine derivative, which was first synthesized in 1962[1] and has been widely used as an anesthetic or analgesic.[2,3] Due to its reinforcing and rewarding properties, ketamine has evolved into a recreational drug worldwide in the past few decades.[4,5] Recreational ketamine use has been reported to induce psychotic symptoms and memory deficits.[6] Acute and chronic use of ketamine-induced psychotic symptoms are similar to the ones observed in schizophrenia.[7-9] Ketamine has thus been used as a potential pharmacological model of schizophrenia.[8,10]

Increasing evidence indicates that the glutamatergic system, particularly the *N*-methyl-D-aspartate (NMDA) receptor, plays an important role in the rewarding effects of addictive drugs.[11-13] As an uncompetitive NMDA receptor antagonist, ketamine can block NMDA receptors on γ-aminobutyric acid neurons and lead to disinhibition of dopaminergic neurons and activation of the rewarding pathway.[14,15]

The NMDA receptor is heterotetramers mainly composed of an NR1 subunit, one of the four NR2 subunits (NR2A-D), or alternatively NR3 subunits (NR3A, NR3B).[16] The NR2B subunit is encoded by the glutamate ionotropic receptor NMDA type subunit 2B gene (GRIN2B), which is located at chromosome 12p12 and consists of 13 exons.[17] Previous studies indicated that single nucleotide polymorphisms (SNPs) in GRIN2B gene are involved in schizophrenia[18,19] and addiction.[20,21] Ohtsuki et al[18] reported a significant difference in the allele frequency of the G366C (rs7301328) SNP between schizophrenic patients and controls in the Japanese population. A meta-analysis showed that the G allele frequency of rs7301328 in schizophrenic patients was higher than that in controls, which implicated that G allele may be a risk gene for schizophrenia.[22] SNP890 (rs890) has also been reported to be associated with schizophrenia.[19,23] Polymorphisms in GRIN2B are also reported to be associated with addiction. Previous studies showed an association between GRIN2B polymorphism with earlier age at onset of withdrawal symptoms in Indian alcohol-dependent subjects,[20] and with early onset of nicotine smoking.[21] Another SNP in GRIN2B gene C2664T (rs1806201) was reported to be associated with alcohol dependence.[20,24]

On the basis of the previous evidences we hypothesized that SNP of GRIN2B may play a role in ketamine use characteristics and the severity of ketamine-induced psychopathologic symptoms. We tested four SNPs of GRIN2B (rs7301328, rs1805502, rs1806201, and rs890) in the Han Chinese population. The differences in genotype and

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allele distributions of GRIN2B gene polymorphisms between chronic ketamine users and healthy controls were compared. The associations between GRIN2B gene polymorphism with ketamine use characteristics and the severity of psychopathologic symptoms in ketamine users were examined.

## MATERIALS AND METHODS

### Subject Recruitment

Chronic ketamine users were recruited from Guangzhou Baiyun drug rehabilitation Hospital and healthy controls were recruited through advertisement. Both ketamine users and healthy controls were males because there were very few female ketamine users. All chronic ketamine users underwent a 2 hours semi-structured interview, which was conducted by clinicians with 3 or more years of clinical experience. Inclusion criteria required that: (1) subjects were chronic ketamine users admitted for detoxification or treatment of ketamine-related symptoms; (2) subjects had no other substance use disorders other than ketamine and tobacco according to DSM-IV-TR; (3) subjects use ketamine as a drug of choice, longer than 6 months. Subjects with a history of psychiatric and neurological diseases were excluded. The control subjects have no history of drug abuse or psychiatric disorders. The study was approved by the Institutional Ethics Committee and written informed consent was provided by all subjects.

### Assessment of Psychopathologic Symptoms

Clinical symptoms among chronic ketamine users were evaluated using the Positive and Negative Syndrome Scale (PANSS),[25] administered by two trained psychiatrists with 3 or more years of clinical experience. The intra-class correlation coefficient (ICC) between raters on the PANSS was greater than 0.8. Ketamine users were asked to complete the Beck Depression Inventory (BDI)[26] and the Beck Anxiety Inventory (BAI),[27] which assessed their depressive and anxiety symptoms in the two weeks prior to their hospitalization.

### Sample Collection and Genotyping

In brief, peripheral blood samples were collected from subjects in 6-mL ethylenediaminetetraacetic acid vacuum tubes. Genomic DNA was isolated from peripheral blood using standard phenol-chloroform extraction method[28] and stored at −80°C until genotyping. After quality assessment, DNA samples were genotyped by the TaqMan Genotyping Assay using an ABI ViiA 7 Real-time PCR System (Applied Biosystem, Foster City, CA). Polymerase chain reaction (PCR) was performed in 25 μL reactions containing Genotyping Master Mix (Applied Biosystems), TaqMan Genotyping Assay, and DNA template. Each 96-well plate was quality-controlled with two no-template controls. PCR was conducted at 95°C for 10 min, followed by 40 cycles of denaturation at 95°C for 15 s and annealing at 60°C for 1 min.

### Statistical Analysis

Statistical analysis was performed using SPSS 18.0. Statistical differences in age and education between ketamine users and control subjects were evaluated by $T$ tests. $\chi^2$ test was used to examine the differences of alcohol consumption, tobacco smoking, and the genotypes between the two groups. Hardy-Weinberg equilibrium tests were performed separately among ketamine users and control subjects for each SNP. Binary logistic regression analysis was used to estimate crude odds ratios (ORs) and the 95% confidence interval (CI) in testing the differences of the genotypes and allele frequencies of SNPs between ketamine users and control subjects, years of education, alcohol consumption, and smoking were evaluated as confounding factors. Bonferroni corrections were applied to adjust for multiple comparisons of different genotype of SNPs in ketamine users and control subjects. To adjust for multiple comparisons the significance level was set to $P < .017$ ($\alpha/3 = 0.05/3$, two-tailed) for all multiple comparisons. Univariate analysis and LSD post hoc test were used for comparisons of subjects of different genotypes in drug use characteristics and clinical symptoms in ketamine group. The $\eta$ coefficient was calculated to reflect the relationship between drug use characteristics, clinical symptom, and genotypes. All statistical significances were considered at $P < .05$ (except multiple comparisons).

## RESULTS

### Participant Characteristics

A total of 151 ketamine users and 80 control subjects were enrolled. Sociodemographic characteristics, drug use conditions, and clinical characteristics of ketamine users and information of control subjects are shown in Table 1. There was no significant difference in age between the two groups, yet years of education, smoking, and alcohol drinking were significantly different ($P < .01$).

### Genotype and Allele Frequencies of SNPs in Ketamine Users and Control Subjects

The genotype distribution of the four SNPs in ketamine users and control subjects are shown in Table 2. Distributions of each SNP genotypes were consistent with Hardy-Weinberg equilibrium in both ketamine users and control subjects ($P > .05$). No significant differences in the overall genotype distribution of the four SNPs in GRIN2B gene were observed between ketamine users and control subjects ($P > .05$). When years of education, alcohol consumption, and smoking were added as covariates into the analysis, the percentage of the CC genotype of rs1806201 was lower in ketamine users than that in control subjects ($P = .004 < 0.05/3$; OR = 0.304 [0.134-0.688]) (Table 2).

The estimated allele frequency for the four SNPs in ketamine users and control subjects are summarized in

**TABLE 1.** Demographics and clinical data of ketamine users and control subjects

| | Ketamine users ($n = 151$) | Control subjects ($n = 80$) | $t/\chi^2$ | $P$ |
|---|---|---|---|---|
| Age, y | 26.00 ± 4.95 | 27.43 ± 7.86 | −1.686 | .093 |
| Education, y | 10.41 ± 2.73 | 12.25 ± 2.02 | −5.302 | .000** |
| Alcohol | | | | |
| Drink frequently[a] | 41 (27.3%) | 5 (7.1%) | 11.765 | .001** |
| Does not drink frequently[b] | 109 (72.7%) | 65 (92.9%) | | |
| Tabacco | | | | |
| Smoke frequently[c] | 142 (94.7%) | 32 (45.7%) | 69.160 | .000** |
| Does not smoke frequently[d] | 8 (5.3%) | 38 (54.3%) | | |
| Age of first ketamine use, y | 19.64 ± 5.00 | – | | |
| Duration of ketamine use, mo | 77.56 ± 36.71 | – | | |
| Average daily dose, g | 3.28 ± 2.71 | – | | |
| Frequency of ketamine use weekly | 6.15 ± 1.60 | – | | |
| PANSS score | | | | |
| Positive symptom subscale | 7.95 ± 1.79 | – | | |
| Negative symptom subscale | 13.11 ± 3.70 | – | | |
| General psychopathology subscale | 24.48 ± 5.02 | – | | |
| Total score | 45.54 ± 8.71 | – | | |
| BDI score | 12.76 ± 6.48 | – | | |
| BAI score | 16.11 ± 10.09 | – | | |

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; PANSS = Positive and Negative Syndrome Scale.
[a]Drinking not less than once a week.
[b]Including abstinence, drinking less than once a week and never drinking.
[c]Smoking not less than 3 days per week.
[d]Including cessation, smoking less than 3 days per week and never smoking.
**$P < .01$.

**TABLE 2.** Genotypic distribution of the GRIN2B gene polymorphisms in ketamine users and control subjects

| Genotypes $n$ (%) | KET ($n = 151$) | CON ($n = 80$) | Crude $\chi^2$ | $P$ | Crude OR (95% CI) | Adjusted $\chi^2$ | $P$ | Adjusted OR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| rs890 | | | | | | | | |
| AA | 97 (64.2) | 46 (57.5) | 1.007 | .316 | 1.328 (0.763-2.311) | 1.814 | 0.178 | 1.653 (0.795-3.434) |
| AC | 44 (29.1) | 26 (32.5) | 0.280 | .597 | 0.854 (0.476-1.533) | 0.176 | 0.675 | 0.848 (0.391-1.836) |
| CC | 10 (6.6) | 8 (10.0) | 0.830 | .362 | 0.638 (0.241-1.687) | 2.685 | 0.101 | 0.382 (0.121-1.208) |
| rs1806201 | | | | | | | | |
| TT | 53 (35.1) | 22 (27.5) | 1.077 | .241 | 1.426 (0.787-2.582) | 2.044 | 0.153 | 1.824 (0.800-4.160) |
| TC | 71 (47.0) | 34 (42.5) | 0.431 | .512 | 1.201 (0.695-2.074) | 1.113 | 0.292 | 1.486 (0.712-3.104) |
| CC[a] | 27 (17.9) | 24 (30.0) | 4.465 | .035 | 0.508 (0.270-0.958) | 8.167 | 0.004* | 0.304 (0.134-0.688) |
| rs7301328 | | | | | | | | |
| CC | 37 (24.5) | 19 (23.8) | 0.016 | .899 | 1.042 (0.552-1.965) | 0.121 | 0.728 | 1.167 (0.489-2.789) |
| CG | 82 (54.3) | 48 (60.0) | 0.689 | .406 | 0.792 (0.457-1.373) | 0.260 | 0.610 | 0.827 (0.399-1.714) |
| GG | 32 (21.2) | 13 (16.3) | 0.814 | .367 | 1.386 (0.681-2.821) | 0.058 | 0.810 | 1.117 (0.454-2.747) |
| rs1805502 | | | | | | | | |
| AA | 111 (73.5) | 58 (72.5) | 0.027 | .869 | 1.053 (0.572-1.936) | 0.005 | 0.941 | 0.970 (0.433-2.174) |
| AG | 34 (22.5) | 18 (22.5) | 0.000 | .998 | 1.001 (0.523-1.915) | 0.002 | 0.963 | 1.020 (0.437-2.381) |
| GG | 6 (4.0) | 4 (5.0) | 0.133 | .715 | 0.786 (0.215-2.871) | 0.000 | 0.989 | 1.014 (0.150-6.836) |

CI = confidence interval; CON = control subjects; KET = ketamine users; OR = odds ratio.
[a]CC compared with TT and TC.
*$P < \alpha/3 = 0.05/3$.

**TABLE 3.** Allele frequency of SNPs in ketamine users and control subjects

| SNP ID | Allele, *n* (%) | | Crude $\chi^2$ | *P* | Crude OR (95%CI) | Adjusted $\chi^2$ | *P* | Adjusted OR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| rs890 | A | C | | | | | | |
| KET | 238 (78.8) | 64 (21.2) | 1.513 | .219 | 1.324 (0.846-2.070) | 3.477 | .062 | 1.729 (0.972-3.076) |
| CON | 118 (73.7) | 42 (26.3) | | | | | | |
| rs1806201 | T | C | | | | | | |
| KET | 177 (58.6) | 125 (41.4) | 4.111 | .043* | 1.489 (1.013-2.189) | 6.906 | .009** | 2.019 (1.196-3.410) |
| CON | 78 (48.7) | 82 (51.3) | | | | | | |
| rs7301328 | C | G | | | | | | |
| KET | 156 (51.7) | 146 (48.3) | 0.184 | .668 | 0.919 (0.626-1.350) | 0.004 | .947 | 1.017 (0.613-1.690) |
| CON | 86 (53.7) | 74 (46.3) | | | | | | |
| rs1805502 | A | G | | | | | | |
| KET | 256 (84.8) | 46 (15.2) | 0.082 | .774 | 1.080 (0.639-1.824) | 0.006 | .939 | 0.973 (0.485-1.955) |
| CON | 134 (83.7) | 26 (16.3) | | | | | | |

CI = confidence interval; CON = control subjects; KET = ketamine users; OR = odds ratio; SNP = single nucleotide polymorphism.
*$P < .05$, **$P < .01$.

Table 3. The T allele frequency of rs1806201 in ketamine users was higher than that in control subjects ($P = .043$; OR = 1.489 [1.013-2.189]). When years of education, alcohol consumption, and smoking were added as covariates into the analysis, the difference was still significant ($P = .009$; OR = 2.019 [1.196-3.410]). For the other three SNPs tested, the allele frequencies were not significantly different between ketamine users and control subjects ($P > .05$).

## Relationship Between Drug Use Characteristics and Genotypes of the Four GRIN2B SNPs

Associations between drug use characteristics and the genotypes of the four GRIN2B SNPs in ketamine users were analyzed (Table 4). The age of first ketamine use were significantly different among the genotype groups of rs1806201 ($F = 3.099$, $P = .048$, $\eta = 0.200$), the subjects of genotype TT and CC had an earlier onset of ketamine use

**TABLE 4.** Association between drug use characteristics and genotypes of four GRIN2B SNPs in ketamine users

| | Genotype (*n*) | | | *F* | *P* | $\eta$ |
|---|---|---|---|---|---|---|
| rs890 | AA (97) | AC (44) | CC (10) | | | |
| Age of first ketamine use | 19.4 ± 4.4 | 20.0 ± 6.2 | 20.4 ± 4.9 | 0.346 | .708 | 0.071 |
| Duration of ketamine use | 80.2 ± 38.6 | 76.0 ± 33.9 | 58.7 ± 24.2 | 1.630 | .199 | 0.148 |
| Average daily dose | 3.3 ± 3.0 | 3.3 ± 2.5 | 2.8 ± 2.0 | 0.170 | .844 | 0.045 |
| Frequency of use weekly | 6.1 ± 1.6 | 6.4 ± 1.5 | 5.5 ± 2.5 | 1.354 | .262 | 0.134 |
| rs1806201 | TT (53) | TC (71) | CC (27) | | | |
| Age of first ketamine use | 18.8 ± 3.8[a] | 20.7 ± 5.8 | 18.5 ± 4.4[b] | 3.099 | .048* | 0.2 |
| Duration of ketamine use | 78.8 ± 37.3 | 78.1 ± 38.5 | 73.8 ± 31.4 | 0.174 | .840 | 0.045 |
| Average daily dose | 3.4 ± 3.0 | 3.3 ± 2.9 | 2.9 ± 2.1 | 0.252 | .777 | 0.055 |
| Frequency of use weekly | 5.9 ± 1.7 | 6.3 ± 1.5 | 6.3 ± 1.7 | 1.417 | .246 | 0.138 |
| rs7301328 | CC (37) | CG (82) | GG (32) | | | |
| Age of first ketamine use | 19.7 ± 4.9 | 19.8 ± 5.2 | 19.2 ± 4.8 | 0.193 | .825 | 0.055 |
| Duration of ketamine use | 79.9 ± 39.2 | 73.9 ± 36.6 | 84.3 ± 34.0 | 1.026 | .361 | 0.118 |
| Average daily dose | 3.5 ± 3.3 | 2.9 ± 2.3 | 4.1 ± 3.1[c] | 2.676 | .072 | 0.187 |
| Frequency of use weekly | 6.3 ± 1.5 | 6.1 ± 1.7 | 6.3 ± 1.6 | 0.327 | .722 | 0.063 |
| rs1805502 | AA (111) | AG (34) | GG (6) | | | |
| Age of first ketamine use | 19.8 ± 5.3 | 19.3 ± 4.5 | 19.0 ± 3.3 | 0.150 | .860 | 0.045 |
| Duration of ketamine use | 75.2 ± 36.0 | 87.0 ± 37.9 | 67.8 ± 39.4 | 1.577 | .210 | 0.145 |
| Average daily dose | 3.3 ± 2.7 | 3.4 ± 3.0 | 3.2 ± 3.2 | 0.040 | .961 | 0.032 |
| Frequency of use weekly | 6.0 ± 1.7 | 6.4 ± 1.3 | 7.0 ± 0.0 | 1.777 | .173 | 0.152 |

[a]$P = .038$, compared with TC genotype, LSD post hoc test.
[b]$P = .049$, compared with TC genotype, LSD post hoc test.
[c]$P = .026$, compared with CG genotype, LSD post hoc test.
*$P < .05$.

than subjects of genotype TC (respectively, $P = .038$; $P = .049$). While the average daily dose were not significantly different among the three genotype groups of rs7301328 ($P > .05$), the LSD post hoc test showed that subjects of genotype GG used more ketamine per day than subjects of genotype CG ($P = .026$). No significant differences in drug use characteristics among genotype groups of rs1805502 and rs890 were observed ($P > .05$).

### Relationship Between Psychotic Symptom Measures and Genotypes of Four GRIN2B SNPs

Associations between PANSS, BDI, BAI scores and the genotypes of four SNPs were also examined. There were no significant differences of the severity of psychopathologic symptoms between different genotypes tested in ketamine users ($P > .05$) (data not show).

## DISCUSSION

Several studies analyzed the GRIN2B polymorphisms in schizophrenia.[18,19,22,23] But there was no study analyzing GRIN2B polymorphisms in ketamine users. To our knowledge, this is the first study to investigate the gene polymorphisms of the GRIN2B in ketamine users. Among the four SNPs of GRIN2B gene examined, we found that the genotype CC of rs1806201 had a significantly lower frequency in ketamine users than that in control subjects, and ketamine users had higher T allele frequency in rs1806201. Several SNPs of GRIN2B examined were found to be associated with early onset of ketamine use and a higher dose of ketamine consumption per day.

Ohtsuki et al[18] presented a mutation analysis in GRIN2B gene in schizophrenic patients. Although they did not find significant differences in the allele frequency between schizophrenia and control subjects, they reported a trend of higher T allele frequency of the C2664T (rs1806201) polymorphism in schizophrenic patients. In the present study, we also found that ketamine users had higher T allele frequency in rs1806201. In a Caucasian population,[29] rs1806201 has been reported to be associated with alcohol abuse. Besides, the SNP rs1806201 in GRIN2B might play an important role in genetic susceptibility to earlier age onset of withdrawal symptoms in Indian alcohol-dependent subjects.[20] We found that subjects of genotype TT and CC in rs1806201 had an earlier onset of ketamine use than subjects of genotype TC. This polymorphism is a silent mutation in the gene region encoding the carboxyl-terminal intracellular domain of the NR2B subunit.[30] While the exact mechanisms are still unknown, these results suggested that the GRIN2B gene polymorphism may play a role in the development of ketamine abuse.

In addition, the dose of ketamine consumption per day was higher in ketamine users of rs7301328 genotype GG than in those with genotype CG. The GRIN2B SNP (rs7301328) has been linked to Parkinson's disease,[31] schizophrenia, and other neuropsychiatric disorders. To our knowledge, this is the first report showing an association between the GRIN2B SNP (rs7301328) gene polymorphism and drug use characteristics of ketamine users, which suggested a specific role of the GRIN2B gene in some aspects of ketamine use. Further studies are needed to illustrate the functional relevance of the SNP rs7301328 and rs1806201 in GRIN2B. Genetic variations and environmental factors such as stress and social defeat all impart vulnerability to drug addiction.[32] Identifying SNPs within the genome, and investigating their interactions with psychological and social factors could promote our understanding of how this biopsychosocial interaction can lead to addictive disease. Future studies to investigate the associations between psychological as well as social factors with GRIN2B gene polymorphism in ketamine users would be informative.

Recreational ketamine use has been reported to produce the undesirable effects of schizophrenia-like symptoms,[6,17] anxiety, and depression.[33] These symptoms in ketamine users were assessed using clinical symptom measures of the PANSS, BDI, and BAI scores. In the present study, no differences were found in the severity of psychopathologic symptoms between different genotypes in ketamine users. In a study on Chinese patients with schizophrenia, PANSS scores were shown to be significantly associated with GRIN2B variations (rs2098469, rs12820037, and rs7298664).[34] Therefore, further studies to test more variants of GRIN2B gene would be necessary.

There were limitations to this study that need to be mentioned. First, subjects were only males, because there were very few female ketamine users. Second, all ketamine users were hospitalized and subjects in the community were not included. Thus, further studies with larger sample size including subjects from the community are necessary. Third, we only analyzed four SNPs of GRIN2B gene. In a male Thai population,[35,36] rs1126442 of gene GRIN1 and rs6265 of gene BDNF were shown to have an association with methamphetamine dependence. Besides, rs17189632 of gene GRIN3A and rs2240158 of gene GRIN3B may contribute to the susceptibility of heroin addiction.[37] Therefore, further genetic and experimental studies with more variants of GRIN2B and other genes would be necessary.

## CONCLUSION

Our results suggest that GRIN2B gene polymorphism may play a role in the vulnerability of ketamine use.

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### *Declaration of Interest*

All authors declare that they have no conflict of interest.

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