Effects of CYP3A4 Polymorphisms on Drug Addiction Risk Among the Chinese Han Population

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Background: Cytochrome P450 3A4 (CYP3A4) regulates pharmacokinetic and pharmacodynamic interactions during the process of drug absorption and metabolism, suggesting CYP3A4 plays an important role in drug addiction. However, the association between CYP3A4 polymorphisms and drug addiction risk is still not clear.

Methods: This case-control study included 504 drug addicts and 501 healthy controls from Xi’an, China. Four single nucleotide polymorphisms (SNP) in CYP3A4 (rs3735451, rs4646440, rs35564277, and rs4646437) were genotyped by Agena MassARRAY platform. After adjusting by age and gender, we calculated odd ratios (OR) and 95% confidence intervals (CI) by logistic regression to estimate the association between CYP3A4 polymorphisms and drug addiction risk.

Results: We found rs4646440 and rs4646437 were associated with decreased risk of drug addiction in codominant (rs4646440: OR = 0.41, 95%CI = 0.19–0.92, p = 0.030; rs4646437: OR = 0.19, 95%CI = 0.04–0.87, p = 0.032) and recessive (rs4646440: OR = 0.41, 95%CI = 0.19–0.91, p = 0.028; rs4646437: OR = 0.20, 95%CI = 0.04–0.90, p = 0.036) models. Rs3735451 and rs4646437 were associated with drug addiction risk in the subgroup of middle-aged people (44 < age ≤ 59) and elderly people (age ≥ 60), individually. For men, rs3735451, rs4646440, and rs4646437 had strong relationship with decreased risk of drug addiction (p < 0.05). The effects of rs3735451 on drug addiction risk were related to drug-using time (p < 0.05). We also observed one block (rs4646440 and rs35564277) in haplotype analysis.

Conclusion: CYP3A4 polymorphisms were associated with drug addiction risk among the Chinese Han population.

Keywords: CYP3A4, drug addiction, case-control study, polymorphisms, Chinese Han population
INTRODUCTION

Drug addiction is a chronic relapse disorder characterized by compulsive drug seeking tendencies and usage, paired with substantial morbidity and mortality (1, 2). Worldwide, 99,000–253,000 deaths a year are attributed to drug addiction (3). It is reported that the number of drug users reached nearly 2.96 million until 2014 in China (4). Epidemiological data showed that women had lower rates of drug use than men (5). Drug addiction is influenced by many factors, including environmental, mental, and genetic factors (6, 7). Accumulating studies had proved that gene variety leads to drug addiction accounting for ∼50% (6, 8). During the drug addiction, age and sex differences are obvious in clinical and preclinical studies (9). Recently, drug-metabolizing enzyme had been addressed as a major target for drug addiction (10).

Cytochrome P450 (CYP) enzymes are monooxigenases that catalyze many reactions involved in the metabolism of drug, environmental contaminants, steroids and other lipids (11). The CYP3A4 enzyme is the most important drug-metabolizing P450s in the liver, which encoded by CYP3A4 gene (12). CYP3A4 enzyme is mainly responsible for methadone metabolism and hence uses for the treatment of drug addiction (13). CYP3A4 polymorphisms were also significantly associated with sedation side effects caused by methadone and several clinical conditions (ischemic stroke and epilepsy) (14–16). Previous study showed CYP3A4 rs2242480 was significantly associated with drug addiction in Xi’an Han Chinese population (17), and CYP3A4*4 allele was related to an increase in the lipid-lowering effects of simvastatin by decreasing CYP3A4 activity (18). In the CYP3A4 gene, rs4646440, and rs4646437 were the most common polymorphisms. Studies revealed that rs4646440 had strong relationship with withdrawal symptoms and adverse reactions in methadone maintenance patients (14). Rs4646437 had effects on the risk of many diseases, such as hypertension, human immunodeficiency virus (HIV) and some cancers (19–21). However, the study of association between CYP3A4 polymorphisms and drug addiction risk among the Chinese Han population is scarcely.

To assess the effects of CYP3A4 polymorphisms on drug addiction risk, we conducted a case-control study to explore the association of CYP3A4 polymorphisms (rs3735451, rs4646440, rs35564277, and rs4646437) with minor allele frequencies >5% in the Chinese Han Beijing population were selected. Genomic DNA was extracted from whole blood samples by GoldMag–Mini Purification Kit (GoldMag Co. Ltd. Xi’an, China) and was quantified by DU530 UV/VIS spectrophotometer (Beckman Instruments, Fullerton, CA, USA). Agena MassARRAY Assay Design 3.0 software was used to design primers in this study (Table 1). Genotyping was performed by the standard protocol from the Agena MassARRAY RS1000 manufacturer, data were managed and analyzed using the Agena Typer 4.0 Software (24).

STATISTICAL ANALYSIS

We used Microsoft Excel and SPSS 18.0 (SPSS, Chicago, IL) to conduct statistical analysis. All p-values were two-sided and p < 0.05 was regard as statistical significance. The Hardy-Weinberg equilibrium (HWE) for each single nucleotide polymorphism (SNP) in controls was evaluated by Chi-square test. The categorical and continuous variables were assessed using Chi-square test and t-test, individually. After adjusted by age and gender, the association of CYP3A4 polymorphisms and drug addiction risk was estimated using logistic regression analysis by calculating odd ratio (OR) and 95% confidence intervals (CI). Genetic models (codominant, dominant, recessive, and additive)
was performed on PLINK software. Linkage disequilibrium (LD) and haplotype construction were conducted by Haploview software (version 4.2) (25).

**RESULTS**

The characteristics of participants were presented in Table 2. Our study included 504 cases (448 men, 56 women) and 501 controls (447 men, 54 women). The mean ages of cases and controls were 48.46 ± 6.88 and 48.67 ± 8.01, respectively. There were no significant differences in age and gender between two groups (age: \( p = 0.308 \), gender: \( p = 0.920 \)). For all cases, 158 (31%) had drug addiction more than 16 years, 144 (28%) had drug addiction equal or <16 years, the other people (205, 41%) did not have the information of drug-using time.

As shown in Table 3, the MAFs of four SNPs in two groups were listed, and all SNPs were in HWE (\( p > 0.05 \)). The association between CYP3A4 polymorphisms and drug addiction risk in allele model was also shown in Table 3. Compared with GG genotype, the individuals with rs4646440 AA genotype had significantly decreased risk of drug addiction (OR = 0.41, 95%CI = 0.19–0.92, \( p = 0.030 \)). In recessive model, rs4646440 had strong relationship with drug addiction risk (OR = 0.41, 95%CI = 0.19–0.91, \( p = 0.028 \)). Additionally, rs4646437 was significantly associated with drug addiction risk in codominant (OR = 0.19, 95%CI = 0.04–0.87, \( p = 0.032 \)) and recessive (OR = 0.20, 95%CI = 0.04–0.90, \( p = 0.036 \)) models.

Furthermore, we performed stratified analysis of association between CYP3A4 polymorphisms and drug addiction risk (Table 4). Rs4646437 had a strong relationship with drug addiction among middle-aged people (44 < Age ≤ 59) in allele (OR = 0.73, 95%CI = 0.54–1.00, \( p = 0.046 \)) and additive (OR = 0.72, 95%CI = 0.52–0.99, \( p = 0.044 \)) models. For the individuals equal or more than 60 years old, rs4646440 was

### Table 2 | Characteristics of participants in this study.

| Variable           | Cases (\( N = 504 \)) | Controls (\( N = 501 \)) | \( p \) |
|--------------------|------------------------|---------------------------|--------|
| Age (Years old)    | 48.46 ± 6.88           | 48.67 ± 8.01              | 0.308  |
| ≤44                | 130 (26%)              | 146 (29%)                 |        |
| 45–59              | 351 (70%)              | 317 (74%)                 |        |
| ≥60                | 23 (4%)                | 38 (7%)                   |        |
| Gender             |                        |                           | 0.920  |
| Man                | 448 (89%)              | 447 (89%)                 |        |
| Woman              | 56 (11%)               | 54 (11%)                  |        |
| Drug-using time (Years) |                 |                           |        |
| >16                | 158 (31%)              |                           |        |
| ≤16                | 141 (28%)              |                           |        |
| Absence            | 205 (41%)              |                           |        |

SNP, single nucleotide polymorphism.

### Table 3 | The association of CYP3A4 polymorphisms and drug addiction risk.

| SNP      | Position         | MAF in cases | MAF in controls | HWE- \( p \) | Model  | Allele/Genotype | OR(95%CI)     | \( p \) |
|----------|------------------|-------------|-----------------|-------------|--------|----------------|--------------|--------|
| rs3753541| Chr7:99758352    | 0.199       | 0.216           | 0.674       | Allele | C/T           | 0.89(0.73–1.08) | 0.227  |
|          |                  |             |                 |             | Codominant | CC/TT   | 0.69(0.42–1.12) | 0.134  |
|          |                  |             |                 |             | Dominant | CC/CT/TT | 0.95(0.73–1.23) | 0.687  |
|          |                  |             |                 |             | Recessive | CC/CT/TT | 0.71(0.44–1.13) | 0.149  |
|          |                  |             |                 |             | Additive | –          | 0.88(0.72–1.08) | 0.214  |
| rs4646440| Chr7:99763247    | 0.059       | 0.072           | 0.599       | Allele | A/G          | 0.90(0.73–1.12) | 0.342  |
|          |                  |             |                 |             | Codominant | AA/GG   | 0.41(0.19–0.92) | 0.030  |
|          |                  |             |                 |             | Dominant | AA-AG/GG | 1.02(0.79–1.32) | 0.885  |
|          |                  |             |                 |             | Recessive | AA/AG-GG | 0.95(0.74–1.23) | 0.722  |
|          |                  |             |                 |             | Additive | A/G        | 0.89(0.71–1.12) | 0.309  |
| rs35564277| Chr7:99764813   | 0.127       | 0.873           | 0.734       | Allele | C/T         | 0.80(0.56–1.14) | 0.222  |
|          |                  |             |                 |             | Codominant | CC/TT   | –              | –         |
|          |                  |             |                 |             | Dominant | CC-CT/TT | 0.83(0.57–1.20) | 0.319  |
|          |                  |             |                 |             | Recessive | CC/CT/TT | –              | –         |
|          |                  |             |                 |             | Additive | –          | 0.80(0.56–1.14) | 0.216  |
| rs4646437| Chr7:99767460    | 0.526       | 0.498           | 0.609       | Allele | A/G         | 0.80(0.62–1.03) | 0.085  |
|          |                  |             |                 |             | Codominant | AA/GG   | 0.19(0.04–0.87) | 0.032  |
|          |                  |             |                 |             | Dominant | AA-AG/GG | 0.87(0.86–1.16) | 0.355  |
|          |                  |             |                 |             | Recessive | AA/AG-GG | 0.83(0.63–1.09) | 0.184  |
|          |                  |             |                 |             | Additive | AA/AG-GG  | 0.20(0.04–0.90) | 0.036  |

SNP, single nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy-Weinberg Equilibrium; OR, odds ratio; CI, confidence interval. Bold data means significant difference (\( p < 0.05 \)). –, No data.
### Table 4: Stratified analysis of association between CYP3A4 polymorphisms and drug addiction risk.

| SNP          | Model      | Age ≤ 44 | 44 < Age ≤ 59 | Age ≥ 60 | Man | Drug-using time |
|--------------|------------|----------|---------------|----------|-----|-----------------|
|              | OR(95%CI)  | p        | OR(95%CI)     | p        | OR(95%CI) | p    | OR(95%CI) | p    |
| rs3735451    | Allele     | 0.84 (0.59–1.22) | 0.365 | 0.92 (0.72–1.16) | 0.467 | 0.81 (0.36–1.85) | 0.621 | 0.89 (0.73–1.09) | 0.273 | 0.76 (0.53–1.09) | 0.140 |
|              | Codominant | 0.46 (0.18–1.18) | 0.106 | 0.82 (0.44–1.54) | 0.544 | 1.13 (0.19–6.61) | 0.892 | 0.39 (0.16–0.97) | 0.042 | 0.29 (0.10–0.81) | 0.018 |
|              | Dominant   | 1.12 (0.68–1.85) | 0.649 | 0.92 (0.67–1.27) | 0.628 | 0.46 (0.13–1.60) | 0.222 | 0.97 (0.73–1.28) | 0.822 | 1.02 (0.62–1.67) | 0.943 |
|              | Recessive  | 0.97 (0.60–1.57) | 0.913 | 0.91 (0.67–1.24) | 0.548 | 0.59 (0.19–1.78) | 0.344 | 0.90 (0.69–1.17) | 0.420 | 0.86 (0.53–1.38) | 0.521 |
|              | Additive   | 0.43 (0.17–1.08) | 0.074 | 0.86 (0.47–1.57) | 0.613 | 1.48 (0.27–8.11) | 0.651 | 0.74 (0.44–1.23) | 0.247 | 0.28 (0.10–0.79) | 0.015 |
| rs4646440    | Allele     | 0.85 (0.58–1.23) | 0.374 | 0.92 (0.72–1.17) | 0.488 | 0.82 (0.37–1.84) | 0.628 | 0.89 (0.72–1.09) | 0.259 | 0.74 (0.50–1.09) | 0.124 |
|              | Codominant | 0.70 (0.46–1.05) | 0.086 | 0.90 (0.69–1.18) | 0.447 | 3.83 (1.22–12.07) | 0.016 | 0.87 (0.69–1.10) | 0.254 | 0.87 (0.58–1.30) | 0.495 |
|              | Dominant   | 0.24 (0.05–1.16) | 0.075 | 0.40 (0.15–1.08) | 0.071 | – – | – – | 0.39 (0.16–0.97) | 0.042 | 0.50 (0.08–3.11) | 0.453 |
|              | Recessive  | 0.78 (0.47–1.28) | 0.321 | 1.03 (0.75–1.42) | 0.850 | 2.78 (0.71–10.84) | 0.141 | 0.97 (0.73–1.28) | 0.822 | 0.89 (0.54–1.46) | 0.634 |
|              | Additive   | 0.71 (0.43–1.16) | 0.168 | 0.97 (0.71–1.32) | 0.823 | 3.18 (0.84–12.00) | 0.087 | 0.91 (0.70–1.20) | 0.508 | 0.86 (0.53–1.41) | 0.554 |
| rs35564277   | Allele     | 0.65 (0.32–1.31) | 0.223 | 0.84 (0.55–1.28) | 0.407 | 1.08 (0.17–6.70) | 0.938 | 0.80 (0.55–1.16) | 0.239 | 0.66 (0.34–1.30) | 0.227 |
|              | Codominant | 0.68 (0.32–1.44) | 0.313 | 0.91 (0.58–1.43) | 0.672 | – – | – – | 0.87 (0.59–1.30) | 0.508 | – – |
|              | Dominant   | 0.65 (0.31–1.36) | 0.253 | 0.87 (0.55–1.36) | 0.531 | 0.89 (0.13–6.10) | 0.909 | 0.83 (0.56–1.23) | 0.357 | 0.68 (0.33–1.39) | 0.288 |
|              | Recessive  | – – | – – | – – | – – | – – | – – | – – | – – |
|              | Additive   | 0.63 (0.31–1.30) | 0.211 | 0.83 (0.54–1.28) | 0.402 | 0.89 (0.13–6.10) | 0.909 | 0.80 (0.54–1.17) | 0.240 | 0.68 (0.33–1.39) | 0.288 |
| rs4646437    | Allele     | 1.21 (0.74–1.97) | 0.450 | 0.73 (0.54–1.00) | 0.046 | 0.36 (0.11–1.14) | 0.074 | 0.80 (0.61–1.05) | 0.111 | 0.97 (0.59–1.60) | 0.918 |
|              | Codominant | 0.59 (0.05–6.61) | 0.666 | 0.14 (0.02–1.18) | 0.071 | – – | – – | 0.12 (0.01–0.97) | 0.046 | – – |
|              | Dominant   | 1.35 (0.78–2.34) | 0.286 | 0.78 (0.55–1.11) | 0.170 | 0.45 (0.12–1.68) | 0.232 | 0.88 (0.65–1.19) | 0.405 | 0.97 (0.55–1.70) | 0.915 |
|              | Recessive  | 1.31 (0.76–2.24) | 0.336 | 0.74 (0.53–1.05) | 0.092 | 0.41 (0.11–1.51) | 0.179 | 0.83 (0.62–1.12) | 0.227 | 1.00 (0.57–1.75) | 0.993 |
|              | Additive   | 0.54 (0.05–6.10) | 0.620 | 0.15 (0.02–1.26) | 0.080 | – – | – – | 0.12 (0.02–1.00) | 0.050 | – – |

SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval. Bold data means significant difference (p < 0.05). –, No data.
related to increased drug addiction risk in allele model (OR = 3.83, 95%CI = 1.22–12.07, p = 0.016). In the subgroup of man, rs3735451, rs4646440, and rs4646437 were related to decreased drug addiction risk in codominant (rs3735451: OR = 0.39, 95%CI = 0.16–0.97, p = 0.042; rs4646440: OR = 0.39, 95%CI = 0.16–0.97, p = 0.042; rs4646437: OR = 0.12, 95%CI = 0.01–0.97, p = 0.046) and recessive (rs4646440: OR = 0.40, 95%CI = 0.16–0.97, p = 0.043) models. Moreover, the effects of rs3735451 on drug addiction were related to drug-using time (codominant: OR = 0.29, 95%CI = 0.10–0.81, p = 0.018; recessive: OR = 0.28, 95%CI = 0.10–0.79, p = 0.015).

And, we did haplotype analysis of association between CYP3A4 polymorphisms and drug addiction risk (Table 5). We did not observe significant relationships between CYP3A4 haplotype and drug addiction risk (p > 0.05). In Figure 1, we detected one block (rs4646440 and rs35564277).

**DISCUSSION**

In this study, we firstly found that CYP3A4 polymorphisms (rs3735451, rs4646440, rs35564277, and rs4646437) were associated with drug addiction risk among the Chinese Han population. Especially, rs4646440 and rs4646437 were significantly associated with decreased risk of drug addiction. Stratified analysis showed that the effects of rs4646440 and rs4646437 on drug addiction risk are dependent on age and gender. Drug-using time also related to the association of rs3735451 and drug addiction risk. In addition, we observed one block (rs4646440 and rs35564277) by haplotype analysis.

CYP3A4 is the major congener of CYP family, which is highly expressed in intestine and liver. In vitro, experiment showed morphine enhances CYP3A4 expression (26). CYP3A4 controls the metabolism of more than 70% of all drugs in human, including cocaine and opiate (27, 28). However, inter-individual variation in drug response is obvious. Growing evidence indicates that inter-individual variability in drug response is related to genetic polymorphisms. CYP3A4 isoenzymes are related to patients with alcohol use disorder by regulating haloperidol concentration (29). The effects of CYP3A4 rs4646437 on drug is the most studied. He et al. found rs4646437 related to voriconazole metabolism, suggesting the impact of CYP3A4 on the pharmacokinetics of antifungal agent (30). Among Chinese renal transplant recipients, rs4646437 could affect the interindividual variability in the metabolism of tacrolimus (31). In addition, rs4646437 was significantly associated with prostate cancer by modifying finasteride concentration (32). In this study, we observed rs4646440 and rs4646437 of CYP3A4 had strong relationships with drug addiction risk. It suggests the role of CYP3A4 polymorphisms in drug addiction. Further functional studies are needed to verify the effects of CYP3A4 polymorphisms on drug addiction.

Although drug addiction generally occurs in the young, increasing prevalence drug use by elderly people is not ignorable (33). It was reported that drug addiction accelerated aging process in aging drug users (33). According to age classification criteria of the World Health Organization (WHO), we divided individuals into three groups (youth, middle-aged people and elderly people). In the subgroup of age ≥ 60, rs4646440 significantly increased risk of drug addiction. Rs4646437 was associated with drug addiction for the middle-aged people (44 < Age ≤ 59). Additionally, sex differences in drug abuse are common in drug addiction. For instance, men are more likely to use heroin than women and men take greater amounts of heroin (34, 35), it may be attributed to the molecular neuroadaptations. For participants in this study, there are more men than women. We hence performed association analysis in man and found CYP3A4 polymorphisms (rs3735451, rs4646440, and rs4646437) decreased drug addiction risk. Finally, we explored the association of CYP3A4 polymorphisms and drug addiction risk in individuals had different drug-using time. We observed that the influence of rs3735451 on drug addiction risk was related to drug-using time. Our

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**TABLE 5 | Haplotype analysis of association between CYP3A4 polymorphisms and drug addiction risk.**

| SNP | Haplotype | Frequency in cases | Frequency in controls | OR(95%CI) | p | OR(95%CI) | p |
|-----|-----------|-------------------|----------------------|-----------|---|-----------|---|
| rs4646440/rs35564277 | AC | 0.942 | 0.929 | 1.26 (0.87–1.80) | 0.220 | 1.26 (0.87–1.81) | 0.217 |
| rs4646440/rs35564277 | AT | 0.859 | 0.855 | 1.03 (0.80–1.34) | 0.800 | 1.04 (0.80–1.35) | 0.780 |
| rs4646440/rs35564277 | GT | 0.800 | 0.783 | 1.12 (0.89–1.40) | 0.322 | 1.12 (0.90–1.41) | 0.310 |

SNP: single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.
results indicated that age, gender and drug-using time affect the relationship between CYP3A4 polymorphisms and drug addiction risk. The exact mechanisms are required to study in the future.

Some limitations could not be ignored in this study. First, study participants are limited to the Chinese Han population. Second, drug addiction is caused by multiple factors, we could not eliminate the effects of all potential factors on drug addiction risk. Third, we could not do more stratified analyses due to limited information of participants or characteristic discrepancy. Hence, more ethnic population and well-designed studies are required to verify the association of CYP3A4 polymorphisms and drug addiction risk.

CONCLUSION

In summary, our study suggests that CYP3A4 polymorphisms could be associated with drug addiction among the Chinese Han population and the associations are related to age, gender and drug-using time. Further studies in larger population with more experiments are required to confirm our results.

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AUTHOR CONTRIBUTIONS

LW, MB, TJ, and JZ performed this study. YW, YH, and DY collected samples. XH supervised this study.

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DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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