Genome-wide pharmacogenomic study on methadone maintenance treatment identifies SNP rs17180299 and multiple haplotypes on *CYP2B6, SPON1*, and *GSG1L* associated with plasma concentrations of methadone *R*- and *S*-enantiomers in heroin-dependent patients

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Abstract

Methadone maintenance treatment (MMT) is commonly used for controlling opioid dependence, preventing withdrawal symptoms, and improving the quality of life of heroin-dependent patients. A steady-state plasma concentration of methadone enantiomers, a measure of methadone metabolism, is an index of treatment response and efficacy of MMT. Although the methadone metabolism pathway has been partially revealed, no genome-wide pharmacogenomic study has been performed to identify genetic determinants and characterize genetic mechanisms for the plasma concentrations of methadone R- and S-enantiomers. This study was the first genome-wide pharmacogenomic study to identify genes associated with the plasma concentrations of methadone R- and S-enantiomers and their respective metabolites in a methadone maintenance cohort. After data quality control was ensured, a dataset of 344 heroin-dependent patients in the Han Chinese population of Taiwan who underwent MMT was analyzed. Genome-wide single-locus and haplotype-based association tests were performed to analyze four quantitative traits: the plasma concentrations of methadone R- and S-enantiomers and their respective metabolites. A significant single nucleotide polymorphism (SNP), rs17180299 (raw $p = 2.24 \times 10\text{-}8$), was identified, accounting for 9.541% of the variation in the plasma concentration of the methadone R-enantiomers. In addition, 17 haplotypes were identified on SPON1, GSG1L, and CYP450 genes associated with the plasma concentration of methadone S-enantiomers. These haplotypes accounted for approximately one-fourth of the variation of the overall S-methadone plasma concentration, in which two significant haplotypes on CYP2B6 accounted for 10.72% of the variation. A gene expression experiment revealed that CYP2B6, SPON1, and GSG1L can be activated concomitantly through a constitutive androstane receptor (CAR) activation pathway. In conclusion, this study revealed new genes associated with the plasma concentration of methadone, providing insight into the genetic foundation of methadone metabolism. The results can be applied to predict treatment responses and methadone-related deaths for individualized MMTs.

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