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Genetic polymorphisms in the opioid receptor mu1 gene are associated with changes in libido and insomnia in methadone maintenance patients

Sheng-Chang Wang [a], Hsiao-Hui Tsou [b], Chia-Hui Chen [a], Yu-Ting Chen [a], Ing-Kang Ho [a,c,d], Chin-Fu Hsiao [b,c,e], Sun-Yuan Chou [f], Yen-Feng Lin [g], Kai-Chi Fang [h], Chieh-Liang Huang [c,i], Lien-Wen Su [j], Yung-Chun Fang [k], Ming-Lun Liu [l], Hsiao-Yu Wu [b], Keh-Ming Lin [a], Shu Chih Liu [a], Hsiang-Wei Kuo [a], I-Chen Chiang [m], Andrew C.H. Chen [n], Jia-Ni Tian [a], Yu-Li Liu [a,o,p,*]

[a] *Division of Mental Health and Addiction Medicine, Institute of Population Health Sciences, National Health Research Institutes, Miaoli County, Taiwan*
[b] *Division of Biostatistics and Bioinformatics, Institute of Population Health Sciences, National Health Research Institutes, Miaoli County, Taiwan*
[c] *Center for Drug Abuse and Addiction, China Medical University Hospital, Taichung, Taiwan*
[d] *Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan*
[e] *Division of Clinical Trial Statistics, Institute of Population Health Sciences, National Health Research Institutes, Miaoli County, Taiwan*
[f] *Department of Psychiatry, Taoyuan Mental Hospital, Department of Health, Taoyuan County, Taiwan*
[g] *Departments of Psychiatry, En Chu Kong Hospital, New Taipei, Taiwan*
[h] *Department of Psychiatry, Far Eastern Memorial Hospital, New Taipei, Taiwan*
[i] *Department of Psychiatry, China Medical University Hospital, Taichung, Taiwan*
[j] *Department of Psychiatry, Taipei City Hospital Song-De Branch, Taipei, Taiwan*
[k] *Department of Psychiatry, Taipei City Hospital Yang-Ming Branch, Taipei, Taiwan*
[l] *Department of Psychiatry, Wei Gong Memorial Hospital, Miaoli County, Taiwan*
[m] *Department of Biological Science and Technology, China Medical University, Taichung, Taiwan*
[n] *Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, NY, USA*
[o] *Graduate Institute of Drug Safety, China Medical University, Taichung, Taiwan*
[p] *Department of Psychiatry, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan*

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* Corresponding author at: 35 Keyan Road, Zhunan, Miaoli County 350, Taiwan. Tel.: +886 2 2653 4401x36716; fax: +886 037 586 453.
E-mail address: ylliou@nhri.org.tw (Y.-L. Liu).

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Abstract

Methadone, a synthetic racemic opioid that primarily works as a μ-opioid receptor (*OPRM1*) agonist, is commonly used for the treatment of heroin addiction. Genetic association studies have reported that the *OPRM1* gene is involved in the physiology of heroin and alcohol addiction. Our current study is designed to test the hypothesis that genetic polymorphisms in the *OPRM1* gene region are associated with methadone dosage, plasma concentrations, treatment responses, adverse reactions and withdrawal symptoms in a methadone maintenance treatment (MMT) cohort from Taiwan. Fifteen *OPRM1* single nucleotide polymorphisms (SNPs) were selected and genotyped using DNA samples from 366 MMT patients. The plasma concentrations of methadone and its metabolite were measured by high performance liquid chromatography. The results obtained using dominant model analysis indicate that the *OPRM1* SNPs rs1074287, rs6912029, rs12209447, rs510769, rs3798676, rs7748401, rs495491, rs10457090, rs589046, rs3778152, rs563649, and rs2075572 are significantly associated with change-in-libido side effects (adjusted $p<0.042$). Using recessive model analysis, these SNPs were also found to be significantly associated with insomnia side effects in this cohort ($p<0.009$). The significance of the insomnia findings was mainly contributed by a subgroup of patients who had a positive urine morphine test ($p<0.022$), and by individuals who did not use benzodiazepine hypnotics ($p<0.034$). Our current data thus suggest that genetic polymorphisms in *OPRM1* may influence the change-in-libido and insomnia side effects sometimes found in MMT patients.

1. Introduction

Methadone, a synthetic opioid, is commonly used as a maintenance therapy for opioid dependence (Mattick et al., 2009). The mechanism of action by which methadone can alleviate opioid dependence is believed to be primarily through its interaction with opioid receptors (Martin et al., 2007). Methadone is a full mu-opioid receptor agonist (Bond et al., 1998) and can produce cross-tolerance with heroin (Donny et al., 2005) or other opioids (Athanasos et al., 2006). This may in turn diminish withdrawal symptoms in affected individuals and enable patients who have recently stopped taking opioids to perform and maintain normal daily functions (Wolff et al., 1991). To decipher the genetic involvement of opioid receptors in the outcome of methadone maintenance treatment (MMT) in our current study, we evaluated the genetic association between the μ-opioid receptors (*OPRM1* or MOR) with methadone treatment responses in a Taiwanese cohort.

The distribution of MOR in human tissues includes the brain, spinal cord, sensory neuron and intestinal tract. MOR is thought to be responsible for the physiological basis of analgesia tolerance, physical dependence, respiratory depression, miosis, euphoria, pain perception, and reduced gastrointestinal motility (Johnson et al., 2008; Kreek, 1996; Lotsch and Geisslinger, 2006; Narita et al., 2001; Roy et al., 1998; Shabalina et al., 2009). There are several alternative spliced variants of MOR (subtypes or isoforms) that mediate the actions of morphine in the physiology of the analgesia and physical dependence on opioids (Bart et al., 2005; Hayashida et al., 2008; Narita et al., 2001). These isoforms of MOR were identified by receptor selectivity (Pan et al., 2009) and bioinformatics analysis (Xin and Wang, 2002). The human gene encoding the OPRM1 protein is located on chromosome 6q24–q25. An A118G polymorphism in this gene (in addition to Asn40Asp (Oroszi et al., 2009) and N40D, and the single nucleotide polymorphism (SNP) ID rs1799971) has been reported to be associated with different types of pain perception (Fillingim et al., 2005; Oertel et al., 2009; Way et al., 2009), the risk of addiction (Deb et al., 2010) including heroin in Han Chinese (Shi et al., 2002), alcohol dependence in Japanese (Nishizawa et al., 2006), and nicotine reinforcement in female Caucasians (Ray et al., 2006). However, inconsistent results have been reported with regards to the association of this polymorphism with pain treatment (Walter and Lotsch, 2009) and in the dependence on other substances (Compton et al., 2003; Franke et al., 2001).

Few studies to date have reported the association between methadone treatment and *OPRM1* genetic polymorphisms (Bunten et al., 2010, 2011; Fonseca et al., 2010). We aimed in our present study to test the hypothesis that the *OPRM1* is associated with the methadone dosage, plasma concentrations of methadone and its metabolites, the methadone treatment response, and the side effects that manifested in a Taiwanese methadone maintenance treatment (MMT) cohort.

2. Experimental procedures

2.1. Subjects

This study was approved by the institutional review boards of the National Health Research Institutes (Zhunan, Taiwan) and the six participating hospitals. Written informed consent was obtained from each participant. The project has also been registered with the National Institutes of Health Clinical Trial database (http://www.clinicaltrial.gov/ct/show/NCT01059747). A total of 366 subjects with heroin dependence undergoing MMT as outpatients were recruited. The inclusion criteria included an age of 18 or above, receipt of MMT for at least three months with regular attendance for the past seven days, and a methadone dosage adjustment of no more than 10 mg in the past seven days. Exclusion criteria included