Opioid dependence is a chronic and relapsing disorder with high costs to individuals, families, and society. Genetic predisposition is a major factor contributing to the development of heroin addiction. Methadone maintenance treatment (MMT) is the most widely used treatment for heroin dependence; however, there is a large inter-individual variability in outcome. The study of patients' genetic backgrounds in the therapeutic response to MMT has become an issue of increasing interest: recent studies have focused in genes coding for methadone-metabolizing enzymes, transporter proteins, dopaminergic receptors, and brain-derived neurotrophic factor.

The study, which was supported by Genoma España and Ministerio de Educacion y Ciencia (SAF2005-01005, SAF2007- 60827 and GEN2003-20651-C06-03), was conducted by the Psychiatric Department, Autonomous University of Barcelona, Barcelona, Spain.

### METHODS

A sample of 116 Opioid dependent subjects (DSM-IV), in MMT were recruited and classified as Responders and Nonresponders according to illicit opioid consumption detected in randomised urinalysis. To be eligible for the study, patients had to be Caucasian, enrolled in MMT for at least six months and receiving a stable methadone dose for the last two months. The following data were obtained: socio-demographic characteristics, serological status (HIV, HCV), history of substance use, and previous psychiatric treatment, substance and non-substance use psychiatric disorders. The degree of addiction-related impairment (ASI) was assessed. Written informed consent was obtained from each subject and the study was approved by the Ethical and Clinical Research Committees of our institution (IMAS-Hospit del Mar).

We included 116 subjects (83 responders; 33 nonresponders). Groups were similar with regard to methadone dose and other substance use disorders and psychiatric comorbidity (table 1). SNPs were in Hardy-Weinberg equilibrium. Significant differences in genotype distributions between groups were found for rs1861591. Subjects carrying the AA genotype had higher risk of being nonresponders (OR=2.99; 95%CI 1.14-7.85; P=0.035), although this difference disappeared with correction for multiple testing. There was an epistatic effect between rs1714984 and rs953741 (P=0.008). Patients carrying the A allele at rs1714984 had an increased risk of being nonresponders only when they were carriers of the AG genotype at rs953741 (OR=10.83, 95%CI 2.52-46.66) [table 2].

### RESULTS

We included 116 subjects (83 responders; 33 nonresponders). Groups were similar with regard to methadone dose and other substance use disorders and psychiatric comorbidity (table 1). SNPs were in Hardy-Weinberg equilibrium. Significant differences in genotype distributions between groups were found for rs1861591. Subjects carrying the AA genotype had higher risk of being nonresponders (OR=2.99; 95%CI 1.14-7.85; P=0.035), although this difference disappeared with correction for multiple testing. There was an epistatic effect between rs1714984 and rs953741 (P=0.008). Patients carrying the A allele at rs1714984 had an increased risk of being nonresponders only when they were carriers of the AG genotype at rs953741 (OR=10.83, 95%CI 2.52-46.66) [table 2].

### CONCLUSIONS

We detected an association between MMT response and different variants in genes CRY1, MYOCD and GRM6. These genes have been involved respectively in the molecular regulation of the clock machinery, in the pathophysiology of neurological and mood disorders and cell proliferation, migration and control of smooth muscle gene expression. There was a pharmacogenetic epistatic effect between SNPs in MYOCD and GRM6 that appear to be modulating the MMT response.

### REFERENCES


### Financial Disclosure

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