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RESEARCH ARTICLE

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Association between rs1799971 in the mu opioid receptor gene and methadone maintenance treatment response

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Abstract

Objective: Genetic variations can affect individual response to methadone maintenance treatment (MMT) for heroin addiction. The A118G variant (rs1799971) in the mu opioid receptor gene (OPRM1) is a potential candidate single nucleotide polymorphism (SNP) for personalized MMT. This study determined whether rs1799971 is related to MMT response or dose.

Methods: We recruited 286 MMT patients from a Han Chinese population. The rs1799971 genotype was determined via TaqMan genotyping assay. The genetic effect of this SNP on MMT response or dose was evaluated using logistic regression. A meta-analysis was performed to merge all available data to evaluate the role of rs1799971 in MMT using RevMan 5.3 software.

Results: No statistical significance was observed in the association between the OPRM1 rs1799971 and MMT response or dose in our Chinese cohort. Meta-analysis indicated that the OPRM1 A118G variation was not significantly associated with MMT response or dose requirement.

Conclusion: The results suggest that rs1799971 in OPRM1 might not play a critical role alone in influencing MMT response or dose.

KEYWORDS
association, heroin, methadone, mu opioid receptor, rs1799971

1 | INTRODUCTION

Heroin dependence is an ongoing public health issue worldwide, and methadone maintenance treatment (MMT) is currently an effective substitution therapy for patients with heroin addiction. Methadone, as a synthetic agonist of the mu opioid receptor, can reduce illicit opiate use and improve social rehabilitation.[1,2] There is an obvious difference in individual response to methadone due to large interindividual variability in its pharmacokinetics and pharmacodynamics.[3–7] Optimal personalized medicine for each patient is vital for successful MMT.[8,9]

Genetic factors are related to the diversity of individuals in responding to MMT.[10–12] Several articles reported that numerous variations in multiple genes are related to modification of the individual MMT response.[13–15] Single nucleotide polymorphisms (SNPs) of several genes are significant associations with MMT, such as the genes

encoding opioid receptors and regulatory factors, drug transporters, and metabolic enzymes.[16–23]

The mu receptor is the major target of opioids, including methadone. The important functional variant A118G (rs1799971) in the mu receptor gene (OPRM1) encodes a nonsynonymous substitution (Asn40Asp). The 118G variation is associated with enhancing receptor-binding affinity,[24] decreasing gene transcription,[25] exhibiting a more robust decrease in synaptic excitability,[26] and increasing risk of heroin addiction, alcohol dependence, and nicotine enhancement.[27–30] A systematic review demonstrated that rs1799971 is a hazard factor for opioid addiction.[31]

Considering that rs1799971 is significantly associated with heroin addiction, this variant is a promising candidate for pharmacodynamic effects on MMT. Individuals with the rs1799971 variation may have differences in receptor activities, resulting in individual variability in the clinical response to methadone. Some research studies explored the correlation of OPRM1 rs1799971 with MMT response or dose, but a definitive conclusion remains elusive.[32–38] For instance, the results are different in different populations. Wang et al.[39] found an association between allele G and higher methadone dosage in a Chinese Han cohort (366 cases), whereas Levran et al.[10] reported no association of rs1799971 with methadone dose in a Caucasian ethnic group (227 patients). However, the limited sample size of these studies may mask the true conclusion. Therefore, it is necessary to provide accurate evidence to prove the association between OPRM1 A118G variation and MMT response or dose.

In general, the interaction of multiple genetic and nongenetic factors combines to determine MMT response or dose. It is better to consider multiple genes together to gain a better understanding of MMT pharmacogenetics. However as mentioned above, it is unclear whether rs1799971 can predict MMT response or dose. In this study, the main goal was to verify whether rs1799971 is the association with the response to MMT in a cohort from China. In consideration of the inconsistent findings from previous articles, we conducted a meta-analysis with the data available to assess the effects of rs1799971 on MMT. The results of this study may provide valuable information for personalized medicine in MMT.

2 | MATERIALS AND METHODS

2.1 | Subjects

Participants were enrolled from the MMT clinic in the Ningbo Addiction Research and Treatment Center (NARTC) in China's Zhejiang Province. In this study, 286 patients with heroin addiction in MMT were from a Han Chinese cohort. Patients with serious mental illness requiring immediate treatment were excluded. The institutional ethics committee of the NARTC approved this study in line with the principles of the Helsinki Declaration. The written informed consent was collected from every subject. The basic information of patients, including gender, age, ethnicity, weight, history of heroin abuse, average daily amount of heroin used in the last month, psychological disorders, and physical diseases, were gathered using questionnaires. The dose of methadone, the duration of methadone use, and the urine checking results were obtained from the methadone administration records.

Subjects were separated into nonresponders and responders based on the response to methadone. Referencing similar studies,[9,20] nonresponse was defined as discontinuing MMT within 6 months or testing positive for heroin or methamphetamine twice in random urine checks in the last month; the response was defined as continuing MMT longer than 6 months and testing negative for urine checks in the last month. The nonresponse group included 154 patients. The response group, including 132 patients, was divided into two subgroups with respect to the MMT dose: low dose (less than 60 mg daily) and high dose (60 mg daily or more) according to a previous study.[9]

2.2 | Genotyping

DNA was obtained from the peripheral blood with the standard phenol chloroform preparation method. DNA concentrations were quantified using spectrophotometry and stored at −20°C before genotyping. The rs1799971 genotype was determined based on previous studies,[40,41] using the TaqMan genotyping assay (Applied Biosystems). In brief, the 10 μl reaction mix included 0.25 μl 40 × SNP genotyping assay, 5 μl 2 × Master mix, and 20 ng DNA. After 95°C for 10 min, the thermal cycling involved 40 cycles at 95°C for15 s followed by 60°C for 60 s. The genotype was identified by the Roche LightCycler 480II quantitative PCR instrument. Two controls of no template and three positive controls of DNA-containing were randomly distributed on each PCR plate for quality control. Finally, 5% of the samples were randomly selected to re-genotype blindly.

2.3 | Statistical analyses

For continuous data, the Student's *t*-test or Mann–Whitney U tests, and analysis of variance (ANOVA) or Kruskal–Wallis test were conducted as appropriate. For categorical data, the chi-squared test was performed. The deviations from Hardy–Weinberg equilibrium (HWE) were checked with χ^2 goodness-of-fit test. And the odds ratio (OR) of the SNP was assessed by logistic regression analysis adjusted for gender, age, weight, heroin abuse time, and dose in the dominant, recessive, or codominant genetic model. SPSS 16 software was used for the analyses. *p* value less than 0.05 was accepted as statistically significant.

2.4 | Meta-analysis

Articles were systematically searched from PubMed (for papers in English), CNKI and Wanfang databases (for papers in Chinese) up to October 1, 2021, using the keywords “OPRM1” or “mu opioid

receptor gene" and "methadone" to search for studies on this topic. The inclusion criteria: (a) studies investigated the association of rs1799971 with MMT response or dose and (b) sufficient genotype data were available for data extraction. The exclusion criteria: (a) literature did not investigate the association of rs1799971 with MMT response or dose, or (b) there were no available data to perform data extraction. The included studies' quality assessment was conducted using the Newcastle-Ottawa scale (NOS). Two independent reviewers assessed article quality and extracted data from eligible articles. The data were merged and analyzed using RevMan 5.3 software (https://training.cochrane.org), and the odds ratio (OR) with 95% confidence interval (CI) was calculated. The heterogeneity among studies was ascertained using I^2 and Q statistics. The fixed effects model was selected at first. Then, a random effect model was chosen if the heterogeneity was high ($I^2 > 50\%$ or $p < 0.1$). Publication bias was evaluated with a funnel plot. Sensitivity analyses were conducted with a leave-one-out method to investigate the consistency of the analysis. Statistical significance was considered as $p < 0.05$.

3 | RESULTS

The main characteristics of the subjects in MMT are shown in Table 1. Excluding methadone dose and duration of treatment, no differences were found in the characteristics among the responder and nonresponder groups. The methadone dose and treatment time of responders were higher than those of nonresponders. Table 1 displays that the heroin abuse amount in the high-dose methadone group was apparently larger than that in the low-dose group, which suggests that methadone dosage is related to heroin dose.

The distribution of A118G polymorphism in both responders and nonresponders is shown in Table 2, as well as in the low- and high-dose groups. No deviation from HWE was observed in any group ($p > 0.05$). The differences in the frequencies in allele and genotype in responders and nonresponders were not significant, as well as in the low- and high-dose groups ($p > 0.05$). There were no significant associations between rs1799971 and MMT response or dose in the dominant, recessive, or codominant genetic model based on the results of logistic regression analysis ($p > 0.05$). In addition, the methadone doses of carriers with AA, AG, and GG genotypes were 62.2 ± 32.9, 57.9 ± 29.4, and 52.7 ± 25.0 mg/day, respectively. The differences between the three genotypes were not significant by ANOVA ($p > 0.05$) and were not significant in the dominant, recessive, or codominant model ($p > 0.05$).

The process flow diagram of the systematic article retrieval and selection is shown in Figure S1. A total of 6 articles were qualified from the databases searched[32,33,35–38]; thus, there were seven studies including our study in the final meta-analysis. All eligible studies received five or more NOS scores, indicating that they were of good quality. Table 3 displays the data extracted from the included articles. No deviations from HWE were observed in any studies. Overall, there was no evidence that OPRM1 rs1799971 moderated efficacy in the meta-analysis using RevMan 5.3 software. No statistically

TABLE 1 Main characteristics of the MMT patients

Characteristics	Responders ($n = 134$)	Nonresponders ($n = 152$)	p	Low dose ($n = 76$)	High dose ($n = 58$)	p
Sex: male	109 (81.3%)	119 (78.3%)	0.522[a]	60 (78.9%)	49 (84.5%)	0.415[a]
Age (years)	34.3 ± 6.2 [22, 51]	33.4 ± 6.2 [20, 53]	0.231[b]	34.1 ± 6.3 [22, 48]	34.5 ± 6.0 [25, 51]	0.668[b]
Body weight (kg)	58.3 ± 7.3 [39, 80]	58.9 ± 8.5 [40, 80]	0.538[b]	57.6 ± 7.9 [39, 80]	59.3 ± 6.4 [45, 75]	0.170[b]
Years of heroin use	7.1 ± 3.3 [0.6, 17.8]	7.2 ± 3.5 [0.5, 15]	0.646[b]	7.0 ± 3.1 [0.6, 12]	7.3 ± 3.6 [1, 17.8]	0.826[b]
Heroin amount (g/day)	1.9 ± 1.0 [0.2, 6]	1.8 ± 0.9 [0.2, 5]	0.529[c]	1.8 ± 0.9 [0.2, 5]	2.2 ± 1.1 [0.5, 6]	**0.011**[c]
Methadone dose (mg/day)	59.2 ± 30.5 [15, 130]	49.9 ± 29.1 [10, 140]	**0.007**[c]	38.4 ± 11.5 [15, 55]	86.4 ± 25.9 [60, 140]	**<0.001**[b]
Duration of MMT (months)	15.1 ± 6.9 [6, 31]	2.4 ± 1.3 [0.2, 15]	**<0.001**[c]	14.8 ± 6.9 [6,31]	15.4 ± 6.9 [7, 30]	0.592[b]

Note: Data are presented as mean ± SD (range).

[a]Chi-squared test.

[b]Student's *t*-test.

[c]Mann–Whitney *U* test.

TABLE 2 Association analyses in the MMT patients

rs1799971	Responders ($n = 134$)	Nonresponders ($n = 152$)	p	Low dose ($n = 76$)	High dose ($n = 58$)	p
A	179 (66.8%)	199 (65.5%)	0.737[a]	98 (64.5%)	81 (69.8%)	0.356[a]
G	89 (33.2%)	105 (34.5%)		54 (35.5%)	35 (30.2%)	
AA	60 (44.8%)	67 (44.1%)	0.879[a]	33 (43.4%)	27 (46.6%)	0.385[a]
AG	59 (44.0%)	65 (42.8%)		32 (42.1%)	27 (46.6%)	
GG	15 (11.2%)	20 (13.1%)		11 (14.5%)	4 (6.9%)	
AA vs. AG+GG	60 vs. 74	67 vs. 85	0.983[b]	33 vs. 43	27 vs.31	0.715[b]
AA+AG vs. GG	119 vs. 15	132 vs. 20	0.689[b]	65 vs. 11	54 vs. 4	0.180[b]
AA vs. GG	60 vs. 15	67 vs. 20	0.800[b]	33 vs. 11	27 vs. 4	0.201[b]
AG vs. GG	59 vs. 15	65 vs. 20	0.621[b]	32 vs. 11	27 vs.4	0.178[b]

[a]Chi-squared test.

[b]Logistic regression analysis adjusted for sex, age, body weight, heroin abuse time, and dose.

TABLE 3 Related data from the studies included in the meta-analyses

		Responders				Nonresponders				
Study	Population	n	AA	AG	GG	n	AA	AG	GG	p
Xie 2022	Han Chinese	134	60	59	15	152	67	65	20	0.879[c]
Crettol 2008	Caucasians	165	118	44	3	73	59	13	1	0.315[b,c]
			AA	AG+GG			AA	AG+GG		
Crist 2018	Caucasians[a]	307	249	58		45	35	10		0.444[b,c]
		Low dose				High dose				
		n	AA	AG	GG	n	AA	AG	GG	
Xie 2022	Han Chinese	76	33	32	11	58	27	27	4	0.385[c]
Hung 2011	Han Chinese	92	49	37	6	229	104	90	35	0.090[c]
Akbari 2021	Iranians	39	31	8	0	85	73	12	0	0.369[c]
		Methadone dose (mg/day) (means ± SD)								
		n	AA	n		AG	n	GG		
Xie 2022	Han Chinese	60	62.2 ± 32.9	59		57.9 ± 29.4	15	52.7 ± 25.0		0.515[d]
Mouly 2015	Caucasians[a]	55	64.8 ± 56.7	23		57.8 ± 38.1	2	65.0 ± 7.1		0.860[b,d]
Tolami 2020	Iranians	130	91.8 ± 36.5	58		96.4 ± 37.2	14	86.7 ± 11.6		0.830[b,e]
			AA			AG+GG				
Crist 2018	Caucasians[a]	249	72.5 ± 34.2	58		74.7 ± 28.5				0.850[b,d]

[a]83.3% patients were Caucasians in Crist's study, 85.2% patients were Caucasians in Mouly's study.

[b]P value from original research.

[c]chi-squared test.

[d]one-way ANOVA.

[e]Kruskal–Wallis test.

significant associations were detected between rs1799971 and MMT response or dose (Table 4 and Figures S2–S11). The differences in the frequencies of allele or genotype in responders and nonresponders were not significant in the dominant, recessive, or codominant model, as well as in the low- and high-dose groups ($p > 0.05$). In addition, the difference in methadone dose between genotypes was not significant in the dominant, recessive, or codominant model (Figure S12–S15). Furthermore, the funnel plots did not have substantial asymmetry, suggesting that there was no significant publication bias. After removing the individual studies one by one, the results did not change significantly, indicating the stability of the outcomes.

4 | DISCUSSION

This study showed that rs1799971 polymorphism in OPRM1 was not related to MMT response or dose in a Chinese cohort. Subsequent meta-analysis also found no significant evidence that rs1799971 plays a critical role in MMT. Our results verified that there is no

TABLE 4 Results of the meta-analyses for rs1799971 and MMT

Model	Responders		Nonresponders		Odds Ratio [95% CI]	*p*
A vs. G	459 (76.8%)	139 (23.2%)	330 (73.3%)	120 (26.7%)	1.07 [0.80, 1.45]	0.64
AA vs. AG+GG	427 (70.5%)	179 (29.5%)	161 (59.6%)	109 (40.4%)	1.09 [0.74, 1.59]	0.62
AA+AG vs. GG	281 (94.0%)	18 (6.0%)	203 (90.6%)	21 (9.4%)	0.87 [0.44, 1.71]	0.68
AA vs. GG	175(90.7%)	18 (9.3%)	126 (85.7%)	21 (14.3%)	0.89 [0.44, 1.82]	0.76
AG vs. GG	103(85.1%)	18 (14.8%)	78 (78.8%)	21 (21.2%)	0.83 [0.40, 1.71]	0.62
	Low dose		**High dose**			
A vs. G	303 (73.2%)	111 (26.8%)	537 (64.4%)	297 (35.6%)	1.00 [0.59, 1.68]	1.00
AA vs. AG+GG	113 (54.6%)	94 (45.4%)	204 (54.8%)	168 (45.2%)	0.95 [0.63, 1.43]	0.65
AA+AG vs. GG	151 (89.9%)	17 (10.1%)	248 (86.4%)	39 (13.6%)	0.90 [0.16, 5.11]	0.90
AA vs. GG	82 (82.8%)	17 (17.2%)	96 (71.1%)	39 (28.9%)	0.71 [0.08, 6.31]	0.76
AG vs. GG	69 (80.2%)	17 (19.8%)	117 (75.0%)	39 (25.0%)	0.93 [0.17, 5.01]	0.94

Abbreviations: CI, confidence interval; P, calculated by Revman software.

apparent association between rs1799971 and MMT response and dose. Recently, we reported no significant associations between four SNPs in the gene of the delta subunit of GABA receptor and MMT in the same cohort.[42] These findings are unsurprising given the complex nature of opioid addiction and tolerance, methadone pharmacokinetic variability, and variability in mu opioid receptor pharmacodynamics, all of which combine to determine MMT outcomes and dose requirements.

The curative effects of MMT are affected by some factors including a patient's subjective will, clinical features, dose and time of MMT, and environmental and genetic influences. Great individual differences exist in MMT response and dose.[3–7] Successful long-term MMT is partially dependent on suitable individual dosage, which can help patients avoid heroin withdrawal and craving, while also reducing some side effects. It is increasingly recognized that genetic influences may play an important role in the response of patients in MMT.[10–12] Most studies have focused on the variants in genes coding transporters (P-glycoprotein), metabolizing enzymes (cytochrome P450), receptors (dopamine, and opioid receptors), and regulatory proteins (neurotrophins, β-arrestin).[6–12] Identifying the genetic factors impacting MMT could contribute to better-personalized therapy.

Prior research had demonstrated an association of OPRM1 rs1799971 with the decreased effect of different opioids,[24–26] and a previous meta-analysis supported the moderating potency of this SNP on naltrexone response in the treatment of alcoholism.[43] The OPRM1 rs1799971 has emerged as one of the most promising candidates to function as a genetic predictor of the MMT response. Several reports have evaluated the association of rs1799971 with methadone treatment outcome or dose, but the results have been contradictory.[10,32–39] Some studies have found that the patients with rs1799971 G allele require a higher methadone dose.[33,39] However, other investigations did not find the association of this polymorphism with MMT response or dose.[32,35–38]

We attempted to find the evidence of rs1799971 as a predictor of the response to MMT. However, we did not find significant evidence that rs1799971 plays a critical role in MMT in our samples or in meta-analysis. In fact, the frequencies of genotype and allele were nearly the same in the responders and nonresponders, as well as in the low- and high-dose groups. Our results indicated that the single variant rs1799971 cannot be regarded as a critical factor alone in MMT. Given the complexity of heroin addiction and the heterogeneity of population in MMT, it is reasonable to assume that this single genetic variant may not fully interpret individual differences in MMT. We may preliminarily hypothesize that the effect of rs1799971 is small and does not alone influence the general treatment response, although this variation may result in some changes in methadone efficacy. When evaluating the impact on MMT, rs1799971 needs to be considered in combination with other genes. For example, in the control of ABCB1 (encodes P-glycoprotein transporter) genetic variability, Barrett et al.[34] detected a significant association of the rs1799971 G allele with higher methadone dosage.

This study has certain limitations. First of all, the size of the sample was relatively small, as well as the number of included studies in the meta-analysis. The meta-analyses for dichotomous outcomes were only two or three studies with heterogeneous findings, limiting the value of the meta-analyses. Second, the rs1799971 allele frequency varied greatly in different populations, and so, the influence on MMT may also vary in different ethnicities. Third, this study only analyzed the rs1799971; however, the interactions between gene and environment may alter the effect of the SNP. Recently, Levran et al. (2021) reported that the allele 118G appeared on at least two haplotypes in East Asia, which could be distinguished by additional SNPs.[29] It is therefore necessary to consider the haplotypes containing A118G. In future, investigating OPRM1 haplotypes (including several tag SNPs and regulatory SNPs, especially rs9397171 and rs9383689) in this cohort will be an improvement on the methods used in the present study. Finally, the reasons for leaving treatment vary, and leaving treatment does not necessarily mean nonresponse. We could not collect the reasons for leaving treatment, which may have affected

the accuracy of the results. Considering the limitations of this study, it is necessary to conduct high-quality research in larger samples of different ethnicities to verify the results.

In summary, our findings provide evidence that the interindividual variability in MMT cannot be fully explained by a single effect of rs1799971. Therefore, taking into consideration polygenetic and environmental factors is important for better comprehending the potential factors of individual responses in MMT. In future, exploring the interactions of multiple genetic factors and clinical characteristics in large samples may illustrate the factors underlying methadone response or dose and will enhance personalized therapy to improve treatment effectiveness.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest. This study was funded by the Zhejiang Medical and Health Leading Academic Discipline Project of China (No. 00-F06). This study was supported by the Natural Science Foundation of China (No. 82071499), the Medical Health Science and Technology Projects of Zhejiang, China (No. 2021KY1065 and 2022KY1175), and the Science and Technology Program of Ningbo, China (No. 2021J273).

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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