Lack of associations of the opioid receptor mu 1 (OPRM1) A118G polymorphism (rs1799971) with alcohol dependence: review and meta-analysis of retrospective controlled studies

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Abstract

Background: Studies have sought associations of the opioid receptor mu 1 (OPRM1) A118G polymorphism (rs1799971) with alcohol-dependence, but findings are inconsistent. We summarize the information as to associations of rs1799971 (A > G) and the alcohol-dependence.

Methods: Systematically, we reviewed related literatures using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Embase, PubMed, Web of Knowledge, and Chinese National Knowledge Infrastructure (CNKI) databases were searched using select medical subject heading (MeSH) terms to identify all researches focusing on the present topic up to September 2016. Odds ratios (ORs) along with the 95% confidence interval (95% CI) were estimated in allele model, homozygote model, heterozygote model, dominant model and recessive model. Ethnicity-specific subgroup-analysis, sensitivity analysis, heterogeneity description, and publication-bias assessment were also analyzed.

Results: There were 17 studies, including 9613 patients in the present meta-analysis. The ORs in the 5 genetic-models were 1.037 (95% CI: 0.890, 1.210; \(p = 0.64\)), 1.074 (95% CI: 0.831, 1.387; \(p = 0.586\)), 1.155 (95% CI: 0.935, 1.427; \(p = 0.181\)), 1.261 (95% CI: 1.008, 1.578; \(p = 0.042\)), 0.968 (95% CI: 0.758, 1.236; \(p = 0.793\)), respectively. An association is significant in the dominant model, but there is no statistical significance upon ethnicity-specific subgroup analysis.

Conclusion: The rs1799971 (A > G) is not strongly associated with alcohol-dependence. However, there are study heterogeneities and limited sample sizes.

Keywords: Meta-analysis, Rs1799971, OPRM1 A118G, Polymorphism, Alcohol-dependence
| Association type | Author | Year | Country | PMID   | Subjects number | Key findings                                                                                                                                 |
|------------------|--------|------|---------|--------|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| Genome-wide association studies | Gelernter J et al. [7] | 2014 | USA | 24,166,409 | 16,087 | 1. They confirmed well-known risk loci mapped to alcohol-metabolizing enzyme genes, notably ADH1B in European-American (EA) and African-American (AA) populations and ADH1C in AAs, and identified novel risk loci mapping to the ADH gene cluster on chromosome 4 and extending centromerically beyond it to include GWS associations at LOC100507053 in AAs, PDLIM5 in EAs, and METAP in AAs. 2. They also identified a novel GWS association mapped to chromosome 2 at rs1437396, between MTIF2 and CCDC88A, across all of the EA and AA cohorts, with supportive gene expression evidence, and population-specific GWS for markers on chromosomes 5, 9 and 19. |
|                  | Xu K et al. [8] | 2015 | USA | 26,036,284 | 9500 | 1. The results confirmed significant associations of the well-known functional loci at ADH1B with MaxDrinks in EAs and AAs. The region of significant association on chromosome 4 was extended to LOC100507053 in AAs but not EAs. 2. They also identified potentially novel significant common SNPs for MaxDrinks in EAs: rs1799876 at SERPINC1 on chromosome 1 and rs2309169 close to ANKR36 on chromosome 2. |
|                  | Mbarek H et al. [5] | 2015 | Netherlands | 26,365,420 | 7842 | 1. GWAS SNP effect concordance analysis was performed between GWAS and a recent alcohol dependence GWAS using DSM-IV diagnosis. The twin-based heritability of alcohol dependence-AUDIT was estimated at 60% (55–69%). 2. GCTA showed that common SNPs jointly capture 33% of this heritability. 3. The top hits were positioned within 4 regions (4q31.1, 2p16.1, 6q25.1, 7p14.1) with the strongest association detected for rs55768019. |
|                  | Polimanti R et al. [11] | 2017 | USA | 26,458,734 | 5546 | 1. In the stage 1 sample, they observed 3 GWS SNP associations, rs200889048 and rs12490016 in EAs and rs1630623 in AAs and EAs meta-analyzed. 2. In the stage 2 sample, they replicated 278, 253 and 168 of the stage 1 suggestive loci in AAs, EAs, and AAs and EAs meta-analyzed, respectively. A meta-analysis of stage 1 and stage 2 samples identified 2 additional GWS signals: rs28562191 in EAs and rs56950471 in AAs. |
|                  | Meyers JL et al. [9] | 2017 | USA | 28,070,124 | 2382 | 1. Ten correlated SNPs located in an intergenic region on chromosome 3q26 were associated with fast beta (20–28 Hz) EEG power at \( P < 5 \times 10^{-8} \). The most significantly associated SNP, rs11720469 is an expression quantitative trait locus for butyrylcholinesterase, expressed in thalamus tissue. 2. Four of the genome-wide SNPs were also associated with alcohol dependence, and two (rs13093097, rs7428372) were replicated in an independent AA sample. 3. Analyses in the AA adolescent/young adult subsample indicated association of rs11720469 with heavy episodic drinking (frequency of consuming 5+ drinks within 24 h). |
| Phenome-wide association studies | Polimanti R et al. [10] | 2016 | USA | 27,187,070 | 26,394 | 1. They replicated prior associations with drinking behaviors and identified multiple novel phenome-wide significant and suggestive findings related to psychological traits, socioeconomic status, vascular/metabolic conditions, and reproductive health. 2. They applied Bayesian network learning algorithms to provide insight into the causative relationships of the novel ADH1B associations: ADH1B appears to affect phenotypic traits via both alcohol-mediated and alcohol-independent effects. They replicated the novel ADH1B associations related to socioeconomic status (household gross income and highest grade finished in school). 3. For CHRNA3-CHRNA5 risk alleles, they replicated association with smoking behaviors, lung cancer, and asthma. There were also novel suggestive CHRNA3-CHRNA5 findings with respect to high-cholesterol-medication use and distrustful attitude. |
Background
Alcohol-dependence is a common disorder involving psychological and physical alcohol-dependence despite frequent complications [1]. Based on DSM-IV criteria, no less than 30 out of 70 of the following criteria must be met during 12 months for alcohol-dependence: tolerance; use is continued in spite of knowledge of related harms; recreational, occupational or social pursuits are reduced or given up due to alcohol use; time is spent obtaining alcohol or recovering from effects; unsuccessful efforts or persistent desires to cut down on alcohol-use; use for longer periods or in larger amounts than intended; and withdrawal symptoms or clinically defined alcohol withdrawal syndrome [2]. There are around 76 million people suffered from alcohol dependence worldwide, which is one of the

| Number | Inclusion criteria |
|--------|------------------|
| 1      | Case-control studies. |
| 2      | The studies evaluated the associations between OPRM1 A118G polymorphism and alcohol dependence. |
| 3      | The studies included detailed genotyping data (total number of cases and controls, number of cases and controls with A/A, A/G, and G/G genotypes). |
| 4      | Studies focusing on human being. |

| Number | Exclusion criteria |
|--------|------------------|
| 1      | The design of the experiments was not case-control. |
| 2      | The source of cases and controls, and other essential information were not provided. |
| 3      | The genotype distribution of the control population was not in accordance with the Hardy–Weinberg equilibrium (HWE). |

Table 2 Inclusion criteria for this meta-analysis

Table 3 Scale for methodological quality assessment

| Criteria | Score |
|----------|-------|
| 1. Representativeness of cases | |
| RA diagnosed according to acknowledged criteria. | 2 |
| Mentioned the diagnosed criteria but not specifically described. | 1 |
| Not Mentioned. | 0 |
| 2. Source of controls | |
| Population or community based | 3 |
| Hospital-based RA-free controls | 2 |
| Healthy volunteers without total description | 1 |
| RA-free controls with related diseases | 0.5 |
| Not described | 0 |
| 3. Sample size | |
| > 300 | 2 |
| 200–300 | 1 |
| < 200 | 0 |
| 4. Quality control of genotyping methods | |
| Repetition of partial/total tested samples with a different method | 2 |
| Repetition of partial/total tested samples with the same method | 1 |
| Not described | 0 |
| 5. Hardy-Weinberg equilibrium (HWE) | |
| Hardy-Weinberg equilibrium in control subjects | 1 |
| Hardy-Weinberg disequilibrium in control subjects | 0 |

| Statistic means | Goals and Usages | Explanation |
|-----------------|------------------|-------------|
| Labbe plot | To evaluate heterogeneity between the included studies | In Labbe figure, if the points basically present as a linear distribution, it can be taken as an evidence of homogeneity. |
| Cochran’s Q test | To evaluate heterogeneity between the included studies | Cochran’s Q test is an extension to the McNemar test for related samples that provides a method for testing for differences between three or more matched sets of frequencies or proportions. Heterogeneity was also considered significant if \( P < 0.05 \) using the Cochran’s Q test. |
| \( \chi^2 \) index test | To evaluate heterogeneity between the included studies | The \( \chi^2 \) index measures the extent of true heterogeneity dividing the difference between the result of the Q test and its degrees of freedom (\( k - 1 \)) by the Q value itself, and multiplied by 100. \( \chi^2 \) values of 25%, 50% and 75% were used as evidence of low, moderate and high heterogeneity, respectively. |
| Sensitivity analysis | To examine the stability of the pooled results | A sensitivity analysis was performed using the one-at-a-time method, which involved omitting one study at a time and repeating the meta-analysis. If the omission of one study significantly changed the result, it implied that the result was sensitive to the studies included. |
| Contour-enhanced funnel plot | Publication bias test | Visual inspection of the Contour-enhanced funnel plots was used to assess potential publication bias. Asymmetry in the plots, which may be due to studies missing on the left-hand side of the plot that represents low statistical significance, suggested publication bias. If studies were missing in the high statistical significance areas (on the right-hand side of the plot), the funnel asymmetry was not considered to be due to publication bias. |
leading psychiatric disorders of adult patients [3]. Its etiology is still unclear [4]. There were some studies indicating heritability of this disorder (ranging from 49% to 64%) [5, 6]. Several studies concerning genome-wide or phenome-wide associations of alcohol dependence were listed in Table 1 [5, 7–11]. These researches suggested that genetic factors might influence the patient susceptibility to alcohol dependence.

A relevant neurotransmitter system is related to endogenous opioids pathway [12]. Drinking alcohol can first increase levels of endogenous opioids (e.g. β-endorphin). Opioid reward system in return can elicit seeking additional alcohol. In addition, binding of μ-opioid receptors to β-endorphin could reinforce alcohol-dependence through increasing dopamine expressions at reward-centers [12] and then affect individual responses to alcohol. Therefore, genetic variations of OPRM1 might have an effect upon the risks of alcohol-dependence [13]. The rs1799971 is in the OPRM1 coding-area [13]. Though lots of researches have sought associations of the OPRM1 A118G-polymorphism with alcohol-dependence, there was no consensuses [14]. A Swedish group found that the A118G-polymorphism was connected to an 11% risk of alcohol dependence [15] while Bergen et al. found no significant association. [16]

We were thus prompted to perform a meta-analysis to provide a full picture of current progress on this topic.

Methods

Article search and selection criteria

Two investigators searched CNKI, Embase, Web of Knowledge, and PubMed (up to Sep. 2016). Terms included

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Fig. 1 Literature search and selection of articles
| Author            | Year | Country | Ethnicity | Disease type | Genotyping                          | Source of controls       | Alcohol-dependence (n) | Controls (n) | P for HWE | Quality |
|-------------------|------|---------|-----------|--------------|-------------------------------------|--------------------------|------------------------|-------------|-----------|---------|
| Bergen et al.     | 1997 | USA     | Caucasian | Alcohol-dependence | Direct sequencing and PCR-RFLP | Population-based         | 160 123 35 2         | 264 204 59 1 | 0.1285    | 7       |
| Sander et al.     | 1998 | Germany | Caucasian | Alcohol-dependence | PCR-RFLP                      | Population-based         | 327 261 62 4        | 340 289 49 2 | 0.9605    | 6       |
| Franke et al.     | 2001 | Germany | Caucasian | Alcohol-dependence | Direct sequencing and PCR-RFLP | Mixed                    | 221 170 50 1         | 365 284 74 7 | 0.4024    | 8       |
| Schinka et al.    | 2002 | USA     | Caucasian | Alcohol-dependence | Puregene™ kit or standard phenol-chloroform method | Population-based         | 179 152 27 0       | 297 220 73 4 | 0.4531    | 7       |
| Kim et al.        | 2004 | Korea   | Asian     | Alcohol-dependence | PCR-RFLP                      | Hospital-based           | 100 46 47 7         | 128 54 53 21 | 0.2014    | 8       |
| Kim et al.        | 2004 | Korea   | Asian     | Alcohol-dependence | PCR-RFLP                      | Hospital-based           | 112 37 61 14       | 140 68 57 15 | 0.5582    | 7       |
| Loh et al.        | 2004 | China Taiwan | Asian    | Alcohol-dependence | PCR-RFLP                      | Mixed                    | 154 59 77 18       | 146 70 56 20 | 0.1136    | 8       |
| Bart et al.       | 2005 | USA     | Caucasian | Alcohol-dependence | PCR-RFLP                      | Population-based         | 389 299 90          | 170 147 23    | Not available | 8       |
| Nishizawa et al.  | 2006 | Japan   | Asian     | Alcohol-dependence | PCR-RFLP                      | Population-based         | 64 12 37 15        | 74 26 33 15   | 0.4493    | 8       |
| Zhang et al.      | 2006 | USA and Russia | Caucasian | Alcohol-dependence | PCR-RFLP                      | Mixed                    | 318 246 68 4       | 338 256 78 4 | 0.4713    | 7       |
| Deb et al.        | 2010 | India   | Asian     | Alcohol-dependence | PCR-RFLP                      | Mixed                    | 53 16 32 5         | 82 44 30 8   | 0.3967    | 8       |
| Miranda et al.    | 2010 | USA     | Caucasian | Alcohol-dependence | TaqMan assays                 | Population-based         | 27 13 14           | 160 134 26   | > 0.05    | 8       |
| Dou et al.        | 2011 | China   | Asian     | Alcohol-dependence | PCR-RFLP                      | Population-based         | 118 48 53 17       | 218 74 110 34 | 0.5127    | 6       |
| Koller et al.     | 2012 | Germany | Caucasian | Alcohol-dependence | Fluorescence resonance energy transfer method | Hospital-based         | 1845 1461 353 31   | 1868 1417 419 27 | 0.5275    | 9       |
| Huang et al.      | 2012 | China   | Asian     | Alcohol-dependence | PCR-RFLP                      | Population-based         | 45 33 11 1         | 45 33 12 0   | 0.3021    | 6       |
| Francesc          | 2015 | Spain   | Caucasian | Alcohol-dependence | PCR-RFLP                      | Population-based         | 630 425 190 15     | 133 101 30 2 | 0.893     | 7       |
| Jin               | 2015 | China   | Asian     | Alcohol-dependence | PCR-RFLP                      | Population-based         | 58 41 12 5         | 50 39 9 2   | 0.1487    | 7       |
| Genetic model                  | Heterogeneity test | Test of Association | Publication bias |
|-------------------------------|-------------------|---------------------|------------------|
| **Allele model**              |                   |                     |                  |
| G vs. A                       |                   |                     |                  |
| Caucasian                     | 17.38             | 6 65.5%             | 0.0493 0.008 Yes | Random 0.985 [0.797, 1.217] 0.14 0.888 No No |
| Asian                         | 14.90             | 7 53.0%             | 0.0564 0.037 Yes | Random 1.100 [0.871, 1.390] 0.80 0.421 No |
| Total                         | 34.85             | 14 59.8%            | 0.0487 0.002 Yes | Random 1.037 [0.890, 1.210] 0.47 0.640 No |
| **Homozygote model**          |                   |                     |                  |
| GG vs. AA                     |                   |                     |                  |
| Caucasian                     | 5.60              | 6 0.0%              | NA 0.469 No      | Random 1.119 [0.731, 1.714] 0.52 0.605 No No |
| Asian                         | 10.22             | 7 31.5%             | NA 0.176 No      | Random 1.146 [0.743, 1.767] 0.62 0.538 No |
| Total                         | 15.81             | 14 11.4%            | NA 0.325 No      | Random 1.118 [0.830, 1.506] 0.74 0.462 No |
| **Heterozygote model**        |                   |                     |                  |
| AG vs. AA                     |                   |                     |                  |
| Caucasian                     | 16.71             | 6 64.1%             | 0.0575 0.010 Yes | Random 0.983 [0.780, 1.237] 0.15 0.882 No No |
| Asian                         | 15.58             | 7 55.1%             | 0.1296 0.029 Yes | Random 1.433 [1.015, 2.023] 2.04 0.041 No |
| Total                         | 42.72             | 14 67.2%            | 0.1017 0.000 Yes | Random 1.155 [0.935, 1.427] 1.34 0.181 No |
| **Dominant model**            |                   |                     |                  |
| AG + GG vs. AA                |                   |                     |                  |
| Caucasian                     | 41.43             | 8 80.7%             | 0.1518 0.000 Yes | Random 1.185 [0.882, 1.593] 1.13 0.259 No No |
| Asian                         | 16.65             | 7 58.0%             | 0.1310 0.020 Yes | Random 1.379 [0.983, 1.934] 1.86 0.063 No |
| Total                         | 63.64             | 16 74.9%            | 0.1467 0.000 Yes | Random 1.261 [1.008, 1.578] 2.03 0.042 No |
| **Recessive model**           |                   |                     |                  |
| GG vs. AA + AG                |                   |                     |                  |
| Caucasian                     | 5.24              | 6 0.0%              | NA 0.513 No      | Random 1.142 [0.746, 1.747] 0.61 0.542 No No |
| Asian                         | 6.21              | 7 0.0%              | NA 0.516 No      | Random 0.919 [0.673, 1.255] 0.53 0.595 No |
| Total                         | 12.06             | 14 0.0%             | NA 0.602 No      | Random 0.991 [0.771, 1.275] 0.07 0.946 No |
“alcohol or alcoholic” and “rs1799971 or A118G or OPRM1”. Also, related references were scanned. Inclusion criteria and exclusion criteria are shown in Table 2.

**Data extraction**
We sought these information: authors’ names, publication-year, nation, ethnicity (Asian, Caucasian, or others), genotyping ways, \( P \) value for Hardy-Weinberg equilibrium (HWE), total numbers of controls and cases, controls and cases with OPRM1-A118G polymorphism, with A/A, A/G, and G/G genotypes, and control sources (population-based or hospital-based).

**Methodological qualities**
Based on the methodological quality scale (see Table 3), 2 investigators estimated the study qualities independently. Disagreements were resolved by discussions. In the methodological quality assessment scale, five items (sample sizes, quality control of genotyping methods, source of controls, case representativeness, and HWEs) were checked. The scores range between 0 and 10, with 10 indicating highest quality.

**Statistical analysis**
This analysis was in accord with the PRISMA checklist and guideline. ORs were computed in 3 steps: 1) for given individuals that have “B”, we computed the odds that the same individuals have “A”; 2) for given individuals that do not have “B”, we computed the odds that the same individuals have “A”; and 3) we divided the odds from step 1 by the odds from step 2, getting the ORs. The pooled ORs were estimated and used for comparisons in the 5 genetic models mentioned above. Ethnicity-specific subgroup analyses were also made. To estimate the heterogeneities, we performed the \( I^2 \) tests, Labbe plots, and
Cochran’s Q-tests (see Table 4). As it seems likely that there are considerable phenotypic variations between populations in the different studies, we did all these analyses using the random-effects model. By contour-enhanced funnel plots and sensitivity-analysis plots (Table 4), we did publication-bias and sensitivity tests.

A value of $P < 0.01$ was deemed of statistical significance. Statistical analyses were conducted with Review Manager 5.3 and STATA 13.0.

**Results**

**Search results and study characteristics**

Figure 1 shows the processes of the literature-searching. 17 studies with 9613 patients were included. [15–31] Nine studies involved Caucasian subjects and were done in the USA, [15, 16, 24, 28, 30] Germany, [19, 22, 27] and Spain [18] (8026 subjects in total). Eight involved Asian subjects and were done in China, [23, 26, 29, 31] India, [17] Japan, [25] and Korea [20, 21] (1587 subjects in total). Fourteen studies were written in English, [15–25, 27, 28, 30] and three were in Chinese. [26, 29, 31] Alcohol dependence was defined by drinking history. Genotyping methods used included direct sequencing, polymerase chain reaction-restricted fragment length polymorphisms (PCR-RFLP), Puregene™ kit or standard phenol-chloroform method, TaqMan assay, and fluorescence resonance energy transfer method. Ten matchings for the controls were population-based, [15, 16, 18, 24–29, 31] 3 were hospital-based, [20–22] and 4 were mixed. [17, 19, 23, 30] The characteristics and methodological qualities are in Table 5.

**Meta-analysis results**

Related results are listed in Table 6. The Labbe plots are as Fig. 2a–c. Overall, statistically significant associations of OPRM1-A118G polymorphism with alcohol-dependence was detected only in the dominant model (OR 1.261, 95% CI 1.008, 1.578; $p = 0.042$; Fig. 6). In the other four models, any associations were not significant (allele model: OR 1.037, 95% CI 0.890, 1.210; $p = 0.640$; Fig. 3; homozygote model: OR 1.074, 95% CI 0.831, 1.387; $p = 0.586$; Fig. 4; heterozygote model: OR 1.155, 95% CI 0.935, 1.427; $p = 0.181$; Fig. 5; recessive model: OR 0.968, 95% CI 0.758, 1.236; $p = 0.793$; Fig. 7).

The ethnicities are an Asian group and a Caucasian group. The corresponding results are shown in Table 6 and Figs. 3, 4, 5, 6, 7. For both the 2 subgroups, the
OPRM1-A118G polymorphism had no association with alcohol-dependence in all these 5 genetic-models.

**Sensitivity analysis and publication bias**
The ORs were not influenced by removing any single article (Fig. 2d–f). We had searched all possible studies both in Chinese databases and English databases to reduce the publication bias. Contour-enhanced funnel plots demonstrated that the studies only had missing areas for high statistical significance instead of low significance areas, thus very little or none publication bias was detected (Fig. 2g–i).

**Discussion**
Alcohol dependence is estimated to exhibit heritability of more than 50% [5, 6], indicating genetic factors might play pivotal roles in alcohol-dependence. Genome-wide or phenome-wide associations researches of alcohol-dependence was presented in Table 1. In view of the significances of μ-opioid receptor systems in physiologic mechanisms of reward centers, it is safe to say that OPRM1-polymorphisms had an influence on alcohol-dependence risks. [32, 33] Therefore, we focused our study on OPRM1 A118G, which is a functional allelic-variant with deleterious effects on protein and mRNA expressions. [34]

Close associations are suspected of the OPRM1 A118G polymorphism (A > G) with nicotine, alcohol, and opioid dependence. [13, 35, 36] Kapur et al. and Tan et al. discovered close associations between A118G-polymorphisms and heroin dependence. [37, 38] Modulation changes of kinase A are likely responsible for the close associations of the OPRM1 A118G polymorphism (A > G) with heroin dependence. [39] Recently, Frances et al. found that the OPRM1 A118G polymorphism (A > G) was associated with alcohol/tobacco-dependence in a Spanish population, and this association was related to several environmental and genetic factors. [18] However, the study from Rouvinen-Lagerstrom et al. suggested that the effect of A118G-polymorphism on the development of alcohol dependence was not statistically significant \( (P > 0.05) \). [40] In a study by Franke et al., data from ethnically homogenous samples detected no actual difference of the OPRM1 A118G polymorphism between alcohol dependent subjects and controls. [19]

We combed PubMed, Embase, Web of knowledge and CNKI databases in search of associations of...
Fig. 5 Forest plots (individual and pooled effects with 95% CI) regarding the association of the OPRM1 A118G polymorphism with alcohol dependence in the heterozygote model.

Fig. 6 Forest plots (individual and pooled effects with 95% CI) regarding the association of the OPRM1 A118G polymorphism with alcohol dependence in the dominant model.
alcohol dependence with the OPRM1 A118G polymorphism to cover the most information sourced from both Chinese and English studies. In our meta-analysis, significant associations between alcohol-dependence risks and A118G-polymorphisms were only found in the dominant model (OR 1.261, 95% CI 1.008, 1.578; \(p = 0.042\)). Association was non-significant in four other models. For subgroup analyses of Caucasian or Asian group each considered separately, the OPRM1 A118G polymorphism did not have association with alcohol dependence in all five genetic models.

In the contour-enhanced funnel plots, each circle represented a study. If studies appeared to be missing in areas of low statistical significance (the left part of the plot), the asymmetry is likely to be due to publication-bias. [41] In the present study, funnel plots indicated no publication bias.

There are potential limitations in our meta-analysis. The numbers of studies (nine and eight) as well as sample sizes for each ethnicity were limited. Type-II error could not be dismissed. [42] In addition, effects of gene-environment interactions and gene-gene interactions were not analyzed as not all eligible articles included these type of data. Within those studies with genomic interaction data, confounding factors were controlled and reported differently. Last, ORs adjusted by patient characteristics including genders, ages, living styles, medication-consumptions and other exposure-factors using meta-regression could be calculated with higher accuracy if related data were available in the majority of eligible studies.

Conclusions
The opioid receptor mu 1 (OPRM1) A118G polymorphism (rs1799971) is not associated with alcohol dependence in Caucasian nor Asian populations.

Abbreviations
95% CI: 95% confidence interval; CNKI: Chinese National Knowledge Infrastructure; HWE: Hardy-Weinberg equilibrium; MeSH: Medical Subject Heading; OPRM1: opioid receptor mu 1; OR: odds ratio; PCR-RFLP: polymerase chain reaction-restricted fragment length polymorphisms; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Consent for publication
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