Author’s response to reviews

Title: Lack of Association of the Opioid Receptor mu 1 (OPRM1) A118G Polymorphism (rs1799971) with Alcohol Dependence: Review and Meta-analysis of Retrospective Controlled Studies

Authors:

Xiangyi Kong (Xiangyi_Kong@hms.harvard.edu)
Hao Deng (XKONG@mgh.harvard.edu)
Shun Gong (gongshunsmmu@foxmail.com)
Theodore Alston (Alstoncorbett@comcast.net)
Yanguo Kong (kongyanguo1@gmail.com)
Jingping Wang (JWANG23@mgh.harvard.edu)

Version: 1 Date: 16 Aug 2017

Author’s response to reviews:

Dear the editor

Thank you for your comments. We have revised the article point by point. The main changes and the responses to the reviewers are as follows:

MGTC-D-17-00085

Association between Opioid Receptor mu 1 (OPRM1) A118G Polymorphism (rs1799971) and Alcohol Dependence

BMC Medical Genetics

Reviewer reports:

Xingnan Li, Ph.D. (Reviewer 1): In this study, Dr. Kong et al. performed a meta-analysis of rs1799971 in OPRM1 gene with alcohol dependence. Some of my concerns are:
(1) Five genetic models (allele, homozygote, heterozygote, dominant, and recessive) were used for statistical analysis, which could introduce multiple tests. P<0.01 should be used as the criterion for statistical significance.

Corrected as suggested.

(2) In the Abstract, "Odd ratios (ORs)" should be Odds ratios.

Corrected as suggested.

(3) This is a meta-analysis or systemic review. In the title, it should be clearly stated.

Corrected as suggested. The title has been changed to “Lack of association between Opioid Receptor mu 1 (OPRM1) A118G Polymorphism (rs1799971) and Alcohol Dependence: a systemic review and meta-analysis of XXX studies”

Renato Polimanti, Ph.D. (Reviewer 2):

Kong and colleagues conducted a meta-analysis of OPRM1 A118G and alcohol dependence. The methods are correct and the discussion is supported by the results. I have minor concerns that should be addressed.

* The authors conducted an analysis about genetics of alcohol dependence. The authors should improve introduction and discussion with information about genome-wide association studies of AD (PMID: 28070124, 26458734, 26365420, 26036284, 24166409), phenome-wide association studies for known AD risk alleles (PMID: 27187070), and GWAS that identified OPRM1 risk alleles (PMID: 28115739).

Thank you for your advice. We improved our manuscript by adding related studies as suggested.

* I suggest the authors to modify the title to immediately highlight the lack of association between OPRM1 A118G and alcohol dependence.

Corrected as suggested. The title has been changed to “Lack of association between Opioid Receptor mu 1 (OPRM1) A118G Polymorphism (rs1799971) and Alcohol Dependence: a systemic review and meta-analysis of XXX studies”
David Jeffries (Reviewer 3): Major comments

The fixed versus random effects model should be based on sampling population and not purely on heterogeneity considerations. It seems likely that there are considerable phenotypic variations between populations in the different studies, so it is difficult to justify a fixed effect model.

Thank you for your advice. According to your advice, we changed some of our fixed models to random effects model after accounting for the phenotypic variations.

The definitions of alcohol dependence were not discussed.

We added the definition of alcohol dependence as suggested.

What is the justification for combining population and hospital based studies? What is the sensitivity to this issue? Although mentioned in the discussion, this could have a major confounding effect.

Many thanks for your comments and questions. We understand that maybe there would be heterogeneity due to different patient sources. However, we do not think whether hospital-based or population-based or mixed could significantly influence the pooled results. We pointed clearly the patient sources for precision and scientificity.

The paper needs proof reading throughout - there are many issues.

We revised our manuscript to correct grammar mistakes to provide a better reading experience.

Minor comments

There is no explicit description of how the odds ratio is defined

As suggested, we added description of how odds ratio is defined.

Figure 2 is difficult to follow - perhaps separate heterogeneity form the other plots.

To make it clear, we have modified the caption of Figure 2 as “Figure 2 Labbe plots, sensitivity analysis plots, and contour-enhanced funnel plots of the included studies focusing on the association of the OPRM1 A118G polymorphism with alcohol dependence risk. Labbe plots in allele model (A), heterozygote model (B), and dominant model (C). Sensitivity analysis in allele
model (D), heterozygote model (E), and dominant model (F). Contour-enhanced funnel plots in allele model (G), heterozygote model (H), and dominant model (I).”

Table 5 is just a repeat of the data in the forest plots.

Thank you for your comments. Because Table 5 gives more detailed data and information than the forest plots, we think it’s necessary to keep this table for readers’ reference.

Are Figures 8 and 9 relevant to the meat analysis?

We have deleted Figure 8 and Figure 9.

The word 'correlation' is used throughout, when it really refers to a more general relationship/dependence.

Corrected as suggested.

Thank you and best regards.

Yours sincerely,

Yanguo Kong, M.D.

Dep. of Neurosurgery, Peking Union Medical College Hospital & Chinese Academy of Medical Sciences, NO.1 Shuaifuyuan Hutong of Dongcheng District, Beijing, 100730 P. R. China

TEL: 86-13661160297 (China)

E-mail: kongyanguo1@gmail.com