Author's response to reviews

Title: Association between epidermal growth factor gene +61A/G polymorphism and the risk of hepatocellular carcinoma: a meta-analysis based on 16 studies

Authors:

Guoping Jiang (jiangguoping@zju.edu.cn)
Ke Yu (yuke2009@gmail.com)
Lifang Shao (lfshao@hotmail.com)
Xiaobo Yu (yuxb@zju.edu.cn)
Chen Hu (huchen@outlook.com)
Pei Qian (cxgp1212@126.cm)
Haiyang Xie (xiehy@zju.edu.cn)
Jinjun Li (lijj64@gmail.com)
Jie Zheng (zhengjie20141@163.com)
Shusen Zheng (shusenzheng@zju.edu.cn)

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Author’s response to reviews:

Dear Editors:

Thanks for reviewing our manuscript. We have already read the comments from the reviewers and here is our reply. To make it clear, we have presented our opinions right below the reviewers’ report. All changes in revised manuscript have been highlighted.

Review: Ping-Chin Lee

Reviewer’s report:

1. How reliable is the overall findings in this study as there was a significant bias (p<0.05) in the overall populations?

Our reply: In this study, the significant Q-statistic indicated heterogeneity in the overall populations. Therefore, the random-effects model (DerSimonian and Laird method) was used to pool all studies. As a result, the EGF +61A/G polymorphism was significantly associated with HCC risk in overall populations under all genetic models. Then, meta-regression analysis was performed to investigate potential sources of heterogeneity. Meta-analysis indicated that both ethnicity and study quality significantly contributed to the heterogeneity. Nevertheless, in the subgroup analyses by ethnicity and study quality, this significant association still existed in the subgroup, and the between-study heterogeneity was not observed in Asian, European or African populations. Moreover, sensitivity analysis further strengthened the validity of the positive association in overall populations, indicating robustness of our results.

The sentences “Overall, the EGF +61A/G polymorphism was significantly associated with an increased HCC risk under all genetic models. Further
subgroup analyses by ethnicity revealed that this association also existed in Asian populations, European populations, and African populations, respectively. Sensitivity analysis further strengthened the validity of the positive association in overall populations, and in Asian populations, indicating robustness of our results. In addition, considerable heterogeneity was detected across studies. Meta-regression showed that both ethnicity and study quality significantly contributed to the heterogeneity for EGF +61A/G polymorphism.” (Line 281-289, Page 12) have been revised as “Overall, the EGF +61A/G polymorphism was significantly associated with an increased HCC risk under all genetic models. However, considerable heterogeneity was detected across studies. Meta-regression showed that both ethnicity and study quality significantly contributed to the heterogeneity for EGF +61A/G polymorphism. Nevertheless, in the subgroup analyses by ethnicity and study quality, this significant association still existed in each subgroup, and the between-study heterogeneity became insignificant in Asian, European or African populations. Moreover, sensitivity analysis further strengthened the validity of the positive association in overall populations, and in Asian populations, indicating robustness of our results.” (Line 272-281, Page 12)

2. Address the suitability to include patients with chronic liver diseases as controls because the risk to HCC in patients with chronic liver diseases was higher to healthy controls in all genetic models.

Our reply: In our study, the controls were not uniformly defined. Eight studies used healthy subjects, and 12 studies used subjects with chronic liver diseases as controls. Considering the impact of chronic liver disease, subgroup analyses based on type of controls were performed. Subgroup analyses showed that the significant association between EGF +61A/G and HCC was present both in healthy controls and in patients with chronic liver diseases, indicating the role of EGF +61A/G in the risk of HCC, regardless of type of controls. Moreover, the pooled ORs for individuals with chronic liver diseases were higher than those for healthy controls under all genetic models. Therefore, the chronic liver diseases may change the environment in vivo and mediate the ability of genetic factors to contribute to HCC. More studies should be designed to investigate the role of EGF polymorphisms in combination with chronic liver diseases in HCC pathogenesis. Nevertheless, as mentioned in Discussion section, the type of controls was still the limitation of our study.

The sentence “The subgroup analyses showed that the effect of EGF +61A/G polymorphism on HCC susceptibility seemed to be identical in healthy and non-HCC Asian populations.” (Line 375-377, Page 16) has been revised as “The subgroup analyses showed that the significant association between EGF +61A/G and HCC was present both in healthy controls and in patients with chronic liver diseases, indicating the role of EGF +61A/G in the risk of HCC, regardless of type of controls. Moreover, the pooled ORs for individuals with chronic liver diseases were higher than those for healthy controls under all genetic models. Therefore, the chronic liver diseases may change the environment in vivo and mediate the ability of genetic factors to contribute to HCC. More studies should be designed to investigate the role of EGF polymorphisms in combination with chronic liver diseases in HCC pathogenesis. Nevertheless, as mentioned in Discussion section, the type of controls was still the limitation of our study.
chronic liver diseases in HCC pathogenesis.” (Line 367-372, Page 16)

Review: Miroslav Blumenberg

Reviewer’s report:

1. There is, however, one problem that the authors should address: it is difficult to slog through the numbers embedded in the text, e.g., lines 224-229 and 255-258 etc., these would be much easier to read and comprehend in tables. Either manuscript much clearer.

Our reply: In this study, the main results of meta-analysis were listed in Table 2. Table 3 has been added.

The sentence “Overall, the results of pooling all studies showed that the EGF +61A/G polymorphism was significantly associated with an increased HCC risk under all genetic models (G vs. A: OR=1.383, P<0.001, 95% CI: 1.174-1.629, I²=75.4%, Pheterogeneity<0.001, Figure 2; GG vs. GA+AA: OR=1.484, P<0.001, 95% CI: 1.198-1.838, I²=69.3%, Pheterogeneity<0.001; GG+GA vs. AA: OR=1.530, P<0.001, 95% CI: 1.217-1.924, I²=53.5%, Pheterogeneity=0.006; GG vs. AA: OR=1.958, P<0.001, 95% CI: 1.433-2.675, I²=65.2%, Pheterogeneity<0.001; GA vs. AA: OR=1.215, P=0.013, 95% CI: 1.041-1.418, I²=19.7%, Pheterogeneity=0.229).” (Line 221-229, Page 10) has been revised as “Overall, the results of pooling all studies showed that the EGF +61A/G polymorphism was significantly associated with an increased HCC risk under all genetic models (G vs. A: OR=1.383, P<0.001, 95% CI: 1.174-1.629, I²=75.4%, Pheterogeneity<0.001, Figure 2; GG vs. GA+AA: OR=1.484, P<0.001, 95% CI: 1.198-1.838, I²=69.3%, Pheterogeneity<0.001; GG+GA vs. AA: OR=1.530, P<0.001, 95% CI: 1.217-1.924, I²=53.5%, Pheterogeneity=0.006; GG vs. AA: OR=1.958, P<0.001, 95% CI: 1.433-2.675, I²=65.2%, Pheterogeneity<0.001; GA vs. AA: OR=1.215, P=0.013, 95% CI: 1.041-1.418, I²=19.7%, Pheterogeneity=0.229) (Table 2).” (Line 221-229, Page 10)

The sentence “Moreover, meta-regression indicated that both ethnicity (G vs. A: t=2.57, P=0.022; GG vs. GA+AA: t=2.18, P=0.047; GG+GA vs. AA: t=1.930, P=0.075; GG vs. AA: t=2.05, P=0.060) and study quality (G vs. A: t=1.83, P=0.088; GG vs. GA+AA: t=2.06, P=0.059; GG vs. AA: t=2.36, P=0.034) significantly contributed to the heterogeneity for EGF +61A/G polymorphism.” (Line 254-259, Page 11) has been revised as “Moreover, meta-regression indicated that both ethnicity and study quality significantly contributed to the heterogeneity for EGF +61A/G polymorphism (Table 3).” (Line 254-259, Page 11)

Shusen Zheng

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