Author’s response to reviews

Title: ATM rs189037 (G>A) polymorphism increased the risk of cancer: an updated meta-analysis

Authors:

Zhi-liang Zhao (zzl81@hotmail.com)
Lu Xia (492193335@qq.com)
Cong Zhao (17036251@qq.com)
Jun Yao (yaojun198717@163.com)

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Author’s response to reviews:

Response to Reviewer #1:

Many thanks for your comments, regarding the advice of our manuscript in BMC Medical Genetics. Overall the comments have been fair, encouraging and constructive. We have learned much from it.

After carefully revision according to your comments, we have made corresponding changes to the manuscript and edit it as following.

Comment 1. In abstract and result section, the author reported that C allele increased the risk of cancer. However, the alleles for this SNP are G and A as listed in the title and Table 2. It's not clear where allele C came from.

Answer. Thank you for your careful reviewing. We are sorry for our mistake. The alleles of rs189037 is G and A. We have modified the relevant description in the revised manuscript.

Comment 2. It raises question to combine all the ethnicity together since there are marked differences in allele frequencies for Asian and Caucasian. A allele frequency in Caucasian study (Damioloa 2913) is > 56% while A allele frequencies in other Asian studies are < 50%. Therefore, a more focused study on Asian is preferable.

Answer. Thank you for your informative suggestion. We performed the subgroup analysis by ethnicity to explore the association between rs189037 and the risk of cancer among different
populations. The results indicated that the SNP was associated with the risk of cancer among East Asian and Latino, but not Caucasian (Table 4).

Comment 3. In statistical analysis section, It’s confusing that A and a were used to denote the alleles but the alleles for rs189037 are A and G. It is not clear which models OR1, OR2, and OR3 refer to for allele contrast, homozygous codominant, heterozygous codominant. It is also not clear which allele the dominant model refers to.

Answer. Thank you for your suggestion. We are sorry for our inaccurate description. We have added the more description of the genetic models in the revised manuscript, as follows:

Three genetic models (allele contrast model, dominant model, and recessive model) were used to measure the overall pooled ORs. As described in the previous study, OR1 (GG vs. AA), OR2 (GG vs. GA), and OR3 (GA vs. AA) were compared, with the definition of A as the risk allele. If OR1 = OR3 ≠ 1 and OR2 = 1, then a recessive model was selected. If OR1 = OR2 ≠ 1 and OR3 = 1, then a dominant model was selected. If OR2 = 1/OR3 ≠ 1 and OR1 = 1, then a complete overdominant model was selected. If OR1 > OR2 > 1 and OR1 > OR3 > 1 (or OR1 < OR2 < 1 and OR1 < OR3 < 1), then a codominant model was selected.


For rs189037 polymorphism, the dominant model was found to be most appropriate, according to the principles of genetic model selection.

Comment 4. Please correct the genotype in figure 1. The alleles for rs189037 are G and A.

Answer. We have corrected the description of the genotype of rs189037 in the revised figure 1. Thank you for your careful reviewing.
Response to Reviewer #2:

We very much appreciate the careful reading of our manuscript and valuable suggestions of the reviewer. We have carefully considered the comments and have revised the manuscript accordingly. The modifications can be summarized as follows:

Comment 1. The article is well-written and endeavours to provide updated and relevant information regarding the involvement of ATM rs189037 polymorphism in determining the risk for cancer. Fort this, the authors have performed a meta-analysis study on the findings of 15 case-control studies. However, it is the opinion of this reviewer that the quality of these 15 articles should first be assessed by tools such as the Newcastle-Ottawa Scale, before the list of studies to be included is finalised. This will significantly improve the relevance of the meta-analysis.

Answer. Thank you for your informative suggestion. We have assessed the quality of the included studies using the NOS scores. The results were showed in Table 1. Based on the results of the NOS scale, 12 studies were regarded as high quality and 3 studies were regarded as low quality. Overall, our final meta-analysis was stable and credible.

Response to Reviewer #3:

Many thanks for your careful reviewing and informative comments, regarding the advice of our manuscript in BMC Medical Genetics. We have learned much from it.

After carefully revision according to your comments, we have made corresponding changes to the manuscript and edit it as following.

Comment 1. about the title :ATM rs189037 (G>A) polymorphism increased the risk of cancer: an updated meta-analysis; however, the ATM polymorphism is not study in "ALL cancer" types, as author review in results, only in lung cancer, breast cancer, oral cancer, leukemia, papillary thyroid cancer, colorectal cancer. so, the conclusion: Results of this meta-analysis suggest that rs189037 is associated with the occurrence of cancer as the risk factor. --> is not suitale.

Suggestion: author should add the cancer types in the abstract and result/discussion parts and mention the limitation of cancer types which were reviewed.
Answer. Thank you for your careful reviewing. We have added the cancer types in the abstract and results/discussion section in the revised manuscript according to your suggestion. The association between rs189037 polymorphism and the risk of lung cancer, breast cancer, oral cancer, leukemia, thyroid carcinoma, glioma, and colorectal cancer was evaluated using the pooled ORs and corresponding 95% CIs. The results showed that rs189037 increased the occurrence of lung cancer, breast cancer, and oral cancer, but not leukemia, thyroid carcinoma, glioma, and colorectal cancer (Table 4).

The limitation of cancer types has been described in the section of discussion, as follows:

When the subgroup analysis was performed by the cancer types, the results showed that rs189037 increased the occurrence of lung cancer, breast cancer, and oral cancer, but not leukemia, thyroid carcinoma, glioma, and colorectal cancer. Clearly, the role of rs189037 polymorphism was influenced by cancer types. Thus, more cancer types need to be included and assessed in the future in order to comprehensively explore the effect of rs189037 in the cancer risk.

Comment 2. the possible biologic mechanism why ATM rs 189037 polymorphism increase risk of these cancer, should be discussed briefly.

Answer. Thank you for your informative suggestion. We have added the relevant description in the revised manuscript in light of your comment, as follows:

Rs189037 is in the promoter region of ATM gene and markedly changes the folding architectures. The secondary structure of rs189037 G/A alleles was significant changed using RNAfold prediction 38. It has been confirmed to be associated with carcinogenesis 38,40. The G allele of rs189037 SNP is an independent risk factor for radiation-induced pneumonitis in Chinese thoracic cancer patients 41. Moreover, rs189037 and other polymorphism in DNA repair genes can serve as candidate prognostic markers of the survival of non-small-cell lung cancer patients 42.


