

Peer Review File

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Reviewer A:

1. This research revealed that CDK8 gene polymorphisms might be related to DCM susceptibility and prognosis in the Chinese population.

Response: Thank you very much. Yes, our purpose of this work is exploring the relationship between CDK8 SNPs and DCM in a Chinese Han population.

2. It is an interesting study. The prognosis may be affected by many factors, especially therapeutic approach and arrhythmias, please explain it in the discussion.

Response: Thank you for this kind suggestion. This was a retrospective study, and the subsequent factors such as arrhythmia maybe affect the prognosis of DCM. This could be a limitation of our study. We have added some discussion about the prognosis factors of DCM (See Page.19, line 8-21).

Reviewer B:

It is not clear why the authors associated the studied polymorphisms of the caspase-8 gene with the activity of messenger RNA, and not with the processes of apoptosis

Response: Yes, you're right. The apoptosis of cardiomyocytes plays a key role in the progress of DCM. The SNPs we studied are located at cyclin dependent kinase 8 gene (*CDK8*), which is a member of cyclin dependent kinase family. We have talked about the critical role of CDK8 in the TGF β /BMP pathways, which is the most important pathway within the process of apoptosis (See Page.17, line 19-22, Page.18, line 1-12). They induce apoptosis through different pathways and no direct relationships between these two genes. We have added more information about CDK8 and apoptosis (See Page.18, line 12-16). And we also added the potential mechanism that how CDK8 affects the RNA transcription and finally induces DCM (See Page.19, line 3-6). We did not mention the caspase-8 gene in our text, but still thank you for the suggestion. According to the literatures, caspase-8 gene is an apoptosis related gene and the caspase-8 plays an important role in the cascade process of apoptosis. In addition, according to your opinion, we would like to incorporate the SNPs research of caspase-8 gene into the next research plan.

Appeal to the activation of caspase - 8 tumor processes is not adequate - another pathophysiological process

Response: Thanks. We have added some mechanisms about how CDK8 act within tumorigenesis (See Page.15, line 17-22).

The principles of selecting patients for the control group are not clear - is the presence of NYHA 1-2 noted in Table 2?

Response: Thanks. We are sorry that we did forget to mention the NYHA cardiac function classification in our text. And we have added the NYHA noted in Table2 to the Study Subjects part (See Page.6, line 5-10, Page.6, line 14-16). We have noted the inclusion and exclusion criteria in the Study Subjects part of our text (See Page.6, line 1-8, line 16-21). All these healthy individuals were recruited from regular routine check-up, and any of them with a history of disease were excluded.

The main results were obtained on the basis of a regression model that establishes a relationship between polymorphic gene markers in genotypes and DCM. In the absence of identifying specific pathophysiological links between phenomena, this model cannot be recognized as adequate.

Response: Thank you. We think this should be the limitation of our current study, hence we have talked about the model in the discussion part (See Page.20, line 6-13).

The authors distribute the obtained data to the entire population, but the work did not note:

1. Has the check of the correspondence of genotype frequencies to the Hardy - Weinberg equilibrium been carried out?

Response: Yes, we have carried out the Hardy–Weinberg equilibrium (See Page.10, line 17-20). Both two SNPs were consistent with the expected Hardy–Weinberg equilibrium, suggesting that all the samples meet the assumption of Hardy–Weinberg equilibrium and representative.

2. Has the statistical significance of the obtained results been corrected taking into account the multiplicity of comparisons?

Response: Thank you this important suggestion. The statistical methods we used in this research were according to previous literatures about SNPs. For the multiplicity of comparisons, we have added the statistical result after Bonferroni correction (See Page.9, line 21-23, Page.10, line 1, Page.11, line 12-13, 20-21), which can reduce the type I error rate. And all results remained statistic significant after Bonferroni correction.

In general, the authors obtained interesting results, but their conceptuality requires improvement.