Author’s response to reviews

Title: Association of a genetic variant in the Angiopoietin-like protein 4 gene with Metabolic Syndrome

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Author’s response to reviews:

Dear Dr. Lai

Thank you very much for your letter of January 4th and for the constructive comments made by yourself and the Reviewers on our manuscript, entitled “Association of a genetic variant in the Angiopoietin-like protein 4 gene with Metabolic Syndrome” (Manuscript No. MGTC-D-18-00465), submitted for consideration to be published as a research article in the Journal of BMC Medical Genetics.

We appreciate the positive and constructive input made by yourself and the reviewers on our manuscript; we are pleased to send you the manuscript carefully revised according to your advice as well as to the criticisms of the Reviewers, within the deadline that you proposed. Concerning the specific points raised by the Reviewers, the point-to-point reply to the Reviewers is enclosed.
Moreover, in order to help you and the Reviewers in the identification of the modifications in the revised manuscript, we enclosed the manuscript in track-change format.

We very much hope that the present version of the manuscript satisfactorily addresses all the observations made by you and the Reviewers and meets the quality standard for publication in the Journal of the BMC Medical Genetics.

Thank you very much for your kind consideration.

Yours sincerely,

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REPLIES TO REVIEWERS’ COMMENTS
(Manuscript No. MGTC-D-18-00465R1)

Scientific Editor

Our manuscript was reviewed by two experts in the field and both recommended major revision before it can be considered for publication. Should you consider to resubmit, I would urge you to read the comments carefully and make an ardent effort to address them.

Reply: we truly appreciate very much the positive inputs and recommendations of the Scientific Editor and the Reviewers on our manuscript. We are pleased to send you the manuscript carefully revised according to your advice. We very much hope that the present version of the manuscript satisfactorily addresses all the observations made by you and the Reviewers.

M Nourbakhsh (Reviewer 1):
The manuscript entitled "Association of a genetic variant in the Angiopoietin-like protein 4 gene with Metabolic Syndrome" presents the results of the study about a genetic risk factor for metabolic syndrome and has found a variant in ANGPTL4 to be linked to metabolic syndrome. The results are interesting but they could be more comprehensive considering some revisions. In the study population the information is very scant.

The ethnic origin of the participants is not explained; this is especially important in population-based studies such as genetic variant analysis. Inclusion and exclusion criteria are not mentioned. Since the study includes investigating the relationship between lipid profile, blood pressure, glycemic control and metabolic syndrome in general the subjects should have been selected carefully and factors such as taking antihypertensive, lipid lowering or anti-diabetic drugs, diet, lacking other inflammatory illnesses (esp. with regard to the CRP) should have been taken into account. Please briefly explain the IDF criteria for the diagnosis of metabolic syndrome.

Reply: In accord with the recommendations of the Reviewer#1, we have added more details about the ethnic origin of the participants [33,34]. Inclusion and exclusion criteria and IDF criteria in the Methods section.

Please explain why ANGPTL4 concentration has not been measured. It would have been beneficial if other parameters such as indices of insulin resistance and cardiovascular risk had been assessed.

The discussion part is not very well-written. It does not have the logical sequence of data, the presentation of the results of the previous studies are very cluttered and disarranged. It is highly recommended that this part is rewritten in a more organized and comprehensible fashion without repetition of the similar findings. Some informative articles about ANGPTL4 are missing from the discussion and are recommended to be included as follows:


Reply: We appreciate very much the positive and constructive comments of this reviewer on our manuscript. As ANGPTL4 concentration was not measured so we have added it in limitation part. In regard to other parameters we have assessed traditional risk factors of CVD such as hypertension, lipid profile, BMI and ect,. Since the main aim of our study was to investigate the association of ANGPTL4 SNP with Mets, therefore, we focused on MetS risk factors according to IDF criteria. As requested, we reorganized and corrected discussion section.

Reviewer2#

Kent Lai (Reviewer 2): The authors of this manuscript set out to study the association of a genetic variant rs116843064 in the ANGPTL4 gene in a selected patient population with Metabolic Syndrome (MetS) in Iran. Overall, the study is interesting and novel with respect to the selected patient population. However, there are some concerns for the data that weaken the overall merit of the study.

(1) In Methods, the authors stated that the study population comprised of 260 MetS patients and 500 healthy subjects. Yet, in Table 1, only 350 non-Mets patients were studied. Moreover, in Table 2, 363 non-MetS subjects were genotyped. Why are all these discrepancies?

(2) In multiple places (abstract, results, etc), the authors stated that the genotype frequency of GG, GA, and AA in MetS group were 83.7%, 15.7%, 6%. If you added these numbers up, you will get more than 100%!

(3) Similarly, for Table 2, if you add up the % for GG, AG, AA for the "Total" and "Non-MetS" columns, you will get more than 100%!

(4) In multiple occasions (Table 1, Table 2), the authors notated the p values as "0.0001">. It will be less confusion to notate it as <0.0001.

(5) For Table 3, it is clearly stated that the data referred to Association between the SNP and serum TG and HDL level in TOTAL POPULATION. But it the results section, the authors stated that:

(a) Association of the genetic variant with METABOLIC SYNDROME (line 40) (b) There relationship between the ANGPTL4 gene …..and HDL level in MetS and non-MetS groups is
presented in Table 3 (lines 57 & 59). This reviewer strongly suggested that the authors should stratify their Total Population into Mets and non-MetS groups in Table 3.

If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English.

Reply: we appreciate very much the valuable advice and recommendations of this reviewer in our paper. In agreement with these kind comments, we have revised our text as requested. Sample size is amended in the methods section and tables (1&2) "The study population comprised 260 and 557 individuals with and without MetS were enrolled from the Mashhad Stroke and Heart Atherosclerosis Disorder (MASHAD) cohort study". Also, we corrected the genotype frequency of GG, GA, and AA in the mentioned groups. As requested we changed the p values as '0.0001'. In regard table 2 and 3, First of all we apologize for our mistake in the number of tables. These errors have been corrected in the revised manuscript and tables has been updated accordingly to text "The distribution of the ANGPTL4 gene rs116843064 polymorphism genotypes were investigated in genetic various models (Table 2). These data indicated that the GA genotype of the rs116843064 polymorphism in codominant model was associated with a lower risk for MetS (e.g., OR in Codominant genetic model: 0.14, 95% CI: (0.06-0.33), p<0.0001) and subject with A allele have lighter risk for MetS (OR: 6.72, 95% CI: (3.05-14.82), p<0.0001)". As requested, we stratified their Total Population into Mets and non-MetS groups in Table 3. Furthermore, we asked our colleague prof. Gordon ferns from Brighton & Sussex Medical School of UK for language improvement.