Author's response to reviews

Title: Possible role of EMID2 on nasal polyps pathogenesis in Korean asthma patients

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Author's response to reviews: see over
Dear Editor,

Thank you for giving us the opportunity to submit a revised version of our manuscript. We are grateful to the reviewers for the comments and have revised our manuscript accordingly. Our responses are given below. Furthermore, the Tables have been incorporated in the Manuscript following the References.

We hope that our responses and the associated changes to the manuscript adequately address the reviewers’ concerns, and that the manuscript would now be acceptable for publication.

With my best regards,

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Reviewer 1

1. Dr. Pasaje and colleagues has investigated EMID2 gene polymorphisms in the pathogenesis of Nasal polyps in Korean asthma patients. The SNPs analyzed in the study is reasonable. However the sample size is limited, to exclude the false negative result, what is the statistical power of the sample size?

   →Reply: Thank you for your comments. As mentioned in the Discussion section of the manuscript that was initially submitted in the journal, the average statistical power of the sample size determined using the Power for Genetic Association Analyses (PGA) software is at 69.59%. However, in order to incorporate your comment on the possibility of obtaining false negative results, we have added texts in the last paragraph of Discussion as follows:

   “After performing power calculations of single associations, the average statistical power to detect the effect sizes of the significantly associated SNPs was 69.59% (Table 2), suggesting insufficient sample size. Thus, the possibility of obtaining false negative findings cannot be excluded. However, in order to address this limitation and to analyze the effect of the polymorphisms in other ethnic groups, further replications in larger sample scales are required.”

2. Needs some language corrections before being published

   →Reply: The revised manuscript has been proofread by a native English speaker.
Reviewer 2

Summary: The authors choose to investigate the association of variants and haplotypes in this gene with the phenotype of nasal polyps in an asthmatic population based on three lines of evidence; i) the human emilin/multimerin domain-containing protein 2 (EMID2) gene has been implicated as a potential marker of aspirin exacerbated respiratory disease (AERD), a condition characterized by the presence of nasal polyps in nasal passages; ii) the accumulation of the ECM in nasal polyp tissues and; iii) the crucial role of subepithelial fibrosis in disease pathogenesis. The question of asthma phenotypes and genetics is still one of interest in research, particularly across populations, and thus this is a relevant scientific question. The stat. gen methods are sound and for the most part very well detailed.

→Reply: Thank you for your positive feedback.

Major Comment: The study is underpowered and this brings into question the rationale for these experiments; this is a major flaw in the manuscript. If this is to be accepted more detail needs to be provided re: power.

→Reply: We are aware that the study is underpowered. In fact, as mentioned in our response to the first question of Reviewer 1, the average statistical power of the sample size determined using the Power for Genetic Association Analyses (PGA) software is at 69.59%, suggesting insufficient sample size. We have added texts on the implication of the small sample size in the last paragraph of Discussion as follows:

“After performing power calculations of single associations, the average statistical power to detect the effect sizes of the significantly associated SNPs was 69.59% (Table 2), suggesting insufficient sample size. Thus, the possibility of obtaining false negative findings cannot be excluded. However, in order to address this limitation and to analyze the effect of the polymorphisms in other ethnic groups, further replications in larger sample scales are required.”

Minor Revisions

1. The authors state “Using the PHASE algorithm ver. 2.0 software [9], haplotypes were inferred from the successfully genotyped SNPs and those with frequency of over 0.05 were selected for association analyses.” It is unclear if the haplotypes analyses were run for “cases” and “controls”
separately or the entire population together. More details of this analysis would be beneficial for the reader.

_reply: Sorry for the confusion. We have improved the texts as follows:

“Using the PHASE algorithm ver. 2.0 software [9], haplotypes were inferred from the successfully genotyped SNPs of the entire study population and those with frequency of over 0.05 were selected for association analyses in the overall asthma patients as well as the AERD and ATA subgroups.”

2. The authors state “The current study shows for the first time that EMID2 may be functionally relevant in the pathogenesis of nasal polyps in the onset of asthma.” This is NOT a test of functional relevance it is a test of association of a variant in a potentially functionally relevant gene. This language should be corrected. While the in silico analyses are interesting above statement is quite bold for these data.

_reply: Thank you for your corrections. We have revised the texts as follows:

“The current study shows for the first time that EMID2 may be associated with the pathogenesis of nasal polyps in the onset of asthma.”