Author’s response to reviews

Title: Association of IL10 and TGFB Single Nucleotide Polymorphisms with Intervertebral Disc Degeneration in Iranian Population: A case control study

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Association of Single Nucleotide Polymorphisms of IL10 and TGFB with Intervertebral Disc Degeneration

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Dear Dr. Pasini,

Thank you for your consideration of the manuscript “Association of Single Nucleotide Polymorphisms of IL10 and TGFB with Intervertebral Disc Degeneration” by the BMC Medical Genetics.

Our responses to the reviewers’ queries are discussed below. A revision-marked draft of the revised manuscript is respectfully enclosed accordingly to the instructions. Meanwhile, all the requested queries in the primary revision were properly answered, and since it has been over 9 months since the first submission, we hoped to get a positive response from journal.

Please address all correspondence concerning this manuscript to me at rezaei_nima@tums.ac.ir.

Thank you for your consideration of this manuscript.

Sincerely,

Nima Rezaei

Reviewer reports:

Georg Omlor (Reviewer 1): Thank you very much.

Bianca Bianco (Reviewer 2): Although the authors have adequately answered most of the reviewers' questions, I still have the following concerns and comments:
Q1: The control group should be better described. The selection criteria to enroll for the control group are not strong enough to identify the people without disc degeneration. Asymptomatic people may have disc degeneration. Ideally, the individuals selected for the control group should have undergone MRI to exclude the disease. It is an important methodological issue which needs to be addressed. Therefore, there are doubts about the validity of the results. In addition, mean age and gender in control group need to be showed.

A1: The selection criteria for control group is revised in the methods (page 5, lines 17-21).

Actually, the selection criteria for the case group in the current study was to include only symptomatic patients who were indicated for surgical intervention. Therefore, even those patients with IVDD who were not indicated for surgery and were managed conservatively were excluded. Therefore, for the control group, in case the healthy subject fulfilled the eligibility criteria and had no signs or symptoms of disc degeneration, the MRI was not performed. Moreover, performing MRI in healthy asymptomatic patients was not ethical without any indications.

The logic for this criteria was that the influence of pro-inflammatory and anti-inflammatory cytokines would be the most in acute phase of symptomatic patients rather than all those who may have degenerated discs but are asymptomatic. Another explanation would be the role of pro-inflammatory and anti-inflammatory cytokines in disc inflammation which would cause the symptoms. Previous studies have also indicated higher expression of these cytokines in symptomatic patients and also those with severe grades of degeneration when compared to both healthy subjects and patients with mild grades of disc degeneration.

Q2: Table 1 should compare some variables between groups, such as age and proportion of men and women. And if there is difference in these variables between the groups, the statistical analysis should be adjusted accordingly.
A2: The age and gender frequencies of control group are added to table 1.

The control group included 70 males and 70 females. The difference between cases and controls for sex was not significant as the P-value was 0.1159.

Actually, as we were looking for inherited mutations and SNP variants (not the somatic ones), which do not change over a person’s lifetime. Therefore, the age was not considered as a causative factor for SNP variation. However, this was mentioned as a limitation in the discussion as well (page 12, lines 12-13):

“Meanwhile, as the inherited SNP variants were of interest in this study, the age of subjects was not considered as a causative factor for SNP variant. However, as the possible role of somatic mutations in pathology of IVDD, it is recommended to consider the SNP investigation in disc tissues in age-matched groups.”