Author’s response to reviews

Title: Association Study of Candidate Genes for Susceptibility to Kashin-Beck Disease in a Tibetan Population

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Author’s response to reviews:

Dear Editor,

Thank you very much for your comments and suggestions.

We have revised the manuscript, according to the comments and suggestions of reviewers and editor, and responded, point by point to, the comments as listed below.

I would like to re-submit this revised manuscript to BMC Medical Genetics, and hope it is acceptable for publication in the journal.

Looking forward to hearing from you soon.

With best regards,
Replies to Reviewer and Editor

First of all, we thank both reviewer and editor for their positive and constructive comments and suggestions.

Replies to the Editors note and suggestions:

a) Please include a cover letter with a point-by-point response to the comments, describing any additional experiments that were carried out and including a detailed rebuttal of any criticisms or requested revisions that you disagreed with. Please also ensure that all changes to the manuscript are indicated in the text by highlighting or using track changes.

Answer: We have revised the manuscript, according to the comments and suggestions of reviewer and editor, and responded, point by point to, the comments as listed below.

Replies to Reviewer:

a) Materials and methods: the diagnosis and exclusion criteria of study subjects are not clear. More information should be provided, such as the diagnostic criterion of KBD and skeletal sites for X-ray examination.

Answer: The diagnosis of KBD was made in accordance with the KBD Chinese diagnosis criteria (GB16003-1995). Antero-posterior radiograph of the hand, elbow, knee, ankle and hip of each patient was taken with portable x-ray equipment. Which we have added and marked in red in the manuscript.

b) Statistical analysis: Multiple test problem should be consider in this study. After strict Bonferroni correction, none of the 15 genotyped SNPs is significantly associated with KBD. At least, the authors should provide a discussion about this problem.

Answer: The Bonferroni correction tends to be a bit too conservative. We have discussed that in the discussion of the manuscript “The fact that significant differences in genetic variants between cases and controls did not exist after Bonferroni correction (P=0.05/ tested loci number) could be explained by the relatively small sample size, with small effects of the variants. Further studies with larger cohorts are needed to confirm the findings of this study”.

c) How many samples are used for exon sequencing? How about the sequencing quality? More information should been provided.

Answer: We carried out Sanger sequencing analyses of COL10A1 and HABP2 gene exons with the goal of identifying coding variants that may contribute to KBD risk in the Tibetan population using 849 KBD patients and 565 normal controls. We have added the information of
samples in the manuscript and marked in red. And we screened several exons primers to ensure
the high quality of sequencing data.
d) Overall the English writing is clear. There are some grammatical mistakes in the
manuscript. The authors should carefully read and correct the mistakes.

Answer: Although we have employed an English language editing service
(Scribendi.com) before submit to BMC Medical Genetics, We have read through carefully and
fix some problems which marked in red.