Reviewer’s report

Title: A Genotype-Phenotype study of hereditary multiple exostoses in forty-six Chinese patients

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Reviewer: Maurizio Pacifici

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This study describes the phenotypic and genetic analyses of 46 patients from mainland China affected by Hereditary Multiple Exostoses (HME). The investigators used a variety of criteria to characterize clinical phenotype and disease severity, including height, age of disease onset, number of affected sites, forearm deformity and lower limb alignment. Mutation analysis with peripheral blood was carried out by PCR and MLPA. The data obtained indicate that about 2/3 of the patients had EXT1 mutations and about 30% had EXT2 mutations. The overall disease score was higher in patients with EXT1 mutations, and there were associations between the number of affected sites and forearm and lower limb deformity and misalignment, respectively. There was also a clear correlation between number of affected sites and age. The study relates well, and extends, clinical/genotypic analyses carried out in western cohorts of HME patients and affirms the conclusion that EXT1 mutations appear to have more disease penetrance and consequences.

The study is of interest since there is just one previous genetic study on Chinese HME patients. The current data reiterate the fact that EXT1 mutations elicit a more severe clinical phenotype, though neither the present study nor previous ones have provided direct and conclusive explanations.

There are no major concerns with the study, but there are several issues to be addressed.

There are several contradictory statements in the manuscript that need to be corrected. For instance, in the Abstract, it is stated that "Male patients have more lesion sites than female patients", but in the Discussion, it is stated that "we found no significant differences in the number of involved anatomical sites between genotypes or genders".

The authors need to emphasize that there is no universally accepted system to correlate genotype to disease phenotype, despite several attempts by many groups over the years. Thus, assessment of disease phenotype can be arbitrary or may rely only on certain traits. This limitation should be openly acknowledged and addressed.

The correlation between total disease score and age is interesting though expected. Was this correlation similar in EXT1 and EXT2 patients?

Table 3 is mis-labeled.

The manuscript is poorly written and needs to be carefully edited.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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Yes

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I am able to assess the statistics

Quality of written English
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Not suitable for publication unless extensively edited

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