Reviewer’s report

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

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Reviewer: Daniel Porter

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This publication reports a genotype-phenotype study in 46 paediatric Chinese patients with germline EXT1 and EXT2 mutations. The database was collected prospectively and a scoring system for disease severity was developed to include upper and lower limb deformity, number of exostoses, height and age of onset.

The authors show that their Chinese population EXT mutations are more common than EXT2; different from a previous study. They confirm the findings in Western publications that EXT1 genotype, male gender and increasing age are associated with worse phenotype. They suggest that height may be normal in their EXT2 children. Forearm and lower limb deformity, age of onset and number of involved sites were not dependent on genotype. Number of sites was greater in males.

The scoring system is interesting as it includes age of onset, and radiographic assessment of involved sites and deformity. However mainly AP x-ray views may have hidden some exostoses, and, of course, axial exostoses would not be counted at all. Nevertheless, the scoring system, although arbitrary, seems reasonable. Rightly the component parts of the score are emphasised in the text rather than the total score.

Some of their findings may be uncertain due to the relatively small cohort of under 50 patients. The authors acknowledge this in their paragraph on 'limitation'.

The authors state that cohort consists of unrelated individuals, but it is not entirely clear how affected siblings or other relatives were excluded from the database...it is my experience that often more than one family member may seek medical advice together...how was it that one member was chosen and others excluded from entry to the database? Also Table 2 identifies 3 sets of two individuals who have the same mutation (26/39, 33/38, 42/43). The authors should confirm that these children are not related.

I may have missed it, but it can the authors please confirm that there is no significant age difference between EXT1 and EXT2 children, which might account for some of the phenotypic differences?

Overall, this paper appears well designed and well written with some interesting findings. If these small points can be addressed I think it is worthy of publication.
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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