Reviewer’s report

Title: Spectrum of phenotypic anomalies in four families with deletion of the SHOX enhancer region.

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Reviewer: Gudrun Rappold

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Deletions of the SHOX gene or its enhancer regions lead to syndromic or isolated short stature which accounts for a considerable number of short stature cases. The manuscript by Gatta et al. gives a detailed clinical characterization of 14 patients, all with a small partial deletion of the downstream enhancer region of the SHOX gene. The 14 patients were derived from 4 different families, thus allowing a very good intra- and interfamilial comparison of variability. This data is helpful, as so far mostly unique cases have been described in the literature. A striking finding was a homozygous deletion of the CNE7 interval (47.5 kb) in one individual with severe bilateral Madelung deformity and normal stature suggesting that the deletion of this region may promote bone deformities. This individual also had the highest clinical score of 16.

The data is well presented and discussed and confirms previous findings that short forearms and muscular hypertrophy are the most consistent indicators of SHOX deficiency.

Minor comments:

1. In the Introduction the authors state “a frequency of 1. 1000”; based on the cited literature it should probably better say “an estimated frequency of less than 1: 1000”

2. In the Introduction, to avoid a misunderstanding, better mention “recently BS. provided a deep characterization of a relatively small deletion of PAR1, previously reported by Ch. and C., uncovering a novel downstream enhancer”.

3. Molecular Analysis: please provide a reference for the Coffalyser software.

4. Spelling mistakes
   Results, line 277: bp; line 281: involved a distinct SHOX enhancer region; line 282: latest MLPA SHOX probemix; line 287: homozygous; Discussion line 294: as demonstrated by immunohistochemistry; line 306: downstream of the SHOX gene

5. In the Discussion it is not quite correct to say “all our patients were females”, as in family 2 and 3 the defective allele was transmitted from an affected father

Level of interest: An article of importance in its field