Reviewer's report

Title: Comparison of orthopaedic manifestations of multiple epiphyseal dysplasia caused by MATN3 versus COMP mutations: a case control study

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Reviewer: Michael Briggs

Reviewer's report:

General Points:

In essence this manuscript is a follow-on to a previous study by several of the same authors (see Kim et al AJMG 2011). However, in this current study the authors provide a statistical analysis of quantifiable clinical/radiographic features in the largest group of mutation positive MED patients to date; 59 in total (37=MATN3 and 22=COMP).

Overall this is an interesting and quantitative study that derives new knowledge for understanding MED-genotype-specific clinical presentation and prognosis. The authors have collated an impressive and comprehensive set of clinical/radiographic data for this study.

Whilst the focus of the study was to compare COMP-MED vs. MATN3-MED, I wonder whether it would be also possible to use these data to look at the variability within each gene group?

For example, in MATN3-MED the majority of patients have the same p.R121W mutation, so do the clinical/radiographic features for that mutation differ from the other MATN3 mutations combined? Does p.R121W produce a consistent phenotype? These investigations might shed new light on the variability within MED and support the hypothesis of genetic modifiers (see further comments below). The authors have the data to hand and could quickly perform these analyses, or at least exclude the possibility that there are any differences.

I think that the final conclusion should just summarize the significant differences only between the two groups (i.e. p<0.05).

Specific Points:

With respect to the relative proportion of COMP/COL9/MATN3 mutation in MED patients (page 3), the authors should really reference Jackson et al Hum Mut 2011, since it is the largest single study to date on the genetic basis of MED.

Page 6 for Table 2

The reason for using a p<0.05 value is to define what can be considered significant. It is therefore not appropriate to use the term 'borderline significant' for a p<0.084. It is NOT significant.
I’m not certain that Pearson’s chi-square can be applied because the number of patients is below 10 for some analyses – this needs double-checking with a statistician. This comment is applicable to all tables.

Page 6 for Figure 4

The authors state that 12/37 MATN3 patients were above average height and it would be useful for them to present more detail. For example, what percentile above average?

Can the authors also comment on whether differences in height were more variable in the COMP vs. MATN3 patient groups. It seems from the figure that COMP-MED is more phenotypically variable (at least for height). In simple terms the errors bars are broader in COMP; is this important?

More comprehensive figure legends, in particular figure 4. For example is 0 taken as average?

Page 6 for Table 3

P values are not presented in the table.

Page 6-7 for Figure 5

Can the authors comment as to whether there is greater variability in the MED-COMP patient group (i.e. larger SEM) for the radiographic analyses?

Discussion

Page 8: The sentence, “Hence, it is likely that COMP-pathy cases may constitute severe MED cases” doesn’t make sense. COMP mutations can also cause mild MED.

Page 9, line 10: Do the authors mean Table 4?

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests