Reviewer's report

Title: Osteopoikilosis and multiple exostoses caused by novel mutations in LEMD3 and EXT1 genes respectively - coincidence within one family.

Version: 2 Date: 17 February 2010

Reviewer: Jan Hellemans

Reviewer's report:

Major Compulsory Revisions

1. Description of the c.1732G>A mutation (page 9): Additional phenotypes are identified in patients with both a LEMD3 and EXT1 mutation. Please check whether parents, sibs or kids that lack a LEMD3 mutation (and osteopoikilosis) show similar phenotypes to distinguish 2 possibilities: a) the extra phenotypes result from the combination of LEMD3 and EXT1 mutations, or b) the extra phenotypes result exclusively from the EXT1 mutations. Related to this remark is the statement that “None of these pathologies was observed in the mutation unaffected family members”. It is impossible to appreciate the value of this statement because it is unclear how many relatives underwent a detailed clinical (and genotypic) analysis.
2. Patient V:1 was screened on both blood and progenitor cells from and exostosis. Is there any indication for additional hits in the affected bone?
3. The hypothesis that LEMD3 inactivation may lead to increased mutation susceptibility may be worked out a bit more. A number of sporadic co-occurrences of osteopoikilosis with other anomalies have been reported in literature – on the other hand I am not aware of an increased risk for cancer which would contradict the author’s hypothesis.

Minor Essential Revisions

1. Use a dot as a decimal separator rather than a comma, 0,4 mM # 0.4 mM. Also 20-µl # 20 µl
2. References to figure 2 at the end of the Clinical History section seem to be inappropriate. A similar comment applies to the reference to figure 2 and 3 at the bottom of page 9.
3. The enumeration of patients on page 8 is not correct: IV:13 # IV:8
4. Figure 1A: in contrast to what the legend is stating, the figure does not contain any arrowheads
5. Figure 2: Use different icons to distinguish the different phenotypes in the pedigree, e.g. half filled symbols, and describe them in the figure legend. Also describe the meaning of the horizontal bars above individual symbols.

Discretionary Revisions
1. It would be better if the preferred mutation nomenclature would be used consistently throughout the manuscript, e.g. p.Arg578Thr, c.123-2T>C

2. Readers that are unfamiliar with the described disorders may find it helpful if adverbs like dominant/recessive or heterozygous/homozygous would be used in the Background section when describing the phenotypes and observed mutations.

3. Table 1: Interpretation may be easier if the EXT1 mutation status would be included as well.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

No competing interests