Reviewer's report

Title: Further delineation of Loeys-Dietz type IV syndrome in a family with mild vascular involvement and a TGFB2 splicing mutation

Version: 2 Date: 4 June 2014

Reviewer: Lut Van Laer

Reviewer's report:

This study describes the further delineation of the phenotype of Loeys-Dietz syndrome (LDS) type IV in a family in which a novel splice site mutation segregates. The number of known TGFB2 mutations is still limited. Moreover, the delineation of the phenotypic spectrum of TGB2 mutations in this disorder with variable disease-expression is certainly relevant. As such, this study provides an important contribution to the field. I have only minor remarks.

Minor remarks/Minor Essential Revisions
There exists some confusion regarding the numbering of the different LDS subtypes. According to OMIM, the following numbering should be applied:
LDS type 1: TGFBR1 (609192, while 608967 no longer exists)
LDS type 2: TGFBR2 (610168, while 610380 no longer exists)
In Loeys et al. 2006 (NEJM), type 1 and type 2 were also introduced but then based on the phenotype (typical LDS versus more vascular Ehlers-Danlos syndrome like). However, these findings are now believed to be part of a continuum within the LDS spectrum of disease (Van Laer L, Dietz H, Loeys B. Adv Exp Med Biol. 2014;802:95-105). LDS subtype A and subtype B have never been defined.
Please adjust the background on page 3 according to the OMIM recommendations.
Part of the sentence on page 8, line13 ("and creates a new potential splice acceptor site 1 bp downstream the consensus site") is not true. Please omit this part of the sentence!
Page 9: The paradoxical activation of TGFB signaling is only in the case of TGFBR1/2, SMAD3 and TGFB2. In case of FBN1 there is indeed an activation, but this is not paradoxical (it is as expected). In case of ATS the exact mechanism is not exactly clear yet. Please reformulate. Easiest solution would be to omit "paradoxical".

Textual
In the title: Loeys-Dietz syndrome type IV
Abstract, page 2, line 5: SMAD3 should be italic
Abstract, page 2, lines 16 and 17: splice site mutation
Abstract, page 2, line 18: PTC: no use of abbreviation in the abstract
Page 4, line 1: aneurysm
Page 4, line 2: at young age
Page 4, line 3: identified an additional gene
Page 4, line 19: presents at later onset
At several places: hyperextensible
Figure 3: p.Tyr99* should be blue

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

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I declare that I have no competing interests