Reviewer’s report

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

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Reviewer: Marcella Zollino

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Ritelli et al. report on an Italian family in which a mild clinical form of Loeys-Diets type IV syndrome segregates with a novel splice site mutation in the TGFB2 gene.

Although on average clinical data are well presented and the performed genetic tests appropriate, several criticisms are in order.

- No clinical information are provided about both parents of the proposita. If they were alive, they should be tested for the mutation.

- The pathogenic role of the reported variant is convincing. However, in considering that it represents a novel gene mutation, caution is needed before transferring its significance into the clinics. A total of 200 alleles were analyzed to verify whether the observed variant can be a novel polymorphism. However they are not sufficient to test the hypothesis of a possible pathogenic role as rare variant with incomplete penetrance (several examples are provided in literature of well tolerated loss-of-function gene variants). After proper genetic counseling, an extended family study could help, including healthy relatives.

- The possibility of a late-onset aneurysmatic vasculopathy should be more extensively discussed.

- Several editing amendments are recommended.