Author’s response to reviews

Title: The Familial Non-Syndromic Thoracic Aortic Aneurysms and Dissections maps to Marfan Disease Gene (Fibrillin 1) locus

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Author’s response to reviews:

Dear Dr. Edmunds,

We appreciate reviewer’s comments and their very constructive criticisms. Based on additional work such as mutation screening, we have thoroughly revised the manuscript. We have incorporated practically all suggestions that are made by the reviewers. In following we respond to reviewers’ comments and suggestions in a point by point fashion.

Reviewer1 states that the case presented in this submission is not the first case of non-syndromic TAAD caused by an FBN1 mutation. This reviewer points to 2 publications by Francke et al., Am. J. Hum. Genet 1995; and Milewicz et al., Circulation 1996. Reviewer 2 makes a similar comment, while he/she acknowledges that the novelty of this study is that “it is the largest family being reported in literature”.

As outlined in our manuscript, association between FBN1 mutation and nonsyndromic aortic aneurysm has been shown previously by two other investigators. Francke et al reported a kindred in which FBN1 mutation segregates in most but not all family members. One affected individual in the family did not have the mutation while one mutation carrier was unaffected, raising the question whether that mutation was causative. Under the least stringent conditions the calculated lod score would meet the significant threshold for linkage. In addition, the diagnoses of nonsyndromic TAAD was in part based on questionnaire or were not done by clinicians. Moreover, some affected individuals had either laxative joints or other musculoskeletal findings of Marfan syndrome such as pes excavates. Milewicz et al reports of FBN1 mutation in individual sporadic non syndromic cases of thoracic aneurysm. These findings are interesting but certainly not definitive. MFS is a pleomorphic disease and within one family there may be affected individuals that lack syndromic findings. The extended kindreds were not examined for phenotypes of MFS. The comments of the reviewer2 are consistent with this argument as he/ she states “We have encountered one Marfan family. The affected mother only has thoracic
aneurysms in absence of any other symptoms/signs of Marfan syndrome. However, two of her affected sons have lens dislocation, dura ectasia and somewhat Marfanoid habitus in addition to mild thoracic dilation (unpublished data). In general, sporadic mutations lack the power to prove the causality. In contrast, we present here a kindred in which all affected family members link to 15q with a peak on fibrillin locus. Although we are unable to identify any nonsynonymous mutations, linkage to a single chromosomal locus is an strong evidence that an unidentified variation within this gene is likely the cause of the non syndromic thoracic aneurysm.

We cite here excerpts of a publication by Harry Dietz in Progress in Pediatric Cardiology Volume 5, Issue 3, June 1996, Pages 159-166: “Of more immediate practical importance, it is now possible to apply molecular methods to the pre-symptomatic and prenatal diagnosis of Marfan syndrome, providing the first opportunity for disease prevention and for presumptive rather than symptomatic intervention. Two genetic methods are routinely applied to determine whether an individual or fetus is at risk for the development of a phenotype concordant with that seen in other affected family members. Linkage analysis is both efficient and accurate, but requires the existence and involvement of many affected and unaffected family members.”

In addition reduced fibrillin deposition in immunofluorescence studies of skin fibroblasts of mutation carriers using monoclonal antibodies is an strong evidence that mutation causing lower fibrillin synthesis is disease causing.

Reviewer 1 has asked for Ghent nosology table, which we have now included this in our manuscript. Reviewer 2 asks for description of the eye conditions and lumbar MRI. We have provided data about every single component of Ghent except for dural MRI. Our mutation carriers have no ophthalmological findings. Although we have no data on lumbar MRI, positive finding on MRI would still not meet the minimum criteria for diagnosis of MFS. Finally, practicing physicians generally do not examine lumbar MRI in patients with aneurysm, particularly in absence of all other syndromic findings. Our message here is that what appears as nonsyndromic TAAD can still have clinical course similar to MFS, and may be caused by mutations in the same gene.

In sum, we believe that our manuscript present the largest reported kindred with nonsyndromic TAAD in the literature that links to FBN1 gene locus, with all affected individuals unambiguously carrying the disease haplotype. This finding may have important clinical implications including need for secondary prevention, as discussed in our manuscript and suggested by one of the reviewers. We thank the reviewers and the editors once again for their careful review of our manuscript and their thoughtful suggestions. We hope that our revised manuscript will now be considered for publication in your prestigious journal.

Best regards
Arya Mani and co-authors