Reviewer's report

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

Version: 1 Date: 3 March 2010

Reviewer: Joerg Schmidtke

Reviewer's report:

This work describes a large kindred of Iranian origin with apparently non-syndromic TAAD. By linkage analysis using an Affymetrix 10K genechip array they mapped the causative gene to a region containing the FBN1 gene locus. They conclude that a mutation in this gene must be causative for non-syndromic TAAD.

Major compulsory revisions:

It has come to my attention that the case presented in this submission is not the first case of non-syndromic TAAD caused by an FBN1 mutation. There at least two reports of this kind: Francke et al., Am. J. Hum. Genet 1995;56:1287-1296 and Milewicz et al., Circulation 1996; 94:2708-2711. (Interestingly, however, FBN1 is not listed as a TAAD-associated gene in OMIM 607086.) The authors must withdraw their assertion that their case is the first of this kind.

There are two other main points of criticism. First, the probands do not seem to have undergone an examination that would exclude with certainty Marfan-related symptoms based on the Ghent nosology. The index patient had aortic dissection, but the only other features that seem to have been looked at are height, dolichostenomelia, wrist and thumb signs, arachnodactyly and hypertelorism. We receive no information on other cardinal features such as other aspects of skeletal involvement, lens (sub)luxation, myopia, dural ectasia, striae, and others. Phenotypic information on other family members is even scantier. The authors should use a complete check-list based on the Ghent nosology and state which of the features have been ascertained, which are present, and which are absent. This is important because it is known that MFS is characterized by markedly variable expressivity, and it must be certain that none of the minor symptoms have been overlooked.

The second point of criticism is the absence of a mutation scanning of the FBN1 gene. It is absolutely necessary to try to identify the causative mutation. The reasons of the authors for not doing so are not acceptable. For example, whether or not a mutation can be regarded as causative can only be discussed after it has been found.

Minor essential revisions:

The paper has apparently not been read and corrected by a native English
speaker, who would certainly have picked up errors like “careers” instead of “carriers”. Before re-submission of the paper a thorough revision of style and grammar must be done. This includes re-stating the title.

**Quality of written English:** Not suitable for publication unless extensively edited

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