

ESPS JOURNAL EDITOR-IN-CHIEF'S REVIEW REPORT

Name of journal: World Journal of Medical Genetics

ESPS manuscript NO: 26568

Title: Mutation in TNXB gene causes moderate to severe Ehlers-Danlos syndrome

Journal Editor-in-Chief (Associate Editor): Hans van Bokhoven

Country: Netherlands

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ACADEMIC CONTENT EVALUATION	LANGUAGE QUALITY EVALUATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Revision
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor		

JOURNAL EDITOR-IN-CHIEF (ASSOCIATE EDITOR) COMMENTS TO AUTHORS

The identification of an heterozygous missense mutation in TNXB suggests a causal relationship to the EDS phenotype present in this patient. However, causality is not beyond doubt. Mutations in this gene are associated with recessive phenotypes, except in some reported EDS cases. Three of these have been characterized in more detail and all three of these showed altered length of elastic fibers in skin biopsies. This was not seen for another patient with a TNXB missense variant that was predicted to be a polymorphism. The variant reported in the current manuscript (c.6074A>T) has been identified previously in a patient also diagnosed with EDS. However, this was in a large exome sequencing study and little or no information was available on the phenotype of that patient. Moreover, assessment of the length of elastic fibers was not performed for either of the patients with the c.6074A>T variant. Thus care needs to be taken before concluding that this variant is causative. The other argument for that is that c.6074A>T variant is seen in the ExAC database at low frequency (0.07%; 86 heterozygous cases and 1 homozygous ! case). In view of that, I would suggest to determine the size of elastic fibers similar as was done in ref 10. Another suggestion I like to give to the authors is to perform DNA analysis of the children of the proband. They apparently are without any features of EDS, so if they were to carry the same variant, causality will become very unlikely.