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ESPS PEER-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
Reviewer's code: 00503828
Reviewer's country: Japan
Science editor: Shui Qiu
Date sent for review: 2016-04-19 10:10
Date reviewed: 2016-04-22 16:12

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The author report a case of Ehlers-Danlos syndrome with a mutation in TNXB gene. The report is interesting, but some concerns exist. Which DNA is used? Does the sample come from skin? Is a deletion analysis of genes necessary? It seems overstatement that the mutation causes severe phenotype of Ehlers-Danlos syndrome based upon only one case. Is the family history necessary.

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ESPS PEER-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
Reviewer's code: 00458932
Reviewer's country: Greece
Science editor: Shui Qiu
Date sent for review: 2016-04-19 10:10
Date reviewed: 2016-04-27 13:37

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[Y] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

One important question: Is this mutation detected in other family members(affected or not), and in healthy individuals? I think the authors should make an effort to contact other family members. Minor comments: Text may be in the past tense throughout the manuscript

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ESPS PEER-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
Reviewer's code: 03595287
Reviewer's country: Italy
Science editor: Shui Qiu
Date sent for review: 2016-04-19 10:10
Date reviewed: 2016-05-11 00:28

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[Y] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Drs Kaufman and Butler report a single adult patient with a phenotype resembling Ehlers-Danlos syndrome hypermobility type in whom they identified the heterozygous mutation c.[6074A>T] in TNXB. The mutation was identified with a NGS approach using a panel which included 34 genes related to known (systemic) hereditary connective tissue disorders. TNXB is a well-known gene related to a rare type of Ehlers-Danlos syndrome: the so-called TNXB-deficient EDS. This is an autosomal recessive form of EDS, most common in The Netherlands, and sharing some features of classic EDS, from which is distinguished by the inheritance pattern. Novel features are actually under analysis by some research groups. Most patients has a homozygous common deletion or compound heterozygosity for the deletion and a point mutation. TNXB is deleted in both allele copies also in the contiguous gene deletion syndrome coupling EDS and congenital adrenal hyperplasia (due to mutation in the neighboring gene CYP21A2). Conversely, the literature concerning the Mendelian role of heterozygous TNXB mutations in a different genetic form of EDS more resembling the hypermobility type is still confusing. In light of this confusion, a more formal demostration of the Mendelian link between the identified mutation and the related phenotype is requested, especially (i)

segregation study with extended clinical examination on the highest number of relatives available and (2) and the rate comparison with an adeguate sample of controls from the same genetic background.