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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Orthopedics
ESPS manuscript NO: 24213
Title: Recurrent missense mutation of GDF5 (p.Jin-Xin Kong38L) causes proximal symphalangism in an British family
Reviewer's code: 02460553
Reviewer's country: Australia
Science editor: Jin-Xin Kong
Date sent for review: 2016-01-15 09:04
Date reviewed: 2016-03-17 08:56

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[ ] 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
[ ] 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

This is an interesting case report, highlighting the importance of thorough history taking. It has great significance to clinical practice, so should be published.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Orthopedics
ESPS manuscript NO: 24213
Title: Recurrent missense mutation of GDF5 (p.Jin-Xin Kong38L) causes proximal symphalangism in an British family
Reviewer's code: 00482956
Reviewer's country: Germany
Science editor: Jin-Xin Kong
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Date reviewed: 2016-03-24 00:01

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
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[Y] 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 ms entitled "A recurrent missense mutation of GDF5 causes proximal symphalangism in an British family." is a clinical description of a family displaying proximal symphalangism due to a dominant mutation in GDF5 (p.R438L). The mutation is already known to cause SYM1B. I have the following specific concerns: 1. I would prefer to name the mutation in the title, like: Proximal symphalangism caused by a missense mutation in GDF5 (p.R438L) in a British family 2. SYMB1 should be SYM1B throughout the manuscript 3. Abstract: Skip SYM1B in the abstract, and just write about proximal symphalangism in general, because you don't know in the beginning if it is SYM1B caused by GDF5 mutations or SYM1A caused by NOG mutations. 4. "This report highlights the importance of thorough history taking, including a three generation family history, and detailed clinical examination of children with fixed planovalgus feet and other family members to detect rare skeletal dysplasia conditions causing pain and deformity, and provides details of the spectrum of problems associated with SYMB1." This argument is not conclusive and should be rephrased. 5. Introduction: "…NOG, encoding noggin, and GDF5, encoding growth differentiation factor 5"

should be "NOG, encoding NOG, and GDF5, encoding Growth Differentiation Factor 5" 6. Case Report: The first sentence is identical with a sentence in the abstract and should be rephrased. 7. "DNA sequencing of the eldest son identified a heterozygous missense mutation c.1313G>T in GDF5, which causes the amino acid substitution arginine to leucine at codon 438 (R438L) which predicted to disrupt GDF5 function." R43L does not disrupt GDF5 function. R438L alters GDF5 signalling. 8. NOGGIN should be abbreviated as NOG throughout the manuscript. 9. Genes and proteins does not follow the standard nomenclature http://www.genenames.org/about/guidelines 10. "transforming growth factor superfamily" should be "transforming growth factor beta superfamily" 11. "The c.1313G>T (R438L) mutations in GDF5 has been previously detected in a family with SYM1 (5) and the causative mechanism is thought to be overexpression of GDF5 leading to joint cartilage overgrowth and subsequent fusion.(1, 4, 5)" R438L has been previously identified in a family with SYM1 and SYNS. The causative mechanism is not due to overexpression, but due to increased biological activity. 12. Table 2: Dawnson et al should be Dawson et al 13. Table 2: Why mutation sites differ between Seemann et al and Dawson et al? 14. Figures: more radiographs, especially from the hands would be helpful to evaluate the phenotypic variations in more detail.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Orthopedics
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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
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[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This is a well written and succinct report identifying a dominant mutation in GDF5 associated with SYNS1. I have the following suggestions that I think will add to the paper. 1. Please have a figure showing the sequencing electropherogram of the mother and son, together with an homozygous control (potentially the father). A multi-species alignment of this mutated region showing the conservation of the R438 would also also add to this figure . 2. If you have DNA from the other affected children, please show evidence that they have the same mutation. 3. Please provide additional data on the predicted effect of the mutation on GDF5 function e.g. PolyPhen/Mutation taster prediction, details of the protein domain where the mutation is located and