HoxD transcription factors define monosynaptic sensory-motor specificity in the developing spinal cord

Yutaka Yoshida, Fumiyasu Imai, Steven Potter and Mike Adam
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Original submission

First decision letter

MS ID#: DEVELOP/2020/191122

MS TITLE: HoxD transcription factors define monosynaptic sensory-motor specificity in the developing spinal cord

AUTHORS: Yutaka Yoshida, Fumiyasu Imai, Steven Potter, and Mike Adam

I have now received the reports of three referees on your manuscript and I have reached a decision. The referees' comments are appended below, or you can access them online: please go to BenchPress and click on the 'Manuscripts with Decisions' queue in the Author Area.

As you will see, all the referees are enthusiastic about your work, but they also have significant criticisms and recommend a substantial revision of your manuscript before we can consider publication. In particular, they recommend that you analyse the dendritic arbour of motor neurons in mutant mice, that you use additional markers of regional identity and that you improve the writing of the manuscript. However the trans-synaptic viral labelling requested by referee 2, point 2 does not seem absolutely necessary to support the conclusions of the paper and would be difficult to achieve during the revision period. If you are able to revise the manuscript along the lines suggested, which may involve further experiments, I will be happy to receive a revised version of the manuscript. Your revised paper will be re-reviewed by the original referees, and its acceptance will depend on your addressing satisfactorily all their major concerns. Please also note that Development will normally permit only one round of major revision.

We are aware that you may currently be unable to access the lab to undertake experimental revisions. If it would be helpful, we encourage you to contact us to discuss your revision in greater detail. Please send us a point-by-point response indicating where you are able to address concerns raised (either experimentally or by changes to the text) and where you will not be able to do so within the normal timeframe of a revision. We will then provide further guidance. Please also note that we are happy to extend revision timeframes as necessary.

Please attend to all of the reviewers' comments and ensure that you clearly highlight all changes made in the revised manuscript. Please avoid using 'Tracked changes' in Word files as these are lost in PDF conversion. I should be grateful if you would also provide a point-by-point response detailing

how you have dealt with the points raised by the reviewers in the 'Response to Reviewers' box. If you do not agree with any of their criticisms or suggestions please explain clearly why this is so.

Reviewer 1

Advance summary and potential significance to field

The manuscript addresses an important question regarding the assembly of spinal motor circuits, namely the mechanisms controlling the exquisite connection specificity between proprioceptive sensory neurons and motor neurons in the stretch reflex arc.
We still have a far from complete picture of the developmental logic and molecular mechanisms underlying the precision that is observed in the patterns of sensory-motor connection. The authors by combining mouse genetics, anatomical and physiological approaches explore the contribution of three genes of the Hoxd cluster (9, 10 11) and find a clear phenotype in the connectivity of the obturator proprioceptive neurons that in the mutant elicit aberrant monosynaptic responses in quadriceps motor neurons. These experiments are novel, convincing and an interesting addition to the field. In addition, the authors also describe an interesting phenotype in the innervation of the rectus femoris muscle.

Comments for the author

I found two major issues and few more minor problems that need to addressed:
1) Unfortunately, the manuscript is poorly written. The conceptual framework for the experiments presented is sometimes missing or not completely clear, explanations of key points are missing both in the introduction and the results section. The introduction is more of a list of facts than a coherent narrative that setup the stage for the experiments presented.

For example, it is not clear why the author chose to focus on these specific Hox genes and not others; why did they choose to investigate the quadriceps reflex arc? What is the overall phenotype of the triple KO mouse? Does it have a locomotor defect? Similarly, in the results section key information for understanding the experiments are missing. For example, when describing the experiments in Figure 1N-Q it is nowhere to be found in the main text that those are retrograde labeling experiments (only mentioned in the figure legends). Why looking at muscle innervation patterns when you are interested in afferents connection to motor neurons? Finally, the discussion is very short, mostly a repetition of the introduction and does not exhaustively address the findings in the context of the known mechanisms of sensory-motor connectivity. I understand it is a report and there are strict limits in space but the discussion, as it is, it is not useful. For example, the possible role of dendritic morphology, regarded in the field as a key determinant of connection specificity is totally missing and should be addressed (Vrieseling and Arber, 2006; Balaskas et al., 2019).
Altogether, the bottom line is that the manuscript is difficult to read and key information is either missing altogether or hard to find. There are also several typos.

2) It is clear from the literature that dendritic morphology and organization is a key factor controlling wiring of these circuits. The authors present experiments studying motor neuron identity, positioning and axonal connectivity but completely ignore dendritic arbors. Without knowing what happens to the dendritic organization of the obturator motor neurons the picture is not complete and it is hard to draw conclusions on the possible causes of the phenotype. Analysis of dendritic elaboration, orientation and overall morphology in the mutants and an appropriate discussion of the findings is, in my opinion, a necessary addition. Given that the authors already performed retrograde labeling experiments both at embryonic and postnatal ages they may already have the data necessary for analysis.

Minor issues:
1) The authors do not provide any evidence that mRNA and/or protein is missing in the spinal cords and DRGs of the KO mice.

2) Figures 1A-H: it would be nice to have a more exhaustive characterization of Hoxd9,10,11 expression at different levels of the spinal cord. This would, maybe, help understanding why the defect is specific to the obturator-quadriceps reflex arc.

3) Figures 1N-S: the retrograde labeling experiments do not seem to be very efficient/specific. There is no quantification. How many embryos have been injected ? How many cells per embryo have been labeled? Have all the motor neurons labeled the correct transcriptional identity? From the pictures it is hard to make any conclusion. In 1N and 1Q there are purple dots all over the place, what are those?

4) Figures 1T-Y: Quantification of MMC and PGC neruons distribution would be a great addition to determine whether the mutant has an effect on columnar organization on the A-P axis.

5) Figure 2: Given the important role of Hox in the control of A-P axis it would be important to add analysis of the distribution of Pea3+/quadriceps neurons also on the A-P axis.
Quantification is missing. It would be nice to compare the numbers of motor neurons in WT and KO. Correlation analysis to quantify the similarity between the cartesian position of WT and KO would be a nice addition.

6) Figures 2J-L: The representative pictures do not seem to be taken from the same segmental level. In L you can see a Chat+ motor neurons in intermediate-lateral spinal cord position.

7) Figure 3: Quantification of branching would be a nice addition. It is not clear how many embryos were analyzed and how reproducible is the phenotype.

8) Figure 4E: In the heteronymous stimulations (Q-Ob) how many responses were found over how many trials?

Reviewer 2

Advance summary and potential significance to field

Imai et al. investigate the intrinsic role of Hoxd9-11 genes in spinal cord (lumbar) motor neurons in determining the specificity of premotor sensory inputs in a position-independent manner. They analyze the phenotype of triple knockout mutants and come to the conclusion that deletion of Hoxd9-11 in motor neurons, while not changing their position and molecular identities, results in selective reorganization of their presynaptic input in a non-cell autonomous manner.

The question addressed in this study is interesting, as previous work has provided alternative deductions (e.g. Surmeli et al., 2011; Baek et al., 2017). However, the conclusions of the current study are not sufficiently supported by the presented data. This work needs to be extensively revised before it can be considered for publication.

Comments for the author

Main points:
1. Additional molecular markers are required to conclude that regional motor neuron identity is not changed in mutants (e.g. RALDH2, ER81, other Hox genes, etc.). Also, a clear visualization of the expression of regional markers along the rostrocaudal axis of the spinal cord (i.e. from the end of thoracic through lumbar levels) must be provided in both wild type and Hox KO mutants by whole-mount and adjacent cross section in situ hybridization.
2. The proposed changes in monosynaptic connectivity of quadriceps motor neurons assessed by electrophysiology should be validated by a trans-synaptic viral strategy.
Minor points:
3. Single and double mutant phenotypes should be shown. Alternatively, in case of absence of altered phenotype, it should be clearly stated that single and double mutants have been analyzed (numbers of mutants should be provided) and their phenotype is similar to that of wild type.
4. For quantifications, p value should be mentioned. Also, significance should be presented in the respective graphs.
5. Scale bars should be added for the images.
6. Typo - 'lumber' should read 'lumbar'.

Reviewer 3

Advance summary and potential significance to field

The manuscript by Imai et al describes intriguing defect in a quadriceps sensorimotor circuit in Hoxd9,d10, d11 triple knockout mice. The authors demonstrate that despite an apparently normal specification of Pea3 positive neurons innervating rectus femoris, the motor neurons receive abnormal afferent monosynaptic inputs from Obturator proprioceptive neurons. These findings contrast most previous studies in which defects in sensori-motor circuits stem from misspecification of motor neuron subtype identities.

Overall, this is an interesting study and the quality of the data is outstanding. However, several points need to be clarified, and some additional data, if available, could be included to make the study even stronger.

Comments for the author

1. "Hoxd9 and Hoxd10 were expressed in the rostral lumber spinal cord (Figure 1A-B) as previously reported (Choe et al., 2006; Wu et al., 2008).
Hoxd11 was expressed in the caudal but not the rostral lumber spinal cord (Figure 1C)" - does this mean there is no overlap of all three HOX genes?
Which ones are expressed in Q motor neurons? If some are not expressed in Q motor neurons, are those not involved in Q circuitry or do the function non-cell autonomously?

2. "quadriceps motor neurons expressed Pea3 but not Islet1in Hoxd9-11-/- mutant mice" - It appears that Pea3 and Isl1 positive motor neurons are either intermixed or co-expressed in Fig 1O,Q. It is necessary to show double-labeled section with Pea3 and Isl1of control and mutant mouse to support the above statement.

3. The retrograde labeling of quadriceps motor neurons is sparse and cells appear to be dispersed across the anterior horn, instead of being clustered in a pool. What are the Pea3 negative retrogradely labeled neurons in Fig 1N,O?

4. "Pea3 is expressed in the rectus femoris muscle" – do you mean "in motor neurons innervating the Rf muscle"?

5. Mutant mice have thinner projections to Rf and vasti muscles. Is it possible that some axons are redirected to Ob muscle? Does retrograde filling of Ob muscle label any Pea3 positive cells – that could potentially explain the ectopic afferent inputs from Ob proprioceptive neurons?

6. Is expression of Sema3E normal in mutant motor neurons innervating quadriceps?

7. Do the triple mutant mice exhibit motor behavior deficits? Hoxd9 Hoxd10 double mutant exhibits defective gait and adduction, due to an abnormal tibial nerve (de la Cruz et al 1999). Does the triple knockout exhibit any quadriceps motor abnormalities? Do the animals exhibit more profound motor deficits compared to double mutants? Is Q innervation and sensori-motor circuitry normal in the double mutant, i.e. are all three genes redundant in the quadriceps circuit?

8. p.5 lumbar instead of lumber

First revision

Author response to reviewers' comments

Dear reviewers,

We are grateful to the reviewers for their helpful critiques and suggestions.
Below, we provide a point-by-point response to the reviewers' comments.

Reviewer 1

1.
Unfortunately, the manuscript is poorly written. The conceptual framework for the experiments presented is sometimes missing or not completely clear, explanations of key points are missing both in the introduction and the results section. The introduction is more of a list of facts than a coherent narrative that setup the stage for the experiments presented.
For example, it is not clear why the author chose to focus on these specific Hox genes and not others; why did they choose to investigate the quadriceps reflex arc? What is
the overall phenotype of the triple KO mouse? Does it have a locomotor defect? Similarly, in the results section key information for understanding the experiments are missing. For example, when describing the experiments in Figure 1N-Q it is nowhere to be found in the main text that those are retrograde labeling experiments (only mentioned in the figure legends). Why looking at muscle innervation patterns when you are interested in afferents connection to motor neurons? Finally, the discussion is very short, mostly a repetition of
the introduction and does not exhaustively address the findings in the context of the known mechanisms of sensory-motor connectivity. I understand it is a report and there are strict limits in space but the discussion, as it is, it is not useful. For example, the possible role of dendritic morphology, regarded in the field as a key determinant of connection specificity is totally missing and should be addressed (Vrieseling and Arber, 2006; Balaskas et al., 2019).
Altogether, the bottom line is that the manuscript is difficult to read and key information is either missing altogether or hard to find. There are also several typos.

Thank you for these helpful comments. We have updated our manuscript to include the information requested. For instance, we chose HoxD9-11 mutant mice because the Potter lab in Cincinnati Children's Hospital Medical Center had generated these mice, and other triple mutants were not available. The HoxD9-11 mutant mice have defects in both kidney development and locomotion, which we have included in the manuscript. The quadriceps reflex arc was chosen as a focus of this study due to it being a well-established monosynaptic sensory-motor circuit that has been well-characterized at lumbar levels. We also examined the peripheral projections of proprioceptive sensory neurons since retrograde signaling from the muscle to sensory neurons is important for monosynaptic sensory-motor specificity.

The possible role of dendritic morphology participating in the development of synaptic specificity is a valid point and we have revised our manuscript to include this possibility.

Since we have added behavioral data and the word limit is 3000, unfortunately we were not able to add discussion much.

2.
Analysis of dendritic elaboration, orientation and overall morphology are needed.

This is a very good point. We have added dendritic analysis including dendrite orientation and morphology (revised Figure 2).

Minor issues:

1) The authors do not provide any evidence that mRNA and/or protein is missing in the spinal cords and DRGs of the KO mice.

The Potter lab generated those *HoxD* triple mutant mice by adding point mutations which cause early termination of the proteins. The Potter lab has confirmed that there are point mutations in the *HoxD* genomic regions, however, truncated mRNAs are still detected in those mutant mice. Regarding protein expression, good antibodies for immunostaining are unfortunately not available.

2) Figures 1A-H: it would be nice to have a more exhaustive characterization of Hoxd9,10,11 expression at different levels of the spinal cord. This would, maybe, help understanding why the defect is specific to the obturator-quadriceps reflex arc.

In response to this comment, we have performed *in situ* hybridizations to generate more detailed expression profiles of *Hoxd9, 10,* and *11* (revised Figure 1).

3) Figures 1N-S: the retrograde labeling experiments do not seem to be very efficient/specific. There is no quantification. How many embryos have been injected ? How many cells per embryo have been labeled? Have all the motor neurons labeled the correct transcriptional identity? From the pictures it is hard to make any conclusion. In 1N and 1Q there are purple dots all over the place, what are those?

We have performed new experiments and added more detailed analyses and descriptions in our revised manuscript.

4) Figures 1T-Y: Quantification of MMC and PGC neurons distribution would be a great addition to determine whether the mutant has an effect on columnar organization on the A-P axis.

We have added quantification data.

5) Figure 2: Given the important role of Hox in the control of A-P axis it would be important to add analysis of the distribution of Pea3+/quadriceps neurons also on the A-P axis. Quantification is missing. It would be nice to compare the numbers of motor neurons in WT and KO. Correlation analysis to quantify the similarity between the cartesian position of WT and KO would be a nice addition.

We have analyzed Pea3 motor neuron positions (revised Figure 1) and have added quantification data for the positions of quadriceps and obturator motor neurons in our revised Figure 2

6) Figures 2J-L: The representative pictures do not seem to be taken from the same segmental level. In L you can see a Chat+ motor neurons in intermediate-lateral spinal cord position.

We have added new data for quadriceps and obturator motor neuron positions including A-P positions in our revised Figure 2.

7) Figure 3: Quantification of branching would be a nice addition. It is not clear how many embryos were analyzed and how reproducible is the phenotype.

We have added branching data as well as numbers of embryos in our revised manuscript.

8) Figure 4E: In the heteronymous stimulations (Q-Ob) how many responses were found over how many trials?

We have added new data in revised Figure 3E (wild-type: 0/8, mutant: 0/13).

Reviewer 2

Main points:

1. Additional molecular markers are required to conclude that regional motor neuron identity is not changed in mutants (e.g. RALDH2, ER81, other Hox genes, etc.). Also, a clear visualization of the expression of regional markers along the rostrocaudal axis of the spinal cord (i.e. from the end of thoracic through lumbar levels) must be provided in both wild type and Hox KO mutants by whole-mount and adjacent cross section in situ hybridization.

We have added nNOS and Pea3 positive motor neurons number along with A-P axis figures in our revised Figure 1.

2. The proposed changes in monosynaptic connectivity of quadriceps motor neurons assessed by electrophysiology should be validated by a trans-synaptic viral strategy.

Due to COVID-19, we had limited access to our laboratory and were unable to perform this experiment. However, we are of the opinion that our electrophysiological data strongly suggests that synaptic specificity has been altered in the *HoxD* triple mutant mice.

Minor points:

3. Single and double mutant phenotypes should be shown. Alternatively, in case of absence of altered phenotype, it should be clearly stated that single and double mutants have been analyzed (numbers of mutants should be provided) and their phenotype is similar to that of wild type.

We have added some descriptions of previous studies about single and double mutant mice in our revised introduction and discussion.

4. For quantifications, p value should be mentioned. Also, significance should be presented in the respective graphs.

We have added p values and indicated statistically-significant data points in our revised manuscript.

5. Scale bars should be added for the images.

We have added scale bars to our figures.

6. Typo - 'lumber' should read 'lumbar'.

We have made this correction.

Reviewer 3

1."Hoxd9 and Hoxd10 were expressed in the rostral lumber spinal cord (Figure 1A-B) as previously reported (Choe et al., 2006; Wu et al., 2008). Hoxd11 was expressed in the caudal but not the rostral lumber spinal cord (Figure 1C)" - does this mean there is no overlap of all three HOX genes? Which ones are expressed in Q motor neurons? If some are not expressed in Q motor neurons, are those not involved in Q circuitry or do the function non- cell autonomously?

We have included detailed expression patterns for the three *HoxD* genes in our revised Figure S1.

2."quadriceps motor neurons expressed Pea3 but not Islet1in Hoxd9-11-/- mutant mice" - It appears that Pea3 and Isl1 positive motor neurons are either intermixed or co-expressed in Fig 1O,Q. It is necessary to show double-labeled section with Pea3 and Isl1of control and mutant mouse to support the above statement.

We have added Pea3 and Islet1 double staining data in our revised Figure 1.

3.The retrograde labeling of quadriceps motor neurons is sparse and cells appear to be dispersed across the anterior horn, instead of being clustered in a pool. What are the Pea3 negative retrogradely labeled neurons in Fig 1N,O?

We have added new data for Pea3 motor neuron locations along the A-P axis (Figure 1).
We have also analyzed the positions of the quadriceps and obturator motor neurons, including information about their medio-lateral and rotsro-caudal distributions (Figure 2).

4."Pea3 is expressed in the rectus femoris muscle" – do you mean "in motor neurons innervating the Rf muscle"?

Yes, this is correct and we have edited our statement.

5. Mutant mice have thinner projections to Rf and vasti muscles. Is it possible that some axons are redirected to Ob muscle? Does retrograde filling of Ob muscle label any Pea3 positive cells – that could potentially explain the ectopic afferent inputs from Ob proprioceptive neurons?

First, we identified specific motor neurons by antidromic responses, then we stimulated the opposite nerve, however, we did not find any aberrant antidromic responses, indicating that quadriceps and obturator motor neurons project specifically to quadriceps and obturator muscles, respectively.

6. Is expression of Sema3E normal in mutant motor neurons innervating quadriceps?

Yes, we have added Sema3E expression data in our revised Figure 1.

7. Do the triple mutant mice exhibit motor behavior deficits? Hoxd9 Hoxd10 double mutant exhibits defective gait and adduction, due to an abnormal tibial nerve (de la Cruz et al 1999). Does the triple knockout exhibit any quadriceps motor abnormalities? Do the animals exhibit more profound motor deficits compared to double mutants? Is Q innervation and sensori-motor circuitry normal in the double mutant, i.e. are all three genes redundant in the quadriceps circuit?

We have further analyzed the locomotion data from the treadmill experiment in our revised Figure 4, and have added detailed discussions [comparing double and triple mutants] in our revised manuscript.

8.p.5 lumbar instead of lumber

We have corrected this.

We hope that our revised manuscript addresses most of the reviewers' concerns and will now be suitable for publication. Please feel free to reach out to me should you have any further requests or concerns.

Second decision letter

MS ID#: DEVELOP/2020/191122

MS TITLE: HoxD transcription factors define monosynaptic sensory-motor specificity in the developing spinal cord

AUTHORS: Yutaka Yoshida, Fumiyasu Imai, Steven Potter, and Mike Adam

I have now received the reports of the three referees who reviewed the earlier version of your manuscript and I have reached a decision. The referees' comments are appended below, or you can access them online: please go to BenchPress and click on the 'Manuscripts with Decisions' queue in the Author Area.

The overall evaluation is positive and we would like to publish a revised manuscript in Development, provided that you satisfactorily address the remaining suggestions and comments of referee 1. Please attend to all these comments in your revised manuscript and detail them in your point-by-point response. If you do not agree with any of their criticisms or suggestions explain clearly why this is so.

We are aware that you may currently be unable to access the lab to undertake experimental revisions. If it would be helpful, we encourage you to contact us to discuss your revision in greater detail. Please send us a point-by-point response indicating where you are able to address concerns raised (either experimentally or by changes to the text) and where you will not be able to do so within the normal timeframe of a revision. We will then provide further guidance. Please also note that we are happy to extend revision timeframes as necessary.

Reviewer 1

Advance summary and potential significance to field

The manuscript addresses an important question regarding the developmental mechanisms controlling the exquisite specificity of sensory-motor connectivity in the spinal cord. The authors by combining mouse genetics, anatomical, and physiological studies describe a novel role for members

of the HoxD family of transcription factor in promoting specific connections in the quadriceps reflex arc.

Comments for the author

I feel that the revised version of the manuscript is significantly improved and suitable for publication pending few minor issues:
- Resolution of the ISH images in Figure S1 is low and as a result it is hard to see expression patterns in details.
- In figure 1K the circle on LMC neurons is in the wrong place and there is no circle around MMC neurons. Panels 1Q-R are not aligned with the others.
- The authors state on page 7: “In addition, at lumber levels, the number of Pea3on motor neurons was similar between control and mutant animals.” Lumbar not lumber, as already pointed out by Reviewers #2 and #3 in the first round of revision.
- In the main text there is no narrative for the dextran retrograde labeling experiments shown in Figure 1Q-R . In addition, as asked in the first round of revision, there is no quantification for these experiments. New experiments presented in Figure 2A-H clarify address the point I raised. However, if the authors choose to leave figures 1Q-R in the manuscript they should be described in the result section and properly analysed (How many embryos have been injected ?
How many cells per embryo have been labeled? Have all the motor neurons labeled the correct transcriptional identity?). Finally the information reagrding number of motor neurons labeled in each animal for the AAV experiments should be provided.

Reviewer 2

Advance summary and potential significance to field

This revised version is much improved. Even though the authors have not fully addressed all my previous concerns, the current study may now be suitable for publication.

Comments for the author

See above.

Reviewer 3

Advance summary and potential significance to field

The authors satisfactorily addressed all my concerns. The study is well performed and clearly described and I support its publication.

Comments for the author

there is still one remaining instance of lumber instead of lumbar

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Second revision

Author response to reviewers' comments

Reviewer 1

- Resolution of the ISH images in Figure S1 is low and as a result it is hard to see expression patterns in details.

We have changed Figure S1 to high-resolution images.

- In figure 1K the circle on LMC neurons is in the wrong place and there is no circle around MMC neurons. Panels 1Q-R are not aligned with the others.

Thank you for pointing out it, and we have corrected

The authors state on page 7: “In addition, at lumber levels, the number of Pea3on motor neurons was similar between control and mutant animals.” Lumbar not lumber, as already pointed out by Reviewers #2 and #3 in the first round of revision.

We apologize our mistake again, and we have corrected it.

- In the main text there is no narrative for the dextran retrograde labeling experiments shown in Figure 1Q-R . In addition, as asked in the first round of revision, there is no quantification for these experiments. New experiments presented in Figure 2A-H clarify address the point I raised. However, if the authors choose to leave figures 1Q-R in the manuscript they should be described in the result section and properly analysed (How many embryos have been injected ? How many cells per embryo have been labeled? Have all the motor neurons labeled the correct transcriptional identity?). Finally the information reagrding number of motor neurons labeled in each animal for the AAV experiments should be provided.

Thank you for pointing out it, and we decided to remove Figure1 Q, R. In addition, we have added that information regarding number of motor neurons into figure legend.

Reviewer 3

there is still one remaining instance of lumber instead of lumbar...

We have corrected it.

We hope that our revised manuscript addresses the reviewers’ concerns and will now be suitable for publication.

Third decision letter

MS ID#: DEVELOP/2020/191122

MS TITLE: HoxD transcription factors define monosynaptic sensory-motor specificity in the developing spinal cord

AUTHORS: Yutaka Yoshida, Fumiyasu Imai, Steven Potter, and Mike Adam
ARTICLE TYPE: Research Report

I am delighted to tell you that your manuscript has been accepted for publication in Development, pending our standard ethics checks.