

Amyloid Precursor Protein ortholog Appl acts with Vnd during mushroom body axon growth in *Drosophila*

Claire Marquilly, Germain Busto, Laure Pasquet, Robert Zinzen, Bassem Hassan, Lee Fradkin, Thomas Preat, Ana Boulanger, and Jean-Maurice Dura

NOTE: The reviews and decision letters are unedited and appear as submitted by the reviewers.

In extremely rare instances and as determined by a Senior Editor or the EIC, portions of a review may be redacted. If a review is signed, the reviewer has agreed to no longer remain anonymous.

The review history appears in chronological order.

Review Timeline:

Submission Date:	2025-07-23
Editorial Decision:	2025-08-20
Resubmission Received:	2025-07-23
Accepted:	2026-04-07

August 20, 2025

GENETICS-2025-308417

Non-autonomous Vnd acts with autonomous Appl during mushroom body axon growth in *Drosophila*

Dear Dr. Dura:

Two experts in the field have reviewed your manuscript, and I have read it as well. I am pleased to inform you that, with minor revisions, it is potentially suitable for publication in GENETICS. The reviewers have comments and concerns that need to be addressed in a revised manuscript. You can read their reviews at the end of this email.

It is most important that you address the following in your resubmission: As recommended by both reviewers, please test for Vnd protein in flies with the Appl alleles (d, C1.2, C1.4) and the new vnd alleles using the antibody that was generated in this study, and, as recommended by Reviewer 2, please determine whether the Appl[d] and Appl[C2.1] phenotypes are rescued by Appl(+) or vnd(+) and provide additional support that Vnd is present in neurons (e.g., use anti-Elav in combination with anti-Vnd or vnd-Gal4 driving the expression of a nuclear-localized marker, such as Stinger).

We look forward to receiving your revised manuscript. Please let the editorial office know approximately how long you expect to need for revisions.

Upon resubmission, please include:

1. A clean version of your manuscript;
2. A marked version of your manuscript in which you highlight significant revisions carried out in response to the major points raised by the editor/reviewers (track changes is acceptable if preferred);
3. A detailed response to the editor's/reviewers' comments and to the concerns listed above. Please reference line numbers in this response to aid the editors.

Additionally, please ensure that your resubmission is formatted for GENETICS.

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Follow this link to submit the revised manuscript: Link Not Available

Sincerely,

Jill Wildonger
Associate Editor
GENETICS

Approved by:
Oliver Hobert
Senior Editor
GENETICS

Reviewer #1 :

The manuscript by the Dura lab describes the roles of two neighboring genes *appl* and *vnd* in mushroom body axon growth in *Drosophila*. Via CRISPR-Cas9 gene editing, they generated a new allele of *Appl* which only deletes *Appl* gene but not *vnd* gene and new alleles that affect either *vnd-B* and *vnd-A* gene. With those new alleles, they can distinguish the roles of *Appl* and *vnd*. The conclusion is that *Appl* is partially required for MB axon outgrowth, whereas *vnd* plays a stronger role than *Appl* in axon outgrowth. Moreover, they found that *Vnd* is not expressed within MB neurons, instead in the neighboring neurons. Thus, *Vnd* is likely to play a non-cell-autonomous role in axon outgrowth. Overall, this is a nice and concrete genetic studies to revisit the role of *Appl* and *Vnd* genes in MB axon outgrowth. The figures are convincing, and the conclusion is well supported by the data. Did the authors see if *Vnd* protein is depleted in two new *vnd* alleles?

Reviewer #2 :

The manuscript by Marquilly et al. describes a role of vnd in the formation of the mushroom body (MB) and specifically in the MB phenotype described in a deletion of the Drosophila APP gene APPL. For the purpose of analyzing vnd function in the MB they have generated two deletion alleles of vnd specific for the two alternative splice forms. They show that the B isoform is not required for the correct formation of the MB and does not interact with the Appl C1.4 deletion while the A isoform does contribute to MB formation in the Appl deletions. The studies show a robust interaction and they indicate that the previously described MB phenotype in the Appld deletion are due to effects on vnd. However, several experiments to confirm this should be included. First, the author generated an antibody against vnd and they should show that the VND protein is affected in Appld and C 1.4 but not in C2.1. They can even address effects specifically on the transcription of the two isoforms by qPCR. They should include rescue experiments with Appld and C2.1 as they show for C1.4 in figure 3A. Lastly, they suggest vnd is expressed in neurons due to the vnd staining not co-localizing with Repo. This could be easily validated by performing co-IHC with a neuronal marker like ELAV.

I did not see a Data Availability Statement

Associate Editor Comments:

Please add a Data Availability Statement.

Do the authors have any ideas about the identify of the vnd(+) neurons that flank the mushroom body? Could the authors comment on the position of these vnd(+) neurons relative to the mushroom body when the beta-lobes extend; in other words, are the neurons in a position to signal locally to beta-lobe axons, or would signaling need to occur over a longer distance?

Figure S2 refers to the "insertion of 821 bp;" it would be helpful to have the full sequence of Appl[C2.1] if possible.

Detailed response to the editor's/reviewer's comments with line numbers.

Responses are in red below each comment.

August 20, 2025

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*** lines 293-295 and Supplementary Fig.3.

and the new vnd alleles using the antibody that was generated in this study, and, as recommended by Reviewer 2,

*** lines 304-306 and Supplementary Fig.3.

please determine whether the Appl[d] and Appl[C2.1] phenotypes are rescued by Appl(+) or vnd(+)

*** lines 325-329 and Supplementary Fig.5.

and provide additional support that Vnd is present in neurons (e.g., use anti-Elav in combination with anti-Vnd or vnd-Gal4 driving the expression of a nuclear-localized marker, such as Stinger).

*** lines 346-347 and Fig.5h-m.

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Follow this link to submit the revised manuscript: <https://genetics.msubmit.net/cgi-bin/main.plex?el=A3NR7HOB3A3dng4I4A9ftdPEzIFDZx6YjsHFyGFCwUAZ>

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Jill Wildonger
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*** lines 304-306 and Supplementary Fig.3.

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*** lines 346-347 and Fig.5h-m.

I did not see a Data Availability Statement

*** lines 671-675

Associate Editor Comments:

Please add a Data Availability Statement.

*** Done: lines 671-675

Do the authors have any ideas about the identify of the vnd(+) neurons that flank the mushroom body?

*** lines 349-350: Presently, we do not know the identity of the *vnd*⁺ neurons that flank the MBs.

Could the authors comment on the position of these vnd(+) neurons relative to the mushroom body when the beta-lobes extend; in other words, are the neurons in a position to signal locally to beta-lobe axons, or would signaling need to occur over a longer distance?

*** lines 427-429: Given the position of the *vnd*⁺ neurons relative to the MBs during larval and pupal stages, we favor the hypothesis that these neurons signal locally to β lobe axons rather than over a long distance.

Figure S2 refers to the "insertion of 821 bp;" it would be helpful to have the full sequence of Appl[C2.1] if possible.

*** This is in the figure legend of Supplementary Fig.2 (lines 594-603).

April 6, 2026

RE: GENETICS-2026-309305

Dr. Jean-Maurice Dura
Institut de Genetique Humaine
Genetics, Cell Biology and Development
141 rue de la Cardonille
Cedex 5
Montpellier, N/A 34396
France

Dear Dr. Dura:

Congratulations, your manuscript titled "Non-autonomous Vnd acts with autonomous Appl during mushroom body axon growth in *Drosophila*" is accepted for publication in GENETICS! Many thanks for submitting your research to the journal.

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Title suggestions:

The roles of Amyloid Precursor Protein ortholog Appl and Vnd in *Drosophila* mushroom body axon growth

Amyloid Precursor Protein ortholog Appl acts with Vnd during mushroom body axon growth in *Drosophila*

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