Response to referee #1 All my corrections and additions are in red letters.

1. I would like to thank the referee for his constructive suggestions to improve the manuscript. The JHEHs that we have cloned are similar to other JHEHs that were described in the literature, and some were shown to be active on JH III see our introduction. The referee asks if JHEH 1, 2 and 3 have JHEH function if they were not expressed and incubated with their substrates ?. Since the JHEHs that we cloned and sequenced are the ONLY JHEHs that are also described in the *D. melanogaster* genome it is unlikely that they are not JHEH. However, to show that indeed, female *D. melanogaster* does have JHEHs that act on JH IIIA we treated female *D. melanogaster* with [12-^{3}H]JH IIIA at different time after adult eclosion and showed that [12-^{3}H]JH IIIA was converted within 60 min into the JH IIIAD (See revised manuscript Table 2 lines 630 to 651). Taniai et al. 2003 also showed that an extract of larval *D. melanogaster* converts JH III into the JH IIID proving that JHEH 1 and 3 can convert JH III into the JH IIID (see revised discussion lines 605-608). The conversion rate of JH III into JH IIID was low because the substrate for JHEH is JH IIIA and not JH III. Our 3D models and docking of JH III and JH IIIA to JHEH 3 including X-ray crystallography studies of JHEH from other insects (described in our introduction and discussion) also show that JH III binds JHEH of other insects at the active pocket thus proving that JHEH act on JH III and on JH IIIA as shown by our results . Our earlier studies on mosquito JHEH (Borovsky et al. 1992) also show that female mosquitoes rapidly convert JH IIIA into JH IIIAD. With all due respect we do not agree with this referee that the data on the cloning, sequencing and 3D models should be published as a separate manuscript. We also do not agree that 3D modeling and docking that are very accurate and at least 90% accurate as X-ray crystallography are not a good way to show binding affinity of JH IIIA or JH III to JHEH of *D. melanogaster*. X-ray crystallography and now CryoEM studies are used extensively to show binding of substrate and potential drug designs as substrate and cannot be dismissed as not a good enough proof of substrate specificity. We hope that the new added Table 2 will convince this referee that JH IIIA is indeed the preferred substrate for JHEH.

2. With the addition of Table 2 I believe that now the abstract is correct in claiming that JH IIIA is the preferred substrate for JHEH in *Drosophila.*

3. As suggested by the referee all the notations of JHEHs are now in Arabic's numbers.

4. I rewrote and tried to shorten the part of the introduction that deals with the reason to study the promoters of JHEH, however, I completely disagree with the referee that it is confusing. It is accurate and describes the role of promoters in controlling genes. Indeed, Referee #2 did not find that section confusing. The explanation why this research was done is found in lines 94-103 following the importance of promoters see lines 73-79 in the introduction.

5. I agree with the referee that too many tables were presented in the methodology section. I have moved all the tables that describe the primers that were used to sequence the 3 JHEHs cDNAs and to amplify the different segments of the 3 promoters into the Supplementary material section, including the graphic presentation of the plasmid pCaSpeR-AUG-bgal (see supplementary material section S1-S4 and S5, S7 and S9). I agree that now the manuscript is easier to read and follow and is less cluttered.

6. See 5 above to answer this referee's question.

7. The references formatting follows the specifications of Biomolecules. All the references are formatted as specified by the journal. We do not understand what the referee means.

8. I have moved the text that was cut as was suggested by the so that the last figure does not cut the text.

   We hope that this referee will endorse our corrections and the improvement of the manuscript and would like to thank the referee again for his constructive suggestions to improve the manuscript.