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Cyclin G: looking for the causes of developmental noise

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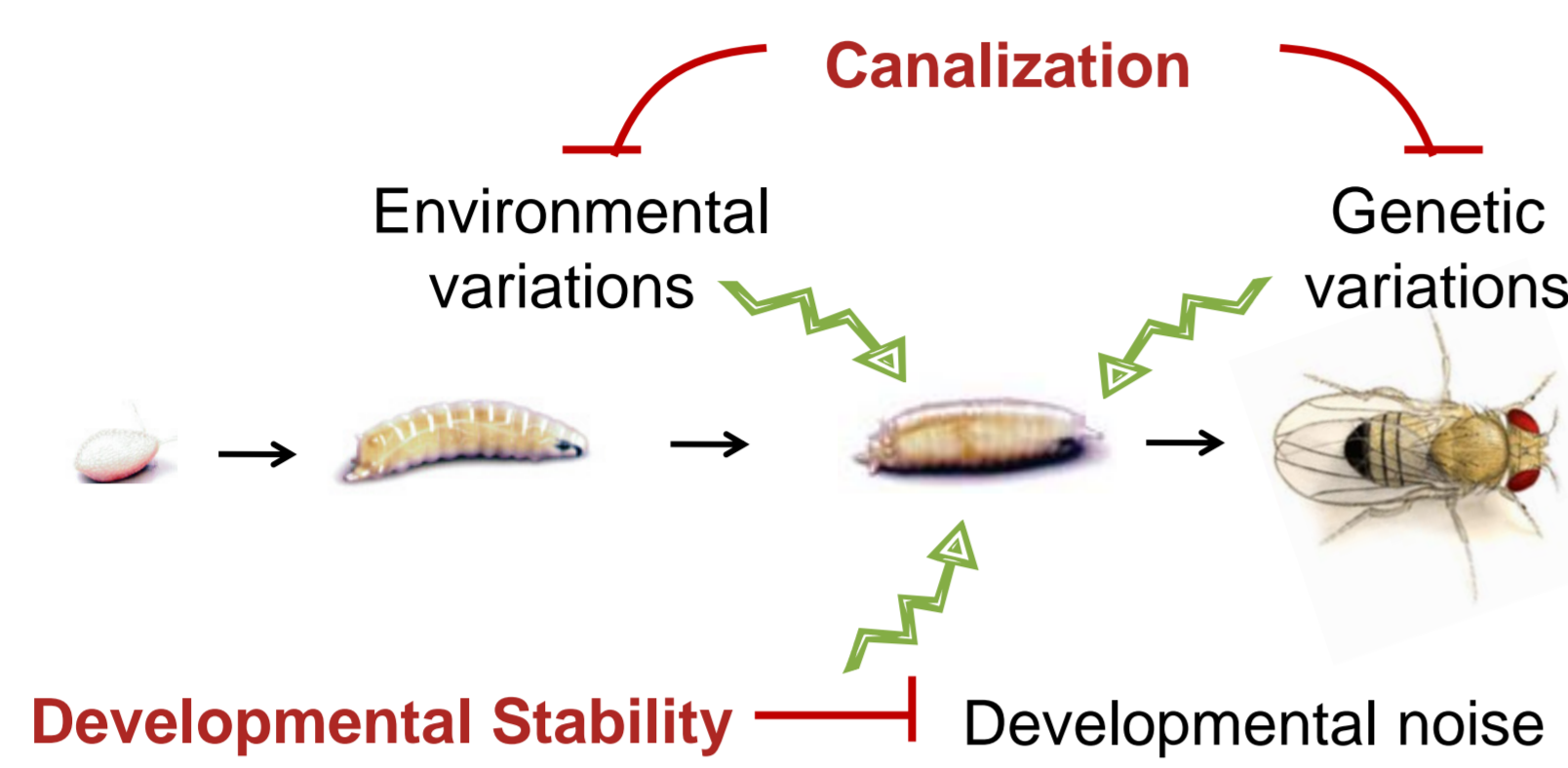
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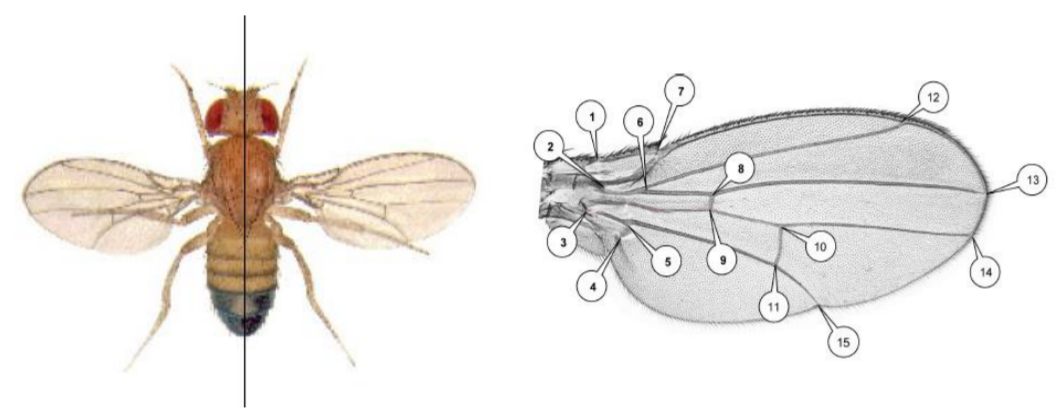
Drosophila melanogaster Cyclin G (dCycG) controls transcription and regulates the cell cycle. We previously determined that dCycG shares many transcriptional targets with the Polycomb PRC1 and PR-DUB complexes¹. Overexpression of a potentially more stable form of dCycG down-regulates genes involved in mitochondrial activity. Interestingly, it also induces a high developmental noise, as estimated by an increase of wing fluctuating asymmetry (FA) in adults². Overexpression of dCycG in background mutants for the Polycomb complexes PRC1 or PR-DUB leads to a previously unseen FA¹. We show here that dCycG directly interacts with dRing, the ubiquitine-ligase of PRC1 and Calypso, the deubiquitinase of PR-DUB. Our results suggest that dCycG undergoes a ubiquitination/deubiquitination cycle driven by these complexes and bookmarks its transcriptional targets during mitosis. We have produced a *dCycG* mutant by CRISPR/Cas9. This mutant displays a high FA. Although its amount of mitochondrial DNA does not vary, wing imaginal disc respiration unexpectedly increases. The next step will be to check the amount of Reactive Oxygen Species in these tissues and address whether an increase in ROS is causal to developmental noise.

I - Developmental Stability and Fluctuating Asymmetry

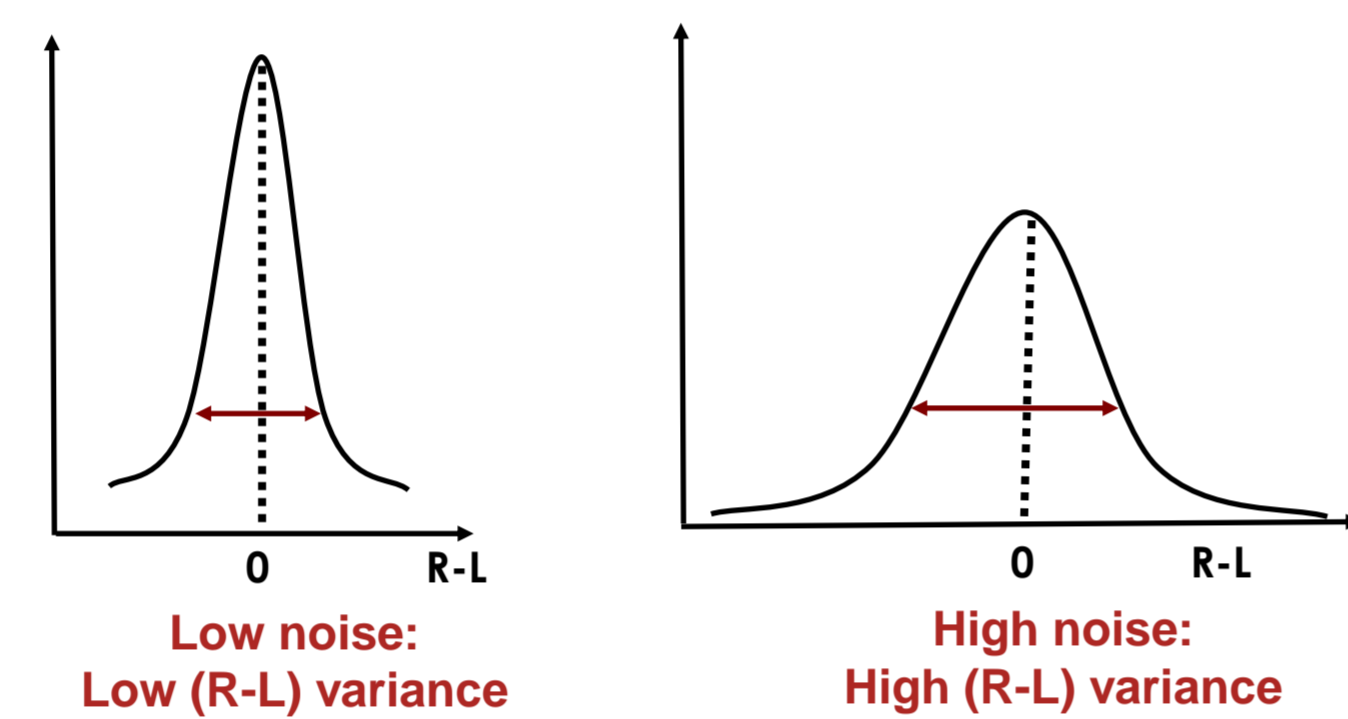


In bilaterians, developmental noise is assessed by Fluctuating Asymmetry (FA) in a population of isogenic flies raised in a standardized environment.

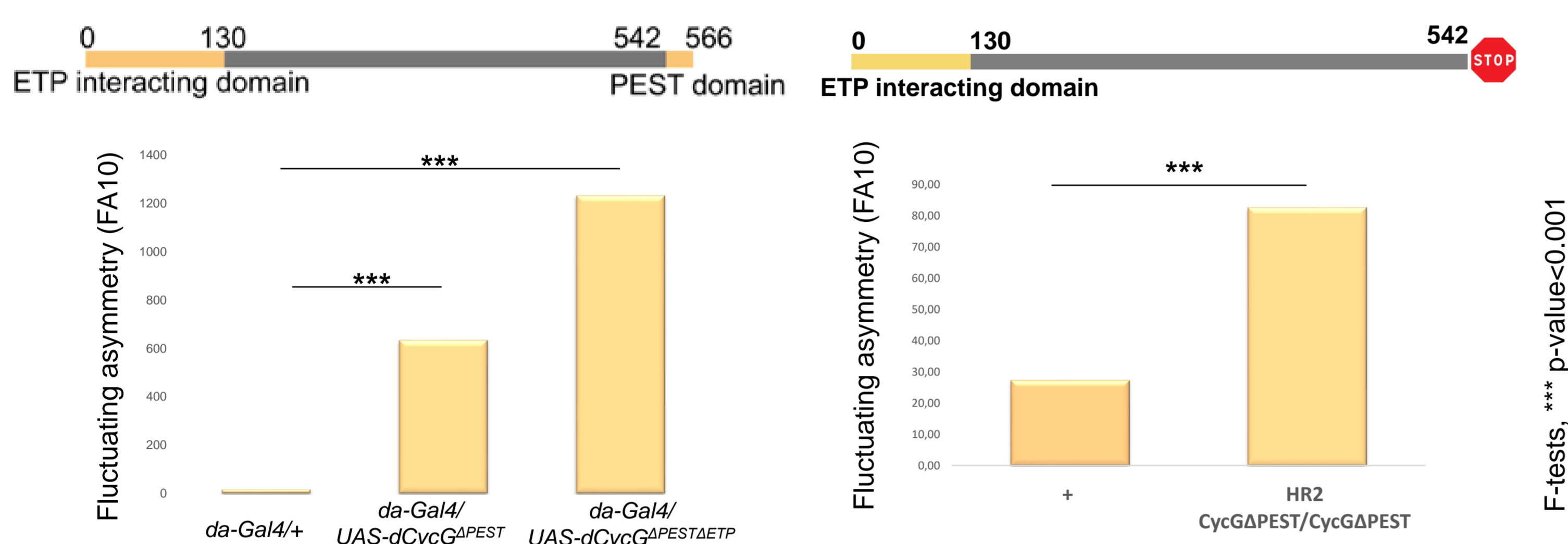
Measure of the centroid size of right (R) and left (L) wings using a set of 15 landmarks (geometric morphometrics)



Distribution of (R-L) within a population



High developmental noise in flies expressing dCycG deleted of the PEST domain

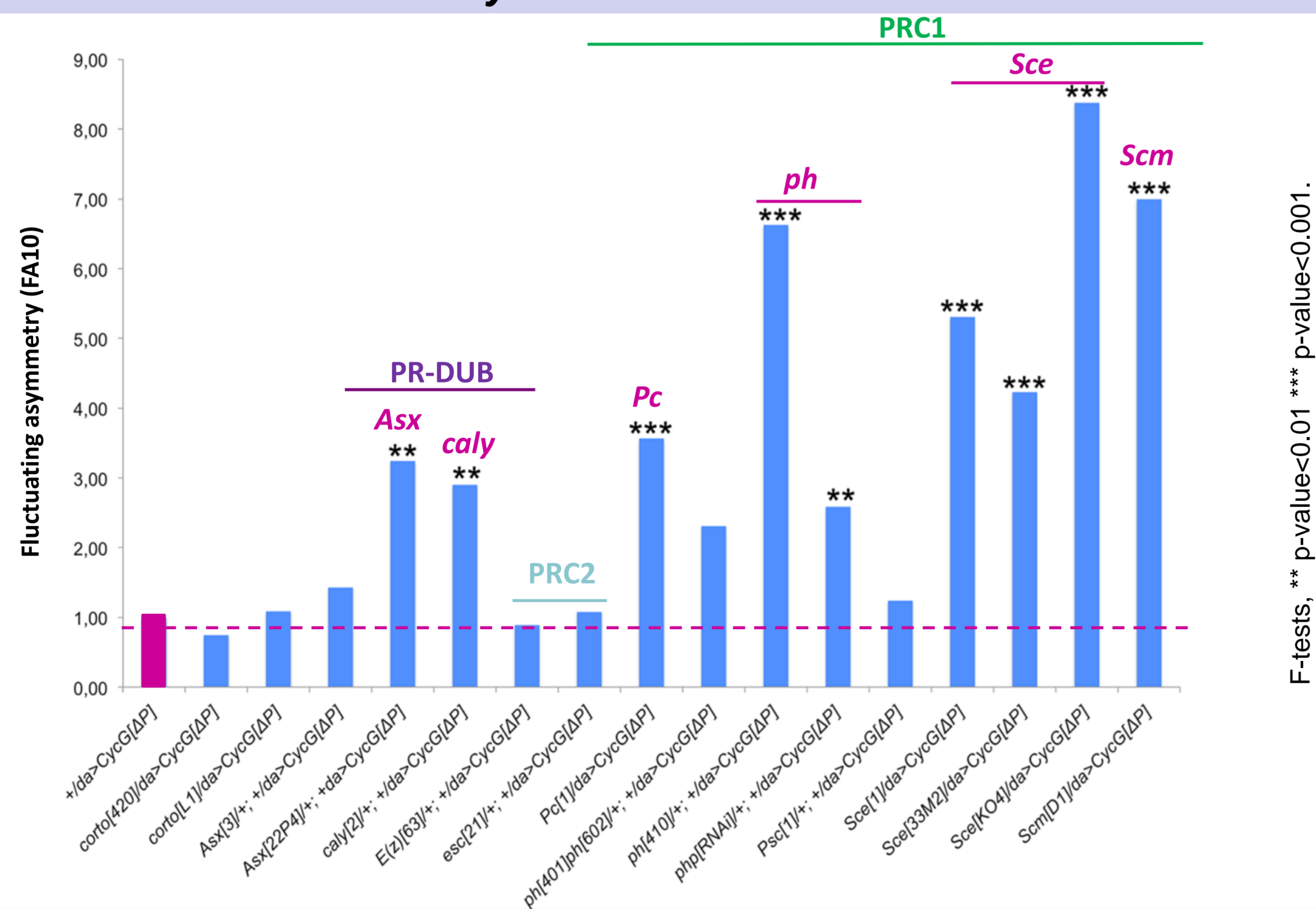


Overexpression of *CycG* in isogenic flies raised in a standardized environment induces very high FA. The ETP interacting domain limits *CycG*-induced fluctuating asymmetry

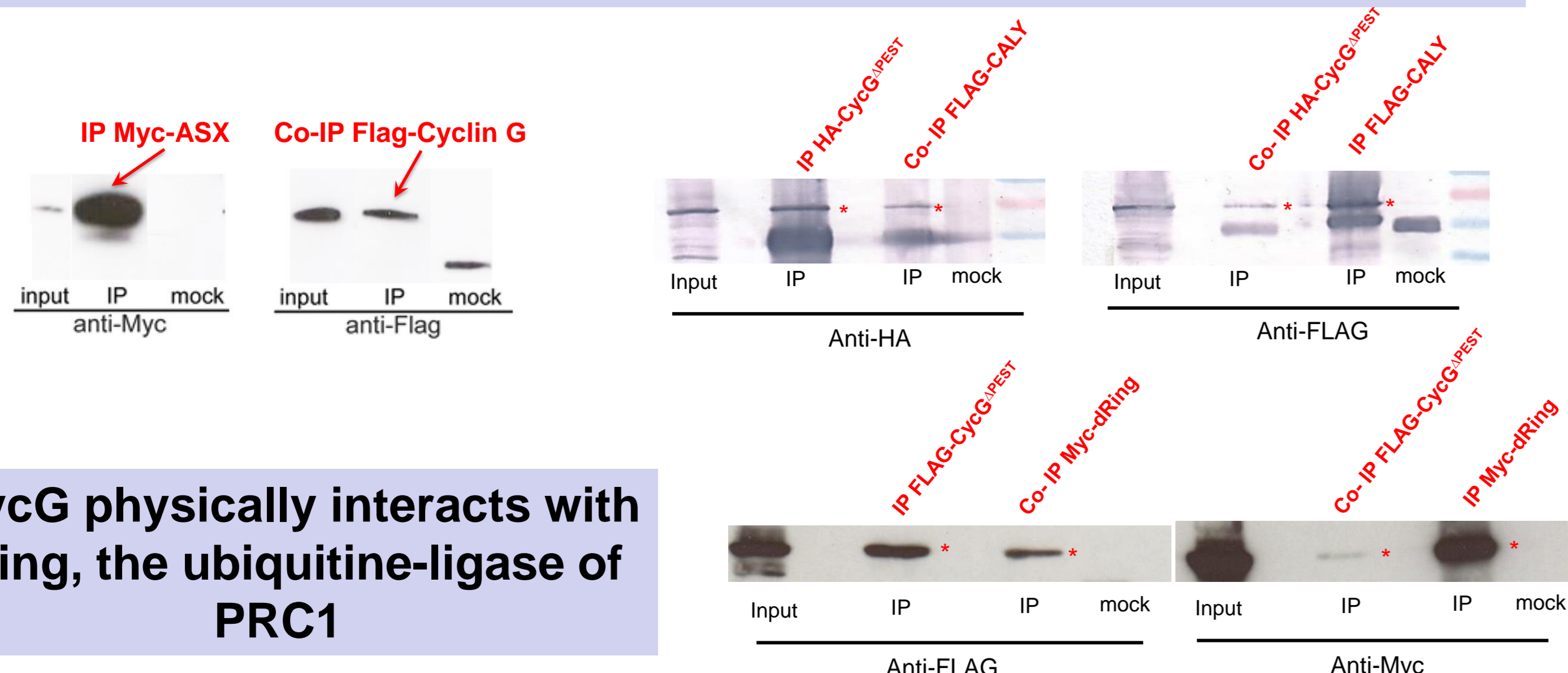
A CRISPR/Cas9 mutant of *CycG* : HR2 raised in a standardized environment induces high FA

II - Cyclin G interacts with PRC1 and PR-DUB

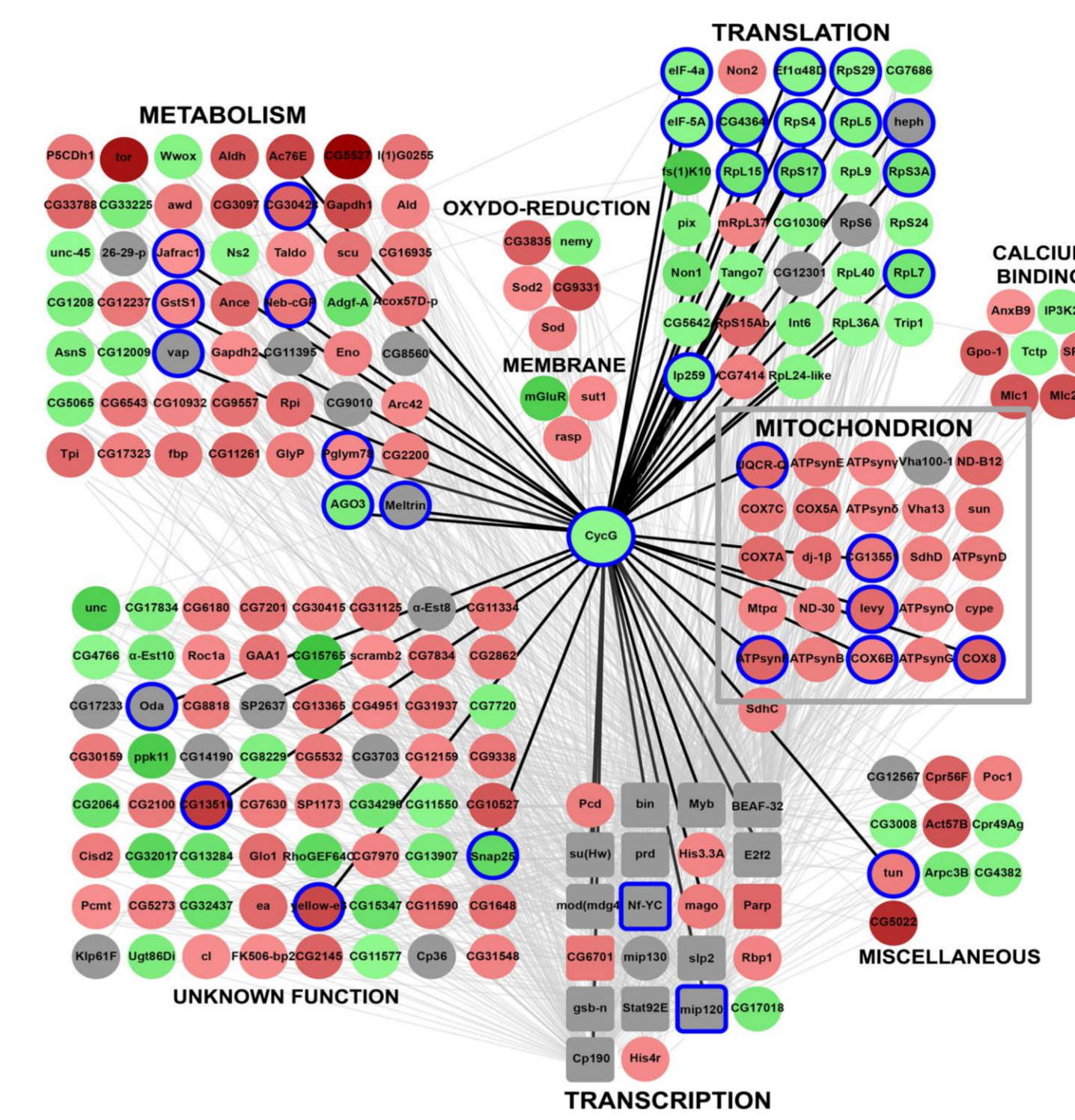
Mutations in the Polycomb complexes PRC1 and PR-DUB increase dCycG-induced FA



dCycG physically interacts with ASX and the deubiquitinase Calypso, the two sub-units of PR-DUB



III - Cyclin G interacts with mitochondrial genes

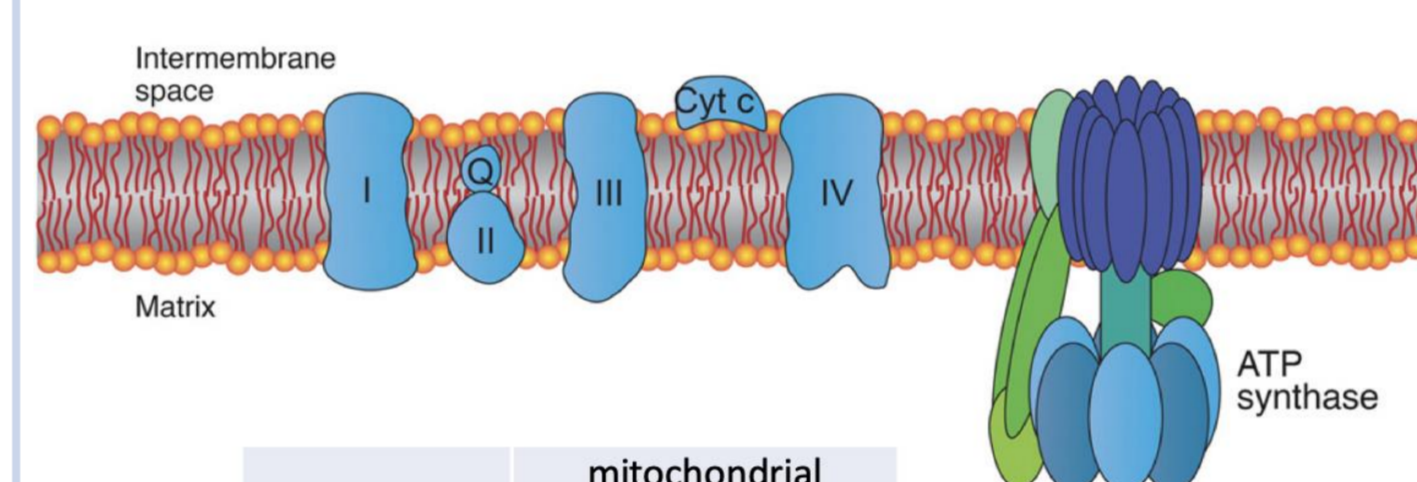


Down-regulation of genes involved in mitochondrial activity in wing imaginal discs expressing dCycG deleted of the PEST domain (RNA-seq)

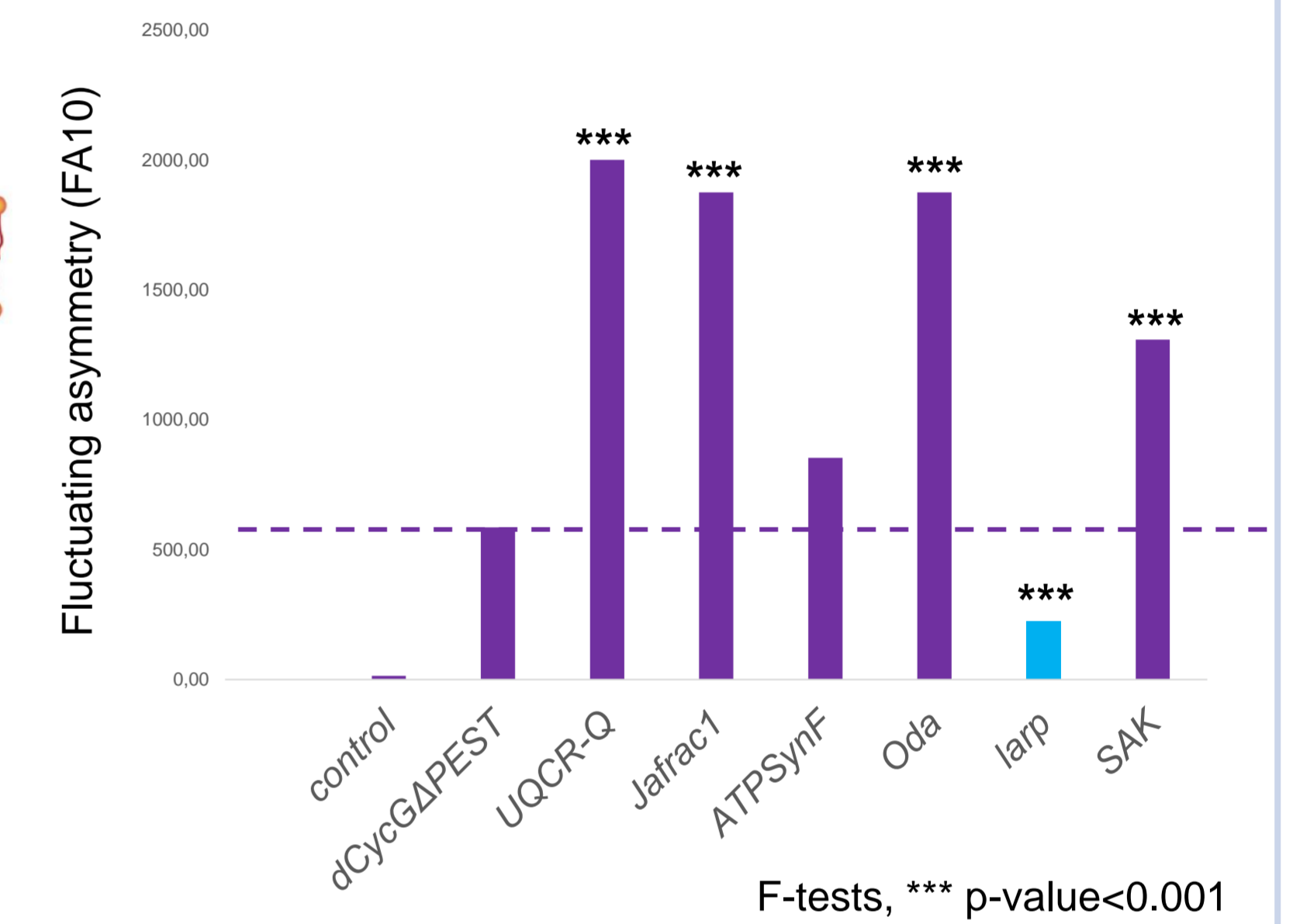
Many direct transcriptional targets of dCycG are shared with PRC1, PR-DUB and RNA pol II (ChIP-seq)

Mutants for most mitochondrial genes increase dCycG-induced FA, whereas a mutant for *larp* decreases it

Electron Transport Complexes and ATP synthase within the inner mitochondrial membrane

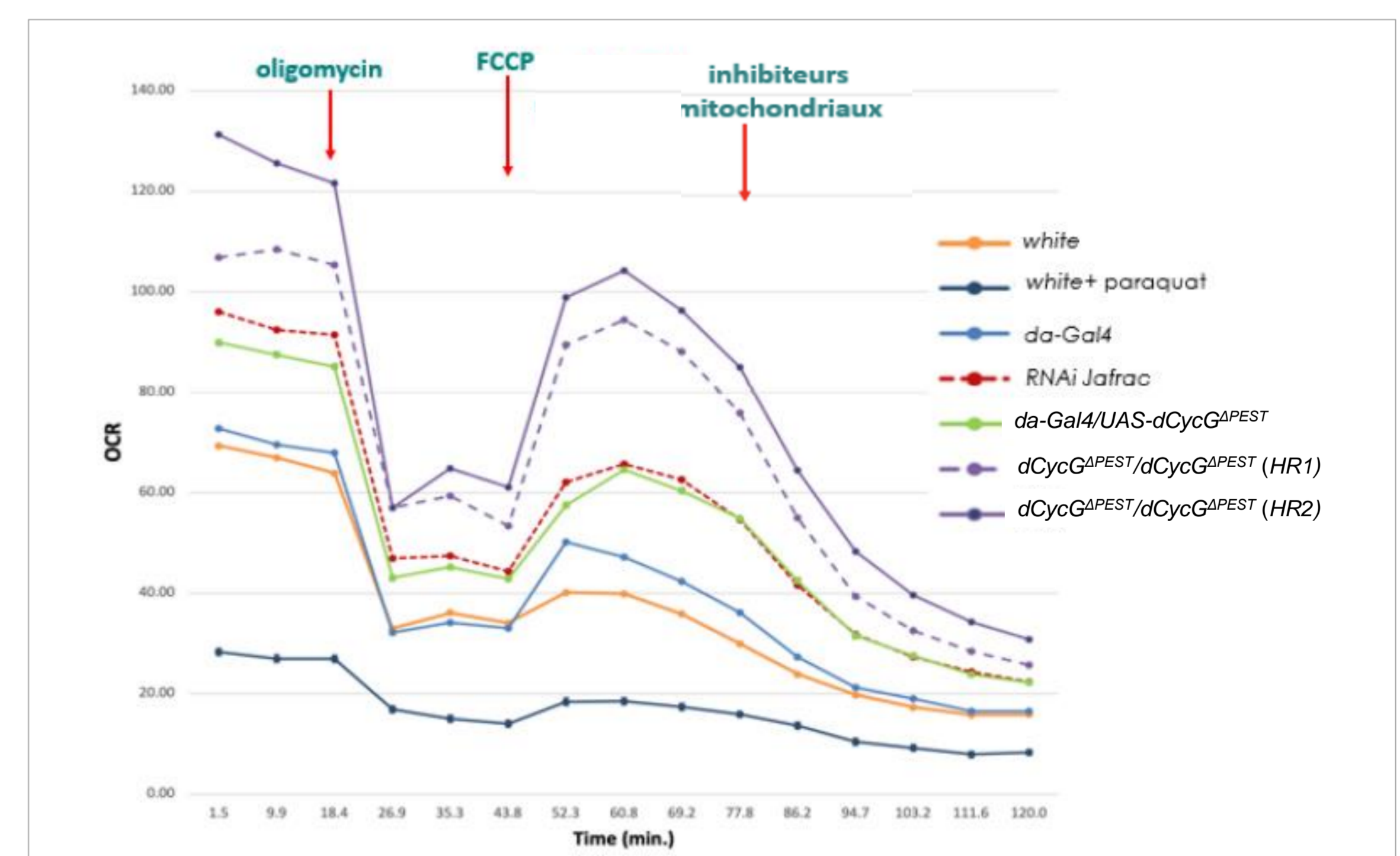
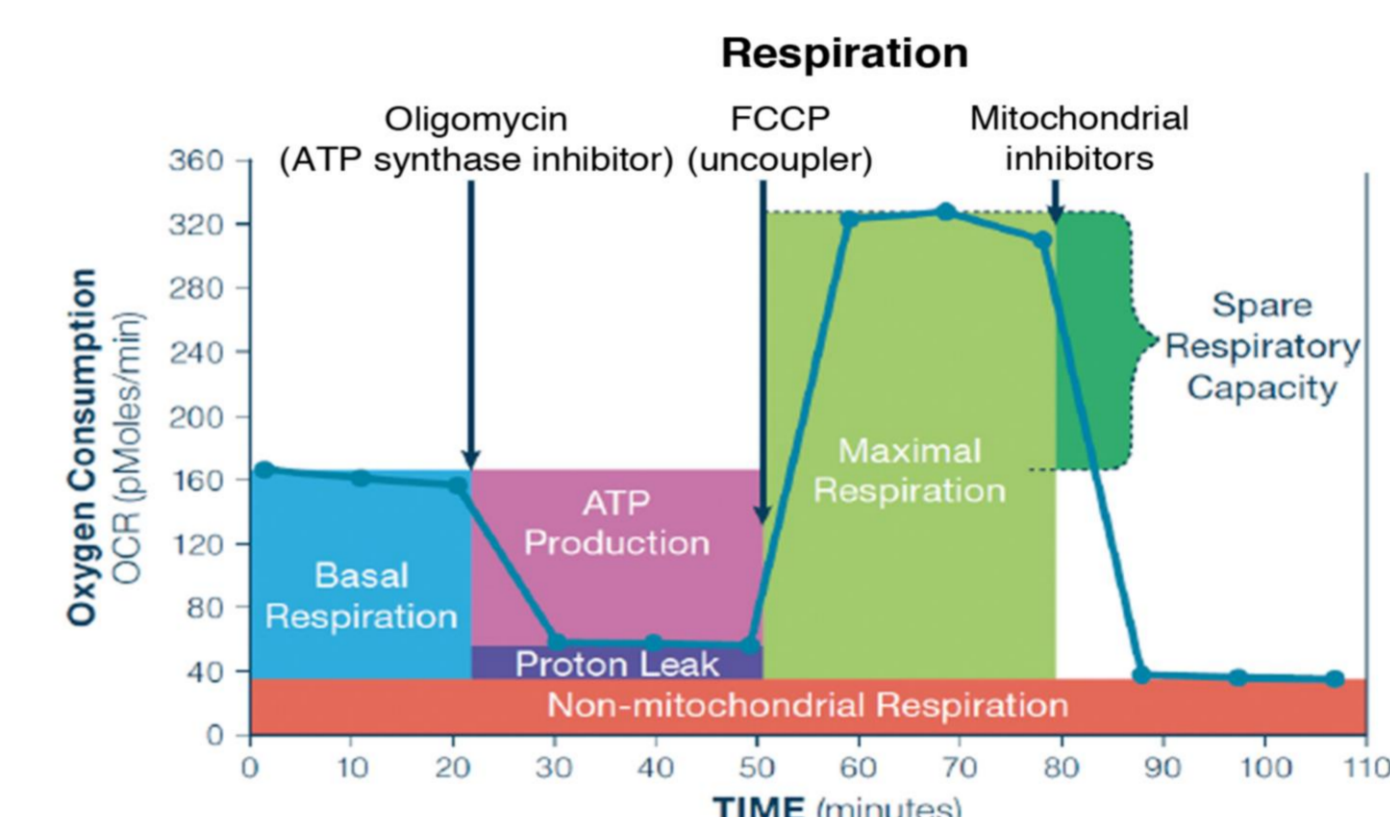


<i>UQCRC-Q</i>	mitochondrial respiratory chain complex III
<i>COX8B</i>	mitochondrial respiratory chain complex IV
<i>Jafracl1</i>	proton transport
<i>ATPsynf</i>	translation at the mitochondrial membrane
<i>larp</i>	translation at the mitochondrial membrane



Higher respiration in flies expressing dCycG deleted of the PEST domain

Seahorse



Ongoing projects

- Is dCycG ubiquitinated/deubiquitinated during the cell cycle? and if so, are PRC1 and PR-DUB involved in this process?
- Binding of dCycG to mitochondrial gene promoters during the cell cycle (Cut&Run experiments on flow cytometry sorted cells): Is dCycG involved in mitosis bookmarking of these genes?
- Amount of reactive oxygen species in wing imaginal discs : are ROS a causal factor in developmental noise ?

References

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