



Cyclin G deregulation, a tool to decipher gene network(s) controlling developmental stability

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Delphine Dardalhon-Cumenal, Camille Dupont, Valérie Ribeiro, Vincent Debat, Neel B Randsholt, et al.. Cyclin G deregulation, a tool to decipher gene network(s) controlling developmental stability. Société Française de Génétique Colloque annuel, Apr 2013, Paris, France. hal-03564702

HAL Id: hal-03564702

<https://hal.science/hal-03564702>

Submitted on 10 Feb 2022

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Cyclin G deregulation, a tool to decipher gene network(s) controlling developmental stability

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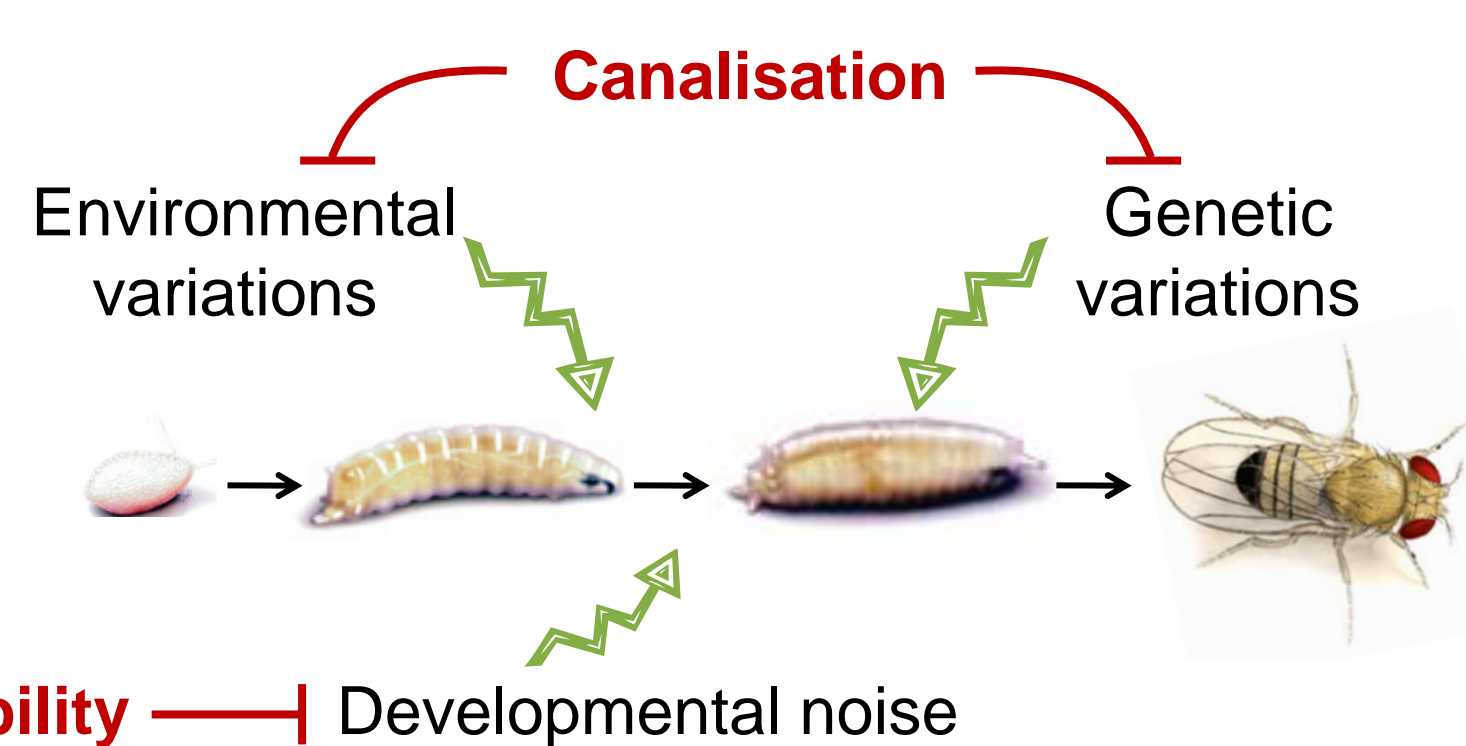
Abstract

Developmental stability, or the buffering of developmental noise, is of paramount importance to maintain symmetry in bilaterians. Noisiness of growth can cause noisiness in organ size, which translates into imperfect symmetry. In an isogenic population bred in a standardized environment, developmental stability can be estimated by fluctuating asymmetry (FA), the random deviation from perfect symmetry. However, addressing the cellular and genetic bases of developmental stability has long been impeded by the very low amplitude of FA in control *Drosophila* lines. We have recently shown that overexpression of the *Cyclin G* gene (*CycG*) induces extremely high FA in different organs of the fly (up to 40-fold increase in wings). This suggests that *CycG* might be a hub in a gene network underlying developmental stability. Deregulation of *CycG* thus provides a unique tool to decipher such a network [1,2].

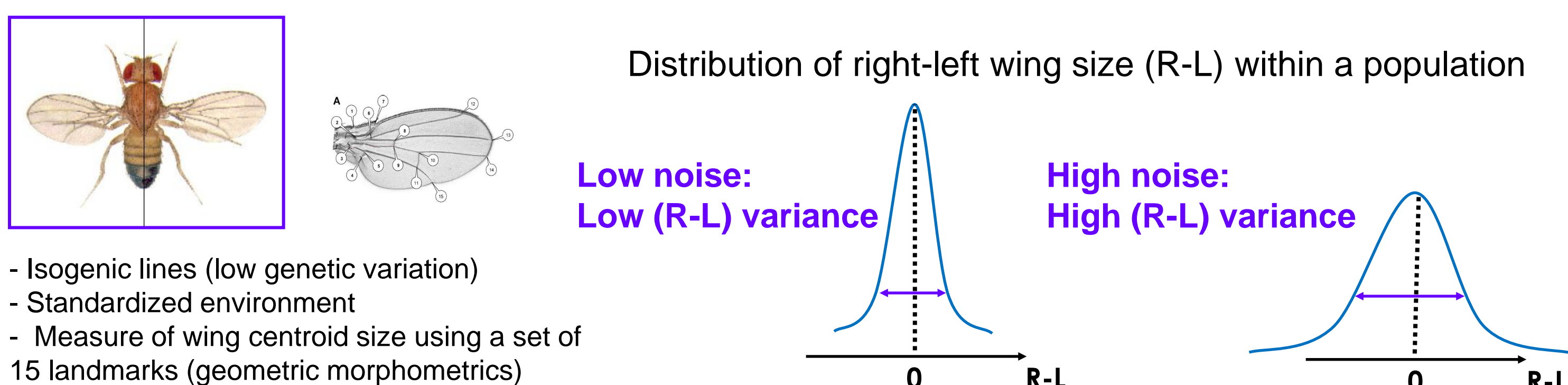
Cyclin G binds two chromatin regulators of the Enhancers of Polycomb and Trithorax (ETP) family *via* its ETP-interacting domain, and is involved in transcriptional control [3]. Moreover, Cyclin G negatively controls the cell cycle by slowing down the G1 and S phases, and directly interacts with CDK2 and CDK4 [4]. Lastly, *CycG* deregulation impairs the tight correlation that normally exists between cell size and cell number in fly wings [1]. Based on these features, we are addressing the molecular and genetic bases of developmental stability. First, we are analyzing wing FA and cell parameters in flies overexpressing truncated forms of *CycG* (deleted of either the ETP-interacting domain or the cyclin domain). Second, we are identifying Cyclin G transcriptional targets by RNA-seq. Third, we are carrying out a candidate gene approach (using mutants for Cyclin G interactors, transcriptional targets *etc.*) to isolate modifiers of the *CycG*-induced FA phenotype. These

I - Developmental stability and fluctuating asymmetry

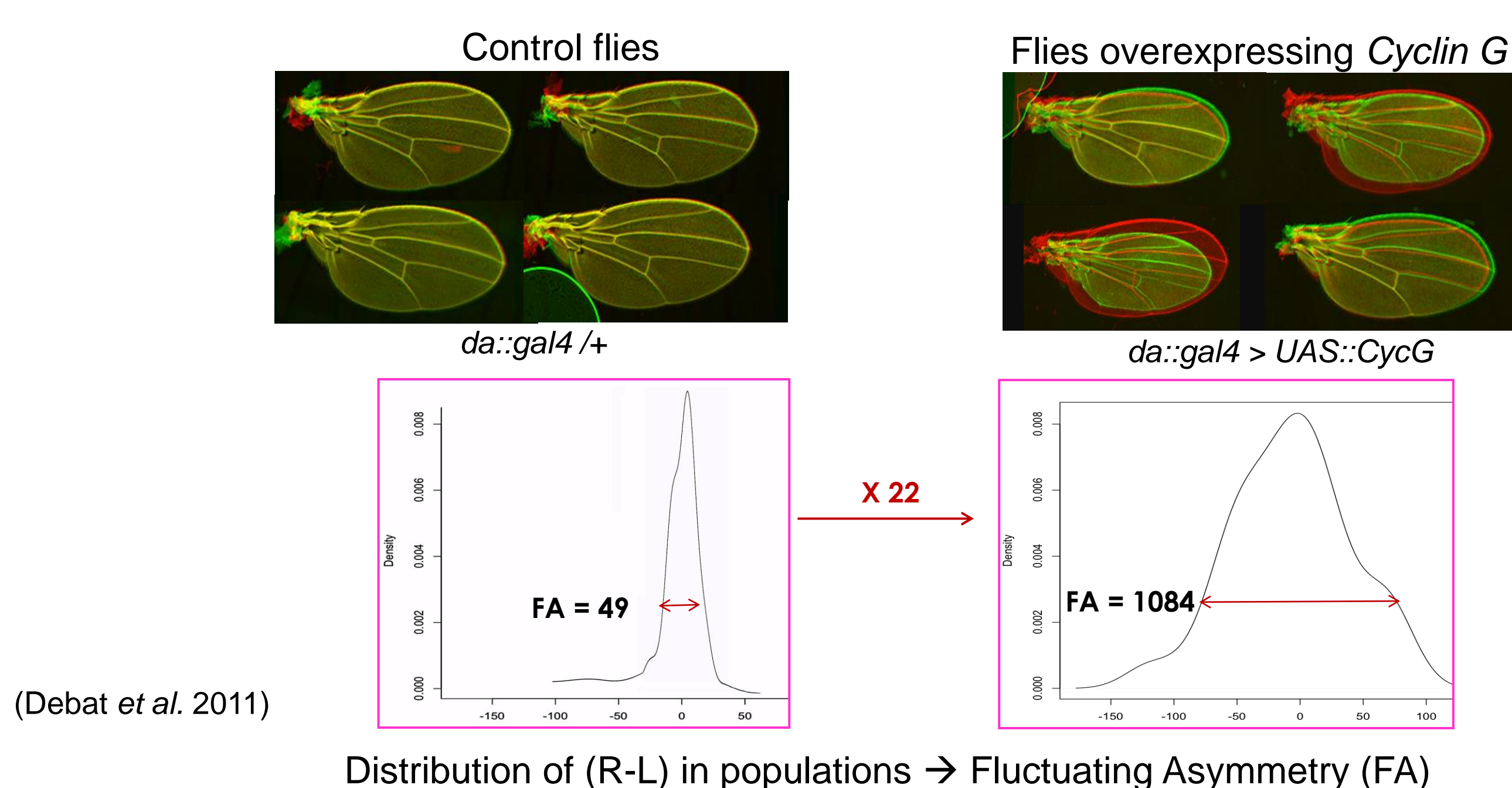
- Developmental robustness buffers different sources of variation



- Developmental noise is measured by fluctuating asymmetry (FA)



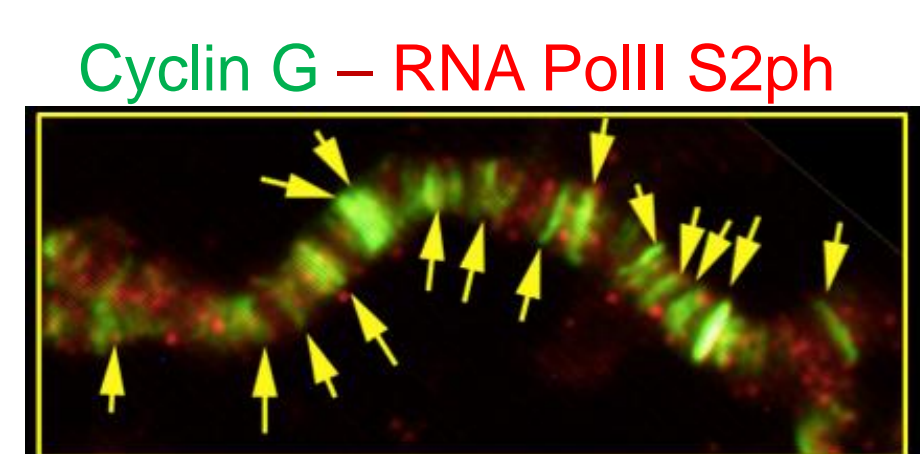
II - CycG misregulation increases developmental noise



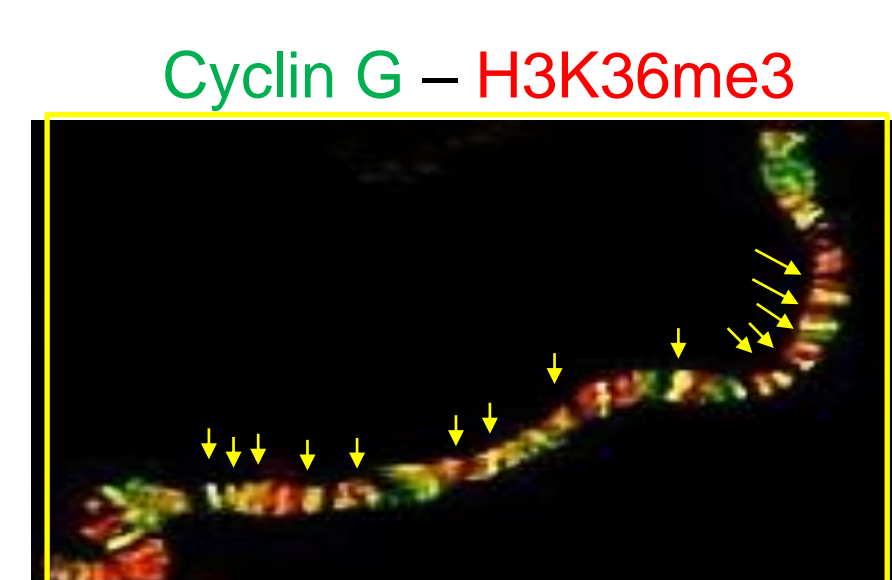
III - Cyclin G is a transcriptional regulator

- Cyclin G maintains *Abd-B* expression (Salvaing *et al.*, 2008)
- Cyclin G directly interacts with the Enhancers of Trithorax and Polycomb (ETP) Corto and ASX (Salvaing *et al.*, 2008; Dupont *et al.*, in preparation)

- Cyclin G co-localizes at many sites with RNA Pol II on polytene chromosomes



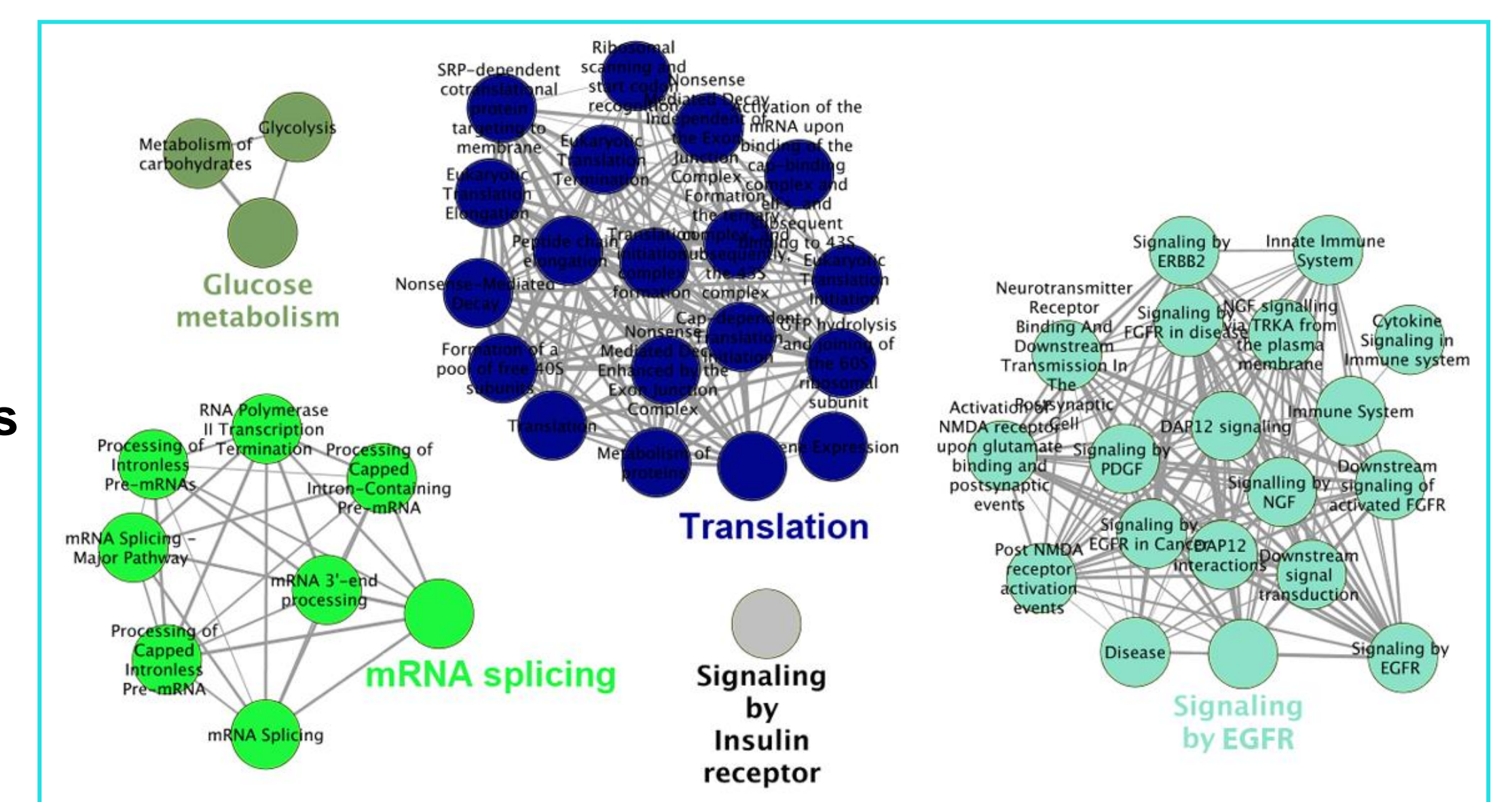
- Cyclin G co-localizes at many sites with H3K4me3 and H3K36me3 (activation marks) on polytene chromosomes



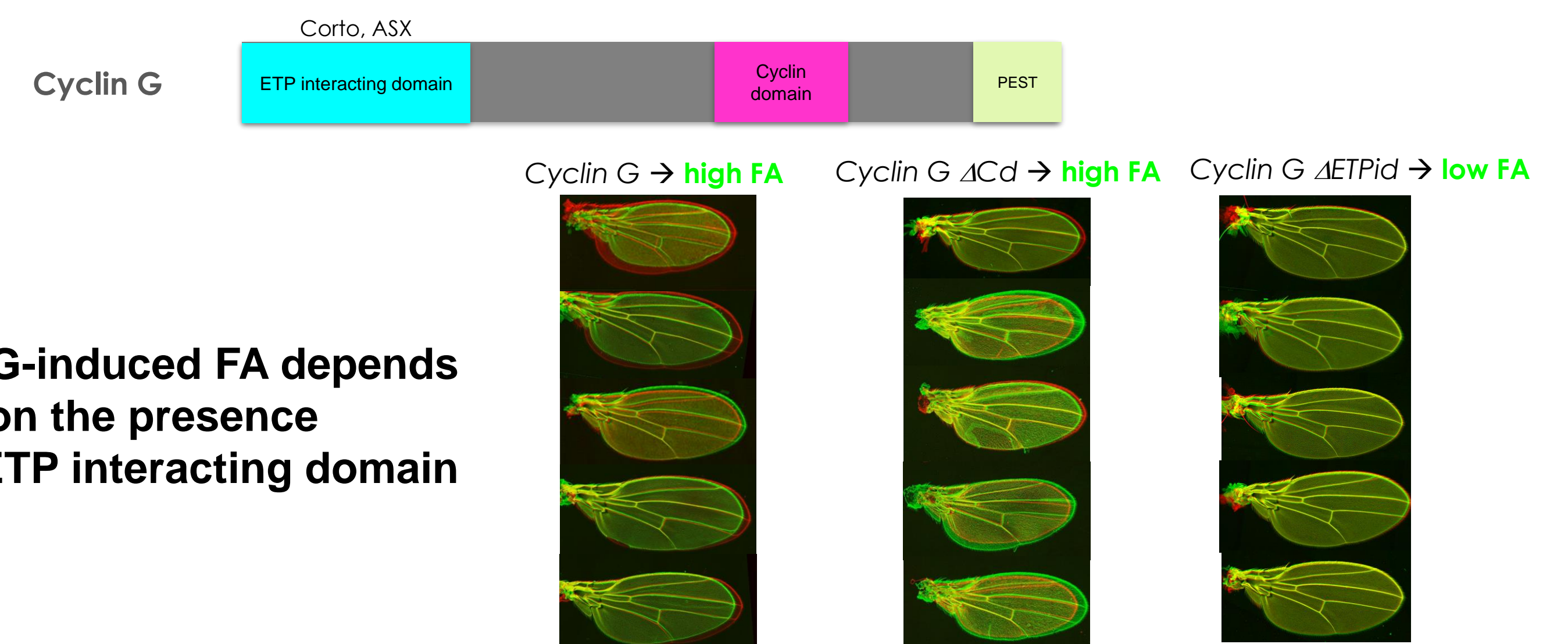
IV – RNA-seq of wing imaginal discs overexpressing CycG

RNAseq analysis of wing imaginal discs overexpressing *Cyc G* reveals a sub-network of 189 deregulated genes potentially involved in developmental stability

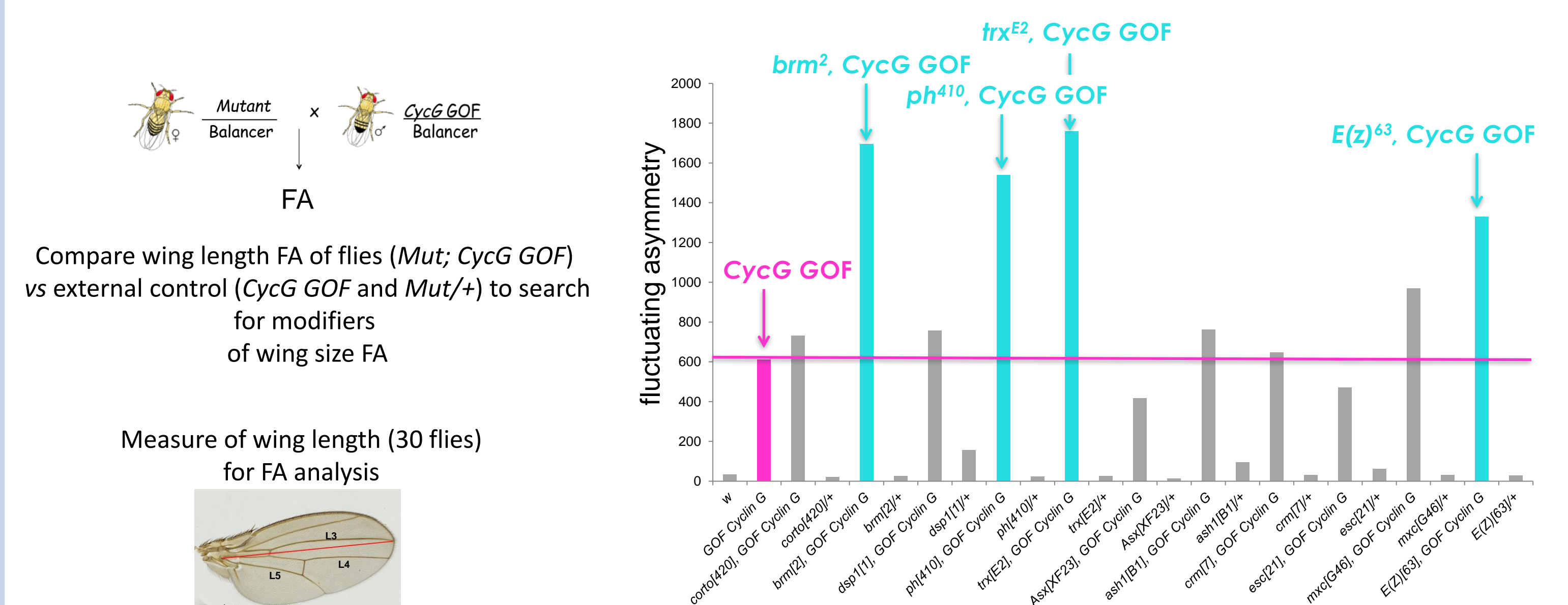
Ontology of co-deregulated genes (mRNA splicing, translation, EGFR and insulin signaling, glucose metabolism)



V - The effect of Cyclin G on developmental noise is related to its role in transcription



VI - Several epigenetic regulators interact with CycG in developmental stability



VII- Ongoing projects and Future investigations

- Determine genome-wide binding sites of Cyclin G (ChIP-Seq), to identify direct transcriptional targets by correlation with RNA-seq
- Continue the candidate gene approach (gene encoding direct interactors, genes involved in epigenetic memory, control of transcriptional elongation, growth pathways, cell competition)
- Building of gene regulatory networks that control developmental stability

References

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