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Cyclin G, Transcriptional Control and Developmental Stability

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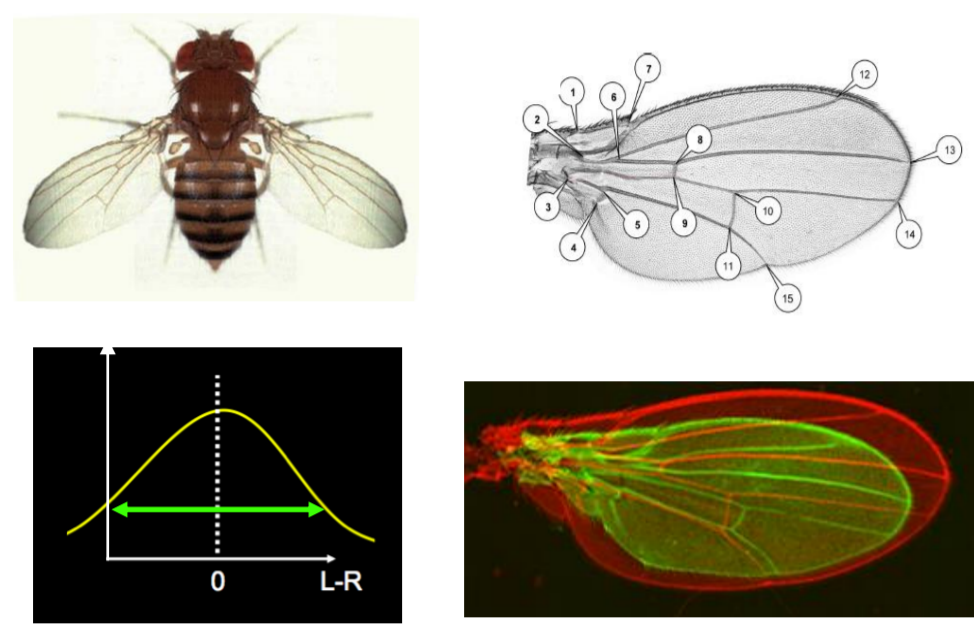
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A central challenge in developmental and evolutionary biology is to understand developmental stability, the process that buffers developmental noise. We recently reported that an individual gene, *Cyclin G* (*CycG*), encoding a cyclin involved in the regulation of transcription and in the cell cycle, plays a central role in developmental stability in *Drosophila* (Debat et al., 2011; Debat and Peronnet, 2013). Indeed, overexpression of *CycG* induces an unprecedented increase in developmental noise.

Using *CycG* overexpression as a tool, we aim to investigate the role of *CycG* in transcription and at highlighting gene networks underlying developmental stability. Our data show that Cyclin G interacts with Polycomb and Trithorax factors as well as with components of the spliceosome. Furthermore, several mutations of both Polycomb/Trithorax members and components of the spliceosome increase *CycG*-induced developmental noise. To understand more precisely the role of Cyclin G in transcription and in developmental stability control, we develop two projects : The first one, identify transcriptional targets of cyclin G by RNA-seq and CHIP-seq. the second one, the Cyclin G involvement in alternative splicing.

I - Cyclin G

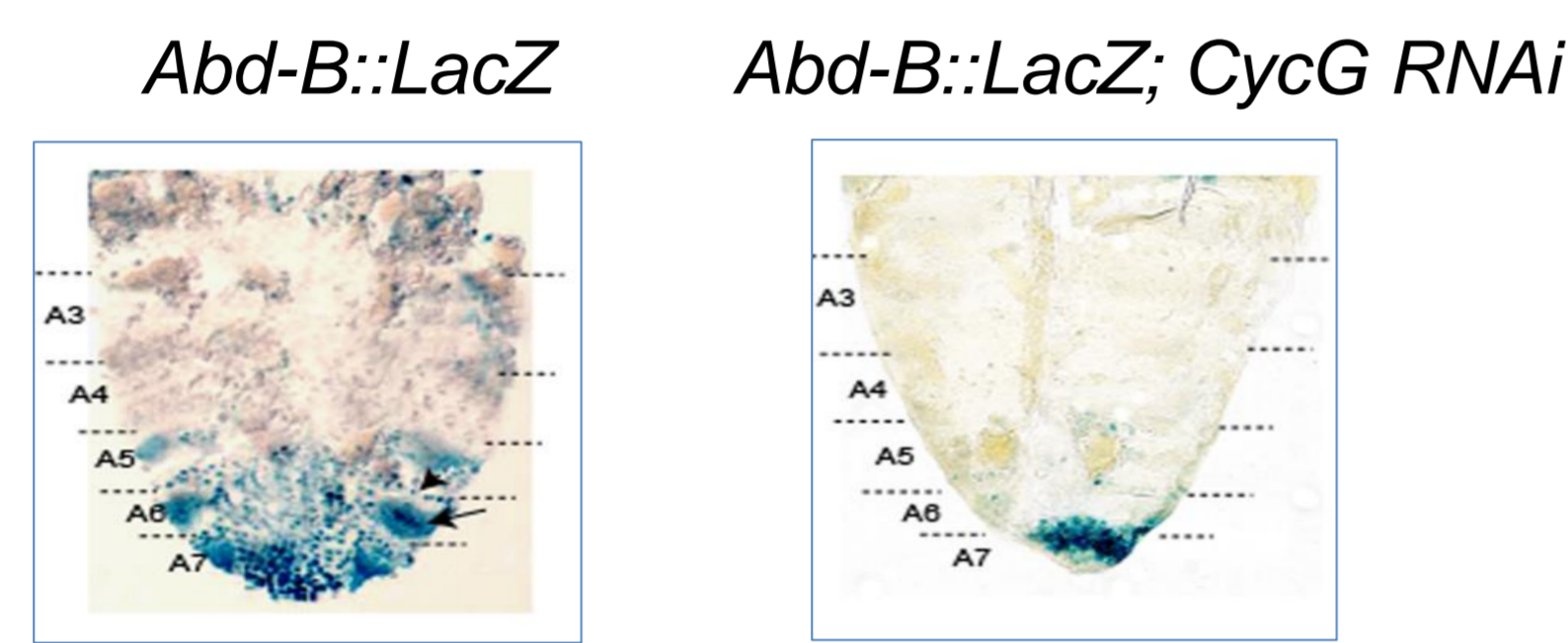


- At low environmental and genetic variations, fluctuating asymmetry is a measure of developmental stability.
- The difference between left and right wing sizes in *da::Gal4>UAS::CyclinG^{ΔPEST}* isogenic siblings follows a normal curve centered on zero: this population presents high fluctuating asymmetry (FA).

da::Gal4>UAS::CyclinG^{ΔPEST}

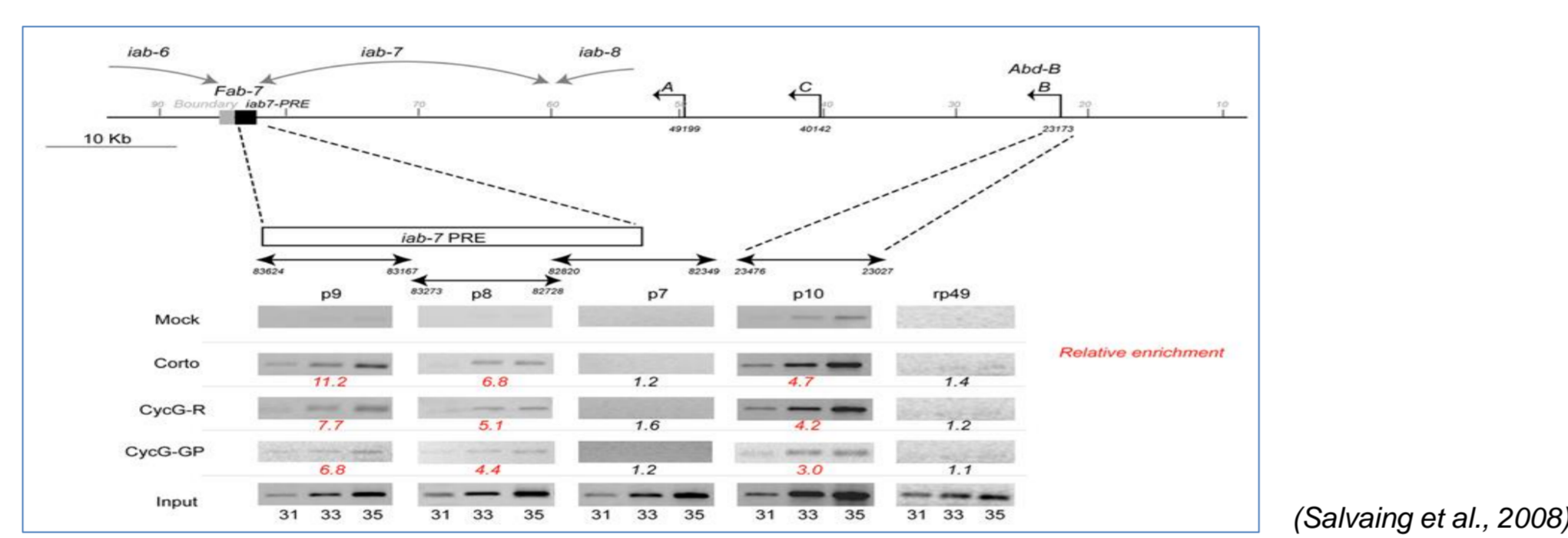
II - Cyclin G regulates *Abd-B* expression

- Expression of *Abd-B* in the abdominal epithelium of pupae



- Cyclin G binds the *cis*-regulatory sequences and the promoter of *Abd-B*

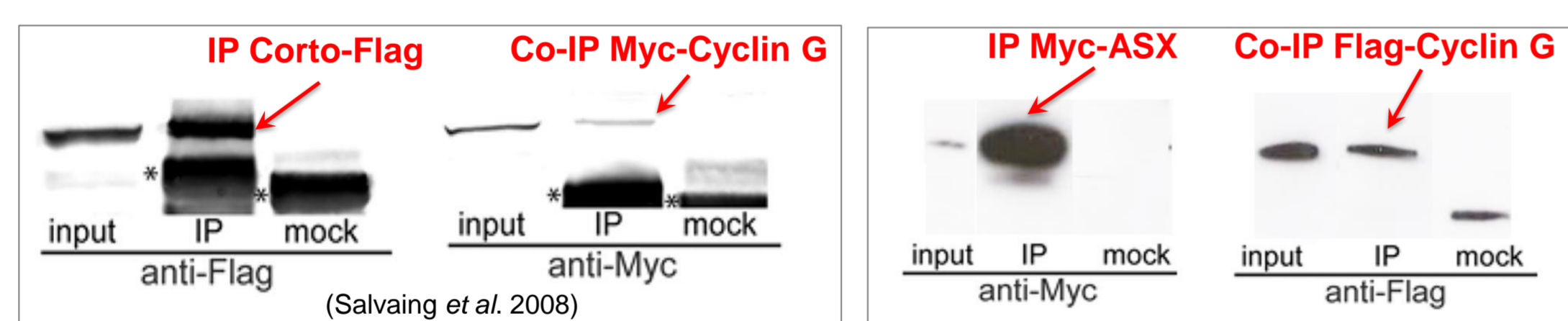
Chromatin Immunoprecipitation (ChIP)



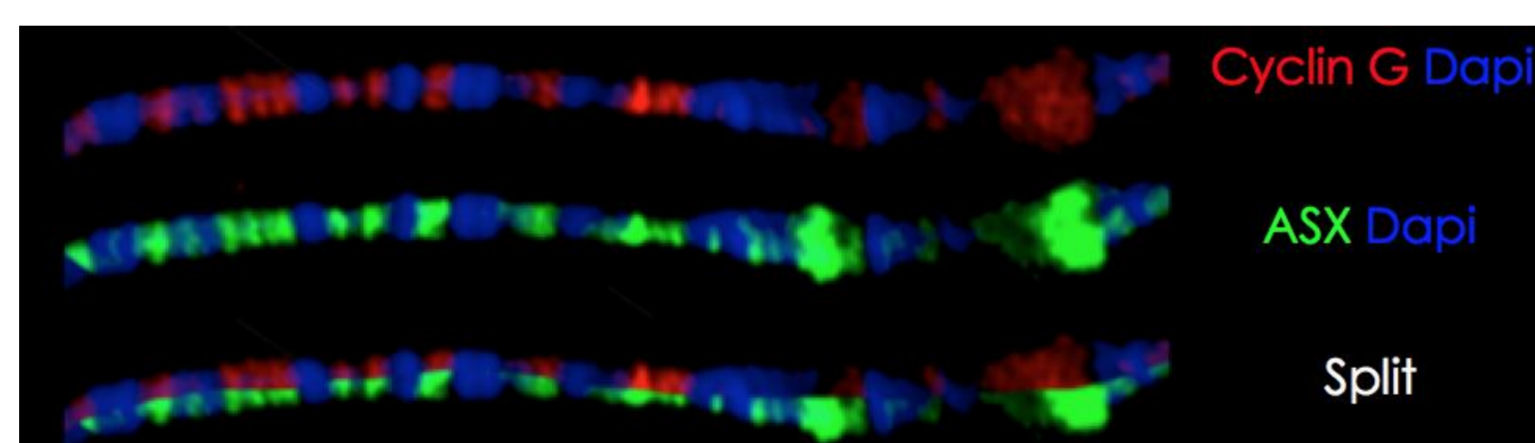
(Salvaing et al., 2008)

III - Cyclin G interacts with Polycomb and Trithorax factors

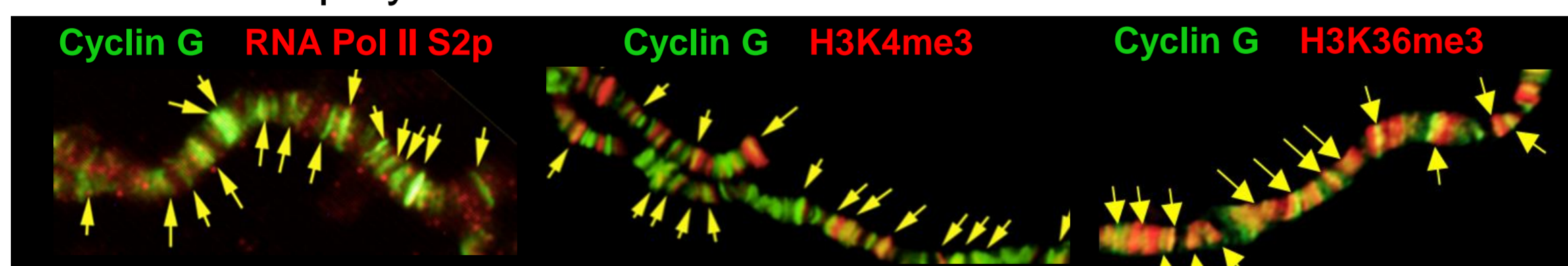
- Cyclin G directly interacts with two chromatin regulators of the Enhancers of Trithorax and Polycomb family (Corto, ASX).



- Cyclin G binds polytene chromosomes where it extensively co-localizes with ASX



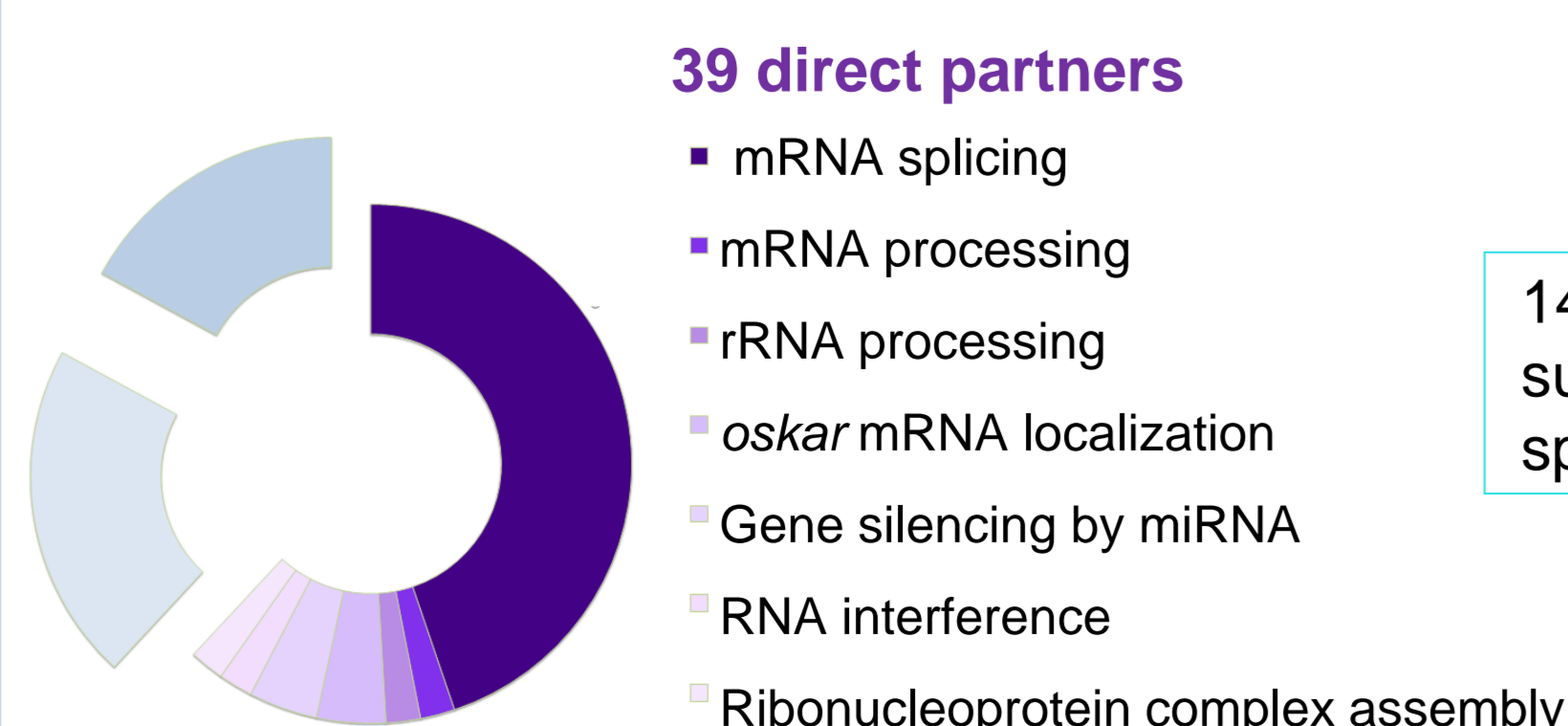
- Cyclin G co-localizes at many sites with RNA Pol II, and with the active marks H3K4me3 and H3K36me3 on polytene chromosomes.



CyclinG might be involved in transcriptional elongation

IV - Cyclin G interacts with components of the spliceosome

Direct partners of Cyclin G identified by pull-down and mass spectrometry (*Drosophila* Protein Interaction Map; interfly.med.harvard.edu)

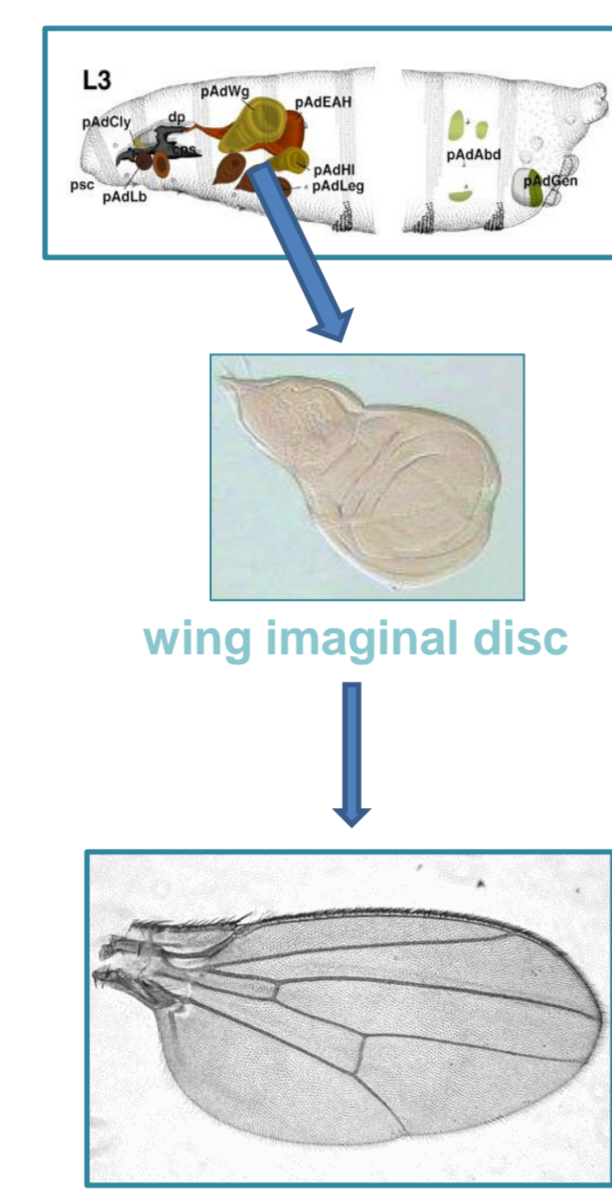


14 of these partners are involved in mRNA splicing, suggesting that Cyclin G might interact with the spliceosome.

Is the role of cyclin G in developmental stability related to its role in transcriptional regulation?
Is developmental noise resulting from global disruption of mRNA splicing via CyclinG?

V - Analysis of *Cyclin G* transcriptional targets (RNA-Seq)

RNA-seq of wing imaginal discs in which Cyclin G is deregulated

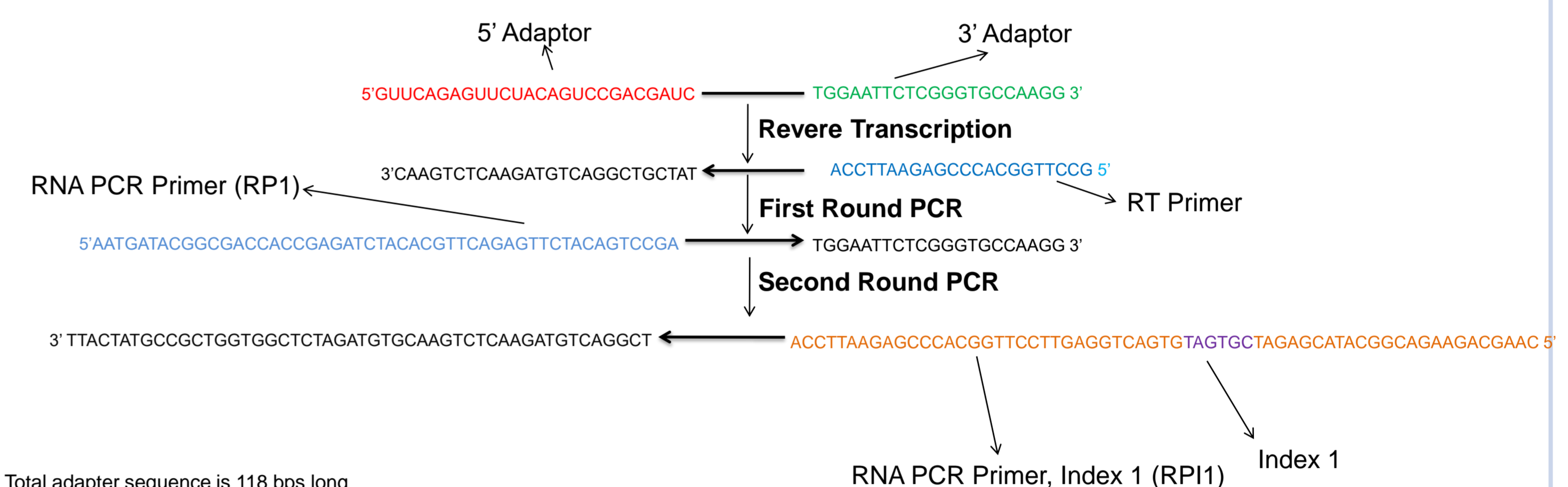


driver scalloped	<i>sd::Gal4>UAS::CyclinG^{ΔPEST}</i>	Cyclin G gain of function	X 2
	<i>sd::Gal4/wnv</i>	control	X 2
	<i>sd::Gal4>RNAiCycG3</i>	RNAi CycG	X 2
driver daughterless	<i>da::Gal4>UAS::CyclinG^{ΔPEST}</i>	Cyclin G gain of function	X 3
	<i>da::Gal4/wnv</i>	control	X 3

Expression driver: *sd Gal4* × *da Gal4*: ubiquitous

ENS genomic plateforme (S. Le Crom)
sequencer: Illumina HiSeq 1000
experimental information: PolyA (RT), Single-End read, Oriented, length reads: 50pb

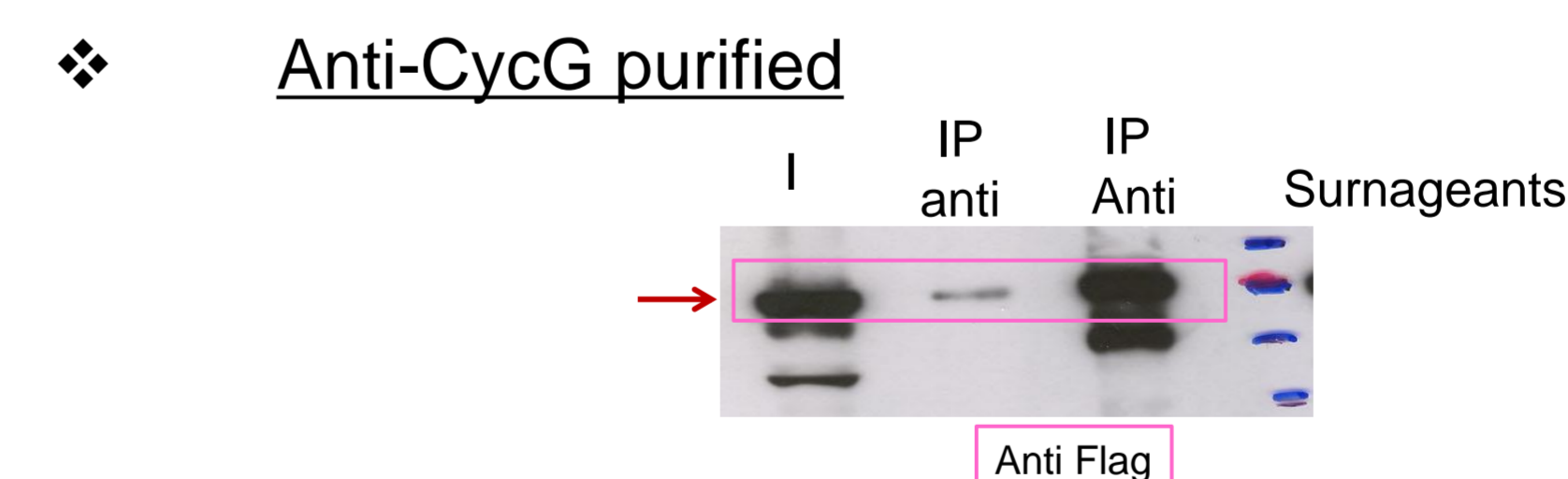
Adaptor illustration for Truseq small RNA Sample Pre



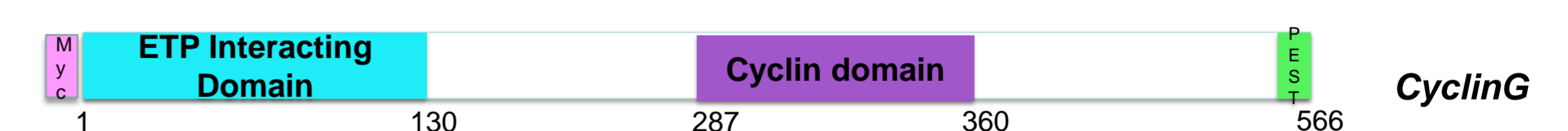
Sample name	Description	Reads	Filtered reads	Alignments	Unmap reads	Reads with multiple alignments	Reads with unique alignment	Reads used for expression
2013_0333	<i>sd::Gal4>RCG76-1</i>	41874452	38087401	50706148	2371828	25237494	23096826	22373671
2013_0334	<i>sd::Gal4>RCG76-2</i>	40533326	37679265	46907856	2625762	18457182	25824912	25067211
2013_0335	<i>sd::Gal4>RNAiCycG3-1</i>	41860928	38169640	47506876	2796805	18674472	26035599	25185942
2013_0336	<i>sd::Gal4>RNAiCycG3-2</i>	38311593	34388807	42047835	2564506	15318056	24165273	23387562
2013_0337	<i>sd::Gal4/wnv-1</i>	41584205	37182626	46006156	2656414	17647060	25702682	24811053
2013_0338	<i>sd::Gal4/wnv-2</i>	32087565	29456407	36187167	2120232	13461520	20605415	19965569
2013_0339	<i>da>RCG76-1</i>	31215180	29044092	32118945	2318058	6149706	23651181	23046534
2013_0340	<i>da>RCG76-2</i>	36051720	33712754	45308733	2116858	23191958	19999917	19308828
2013_0341	<i>da>RCG76-3</i>	37581632	34042979	40807620	2531374	13529282	24746964	23965786
2013_0342	<i>da::Gal4/wnv-1</i>	41841815	37569578	45248737	3210933	15358318	26679486	25837134
2013_0343	<i>da::Gal4/wnv-2</i>	45170847	40869061	43438167	3484699	5138212	34815256	33961840
2013_0344	<i>da::Gal4/wnv-3</i>	36799853	34016644	41249793	2498754	14466298	24284741	23536471

VI - Analysis of *Cyclin G* transcriptional targets (CHIP-Seq)

- Determine genome-wide binding sites of Cyclin G (Chip-Seq)



Anti-Myc tag antibody- ChIP Grade



sd::Gal4>UAS::mycCyclinG^{ΔPEST}

sd::Gal4>UAS::mycCyclinG^{FL}

- Identification of its direct transcriptional targets by correlation with RNA-seq

projects

- Analyze alternative transcripts in *CycG* overexpressing flies.
- Test the role of genes belonging to the identified sub-network in developmental stability.

References

Debat, V., Bloyer, S., Faradji, F., Gidaszewski, N., Navarro, N., Orozco-Terwengel, P., Ribeiro, V., Schlotterer, C., Deutsch, J.S., and Peronnet, F. (2011). Developmental Stability: A Major Role for Cyclin G in *Drosophila melanogaster*. *PLoS Genet* 7, e1002314.

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Salvaing, J., Nagel, A.C., Mouchel-Vielh, E., Bloyer, S., Maier, D., Preiss, A., and Peronnet, F. (2008). The Enhancer of Trithorax and Polycomb Corto interacts with Cyclin G in *Drosophila*. *PLoS One* 3, e1658.