

Using gene expression level as complex traits: *cis*- and *trans*- regulatory effects

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What is the role of non coding DNA?

Jacob and Monod (1961): “the proper function of every gene depends on 2 distinct components: what is produced and the circumstances under which it is produced”

Britten and Davidson (1971): repetitive sequences regulate transcription and play a crucial role in evolution.

King and Wilson (1975) Human and Chimps diverge only by 1.6% in DNA, but don't look or act alike.



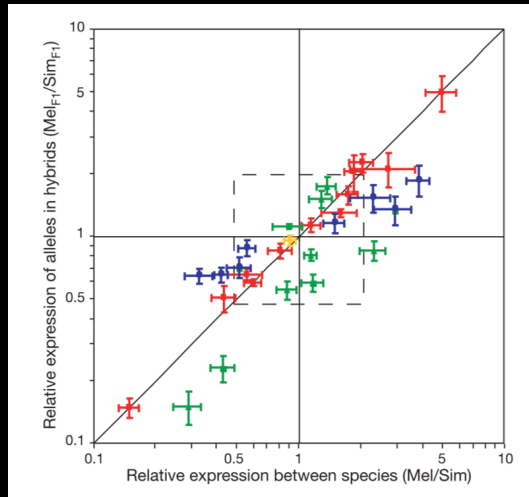
Contribution of *cis*- and *trans*-effects in phenotypic evolution



- 2 scales of studies : within and between species
- eQTL mapping and genetical genomics

The relative contribution of effects

- *cis* regulatory changes contribute to interspecific expression differences (Wittkopp, 2004 & 2007)



- *trans* regulatory changes in yeast (Brem and Kruglyak, 2002)

Two models were tested in *Drosophila melanogaster* (Genissel et al 2008)

Is transcriptional variation highly polygenic and epistatic?

- Infinitesimal model among offspring
 - *cis* effect is the allele at the gene
 - *trans* effect is '*Ore fraction*' in the background

Does transcriptional variation depend on a few regulatory effects of large magnitude?

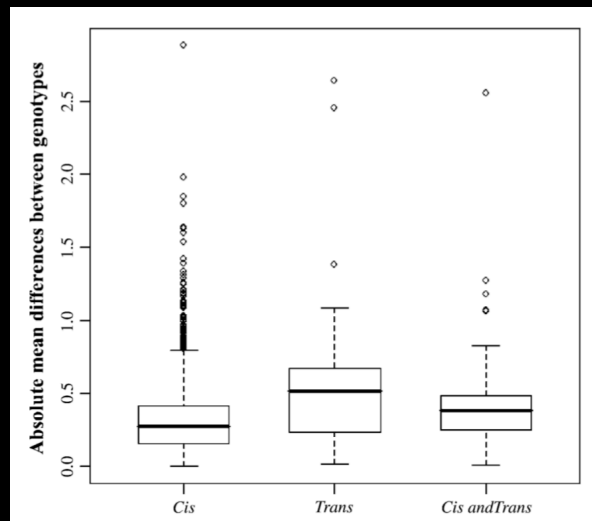
- Contrast models compare transcriptional variation among offspring and between offspring and parents.

Cis effects are major contributors

<i>oOre</i> versus <i>o2b</i>	<i>pOre</i> versus <i>oOre</i>	<i>p2b</i> versus <i>o2b</i>	Regulatory Effects	Simple Model ^b	Nested Model ^b
NS	NS	NS	Unknown	3,087(2,701)	2,340(2,055)
***	NS	NS	<i>Cis</i>	571(545)	1,225(1,154)
NS	***	NS	<i>Trans</i>	1	25
NS	NS	***		11	16
NS	***	***		0	0
***	***	NS	<i>Cis and trans</i>	0	55(53)
***	NS	***		14	23
***	***	***		1	1

10% of differential
expression

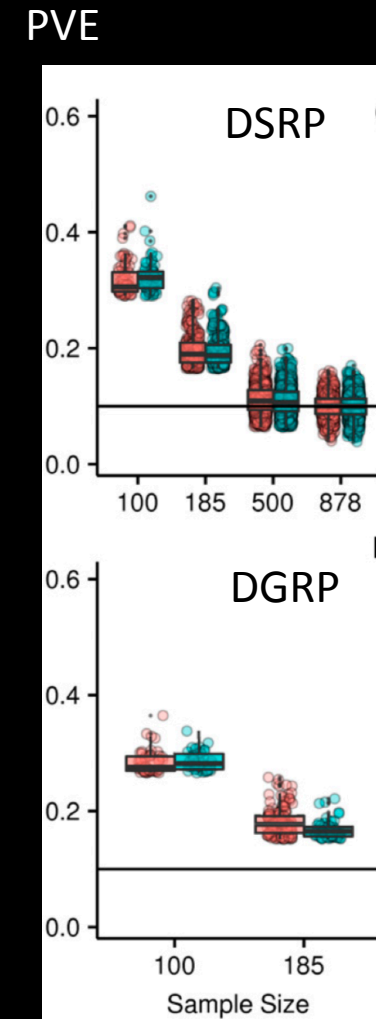
90% of *cis*-effects



Larger phenotypic effect
in *trans*?

Not so easy to detect the effects

- More eQTL near genes because it is easier to detect? if larger phenotypic effects, if *trans* depends on several interactions and more mutations
- Beavis effect in eQTL mapping (Xu, 2003) : overestimation of effects (100, 500, 1000 progenies)



King and Long, 2017

Reconcile with DRGP eQTL? (Huang et al 2015)

- Introduce variance eQTL: 'veQTL' involved in epistatic interactions with *cis* variants

Sex	FDR threshold (<i>cis</i> + <i>trans</i>)*			
	0.05	0.10	0.15	0.20
Female	503 (263 + 240)	671 (287 + 384)	807 (297 + 510)	941 (308 + 633)
Male	837 (533 + 304)	1,029 (568 + 461)	1,189 (594 + 595)	1,339 (608 + 731)

*Number of genes with at least one *cis*-eQTL (within 1 kb of genes) and number of genes with only *trans*-eQTLs.

Sex	FDR threshold (<i>cis</i> + <i>trans</i>)*			
	0.05	0.10	0.15	0.20
Female	319 (6 + 313)	544 (8 + 536)	743 (9 + 734)	925 (9 + 916)
Male	162 (3 + 159)	247 (6 + 241)	353 (7 + 436)	412 (7 + 405)

*Number of genes with at least one *cis*-veQTL (within 1 kb of genes) and number of genes with only *trans*-veQTLs.

Conclusion on Allele Specific Expression (ASE)

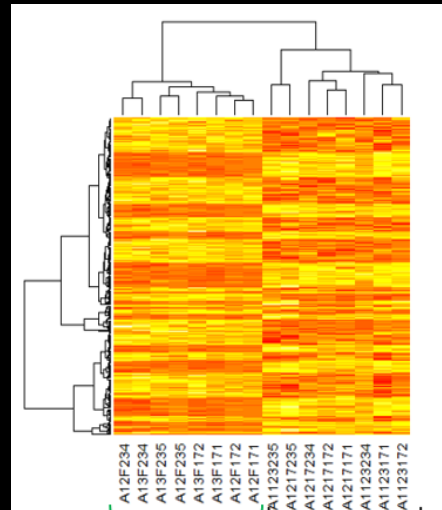
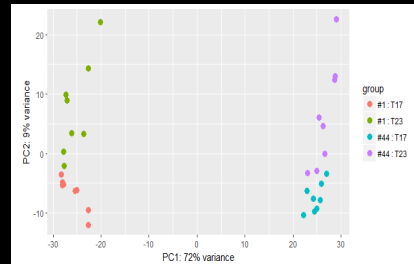
- Need for large scale studies : genome-wide expression profile and known genetic variation
- Mode and tempo of regulatory variation

Evolution of transcriptome after fluctuating temperature (PhD Arthur Jallet)

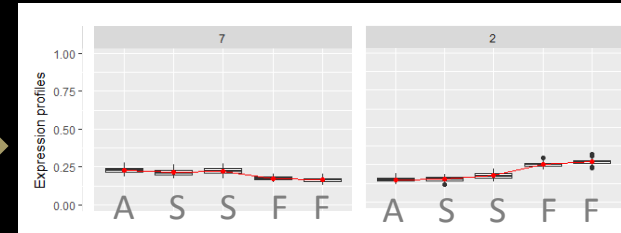
Fungi (clones)



Stable or
Fluctuating
temperature



- Transcriptome rewiring associated with fluctuations



- Fluctuation favors loss of gene expression plasticity
- Next: *cis* regulatory variation