

Heritable expression regulation in aging *C. elegans*.

Ana Viñuela



Ozzy Osbourne's Genetic Code Being Mapped

Scientists Trying to Figure Out How He Survived Decades of Drug, Alcohol Abuse

7:26am UK, Wednesday June 16, 2010

Elizabeth Scott, Sky News Online

Scientists are to map Ozzy Osbourne's genetic code in a bid to find out how he is still alive after decades of drug and alcohol abuse.



Ozzy, 61, has lived a life that would presumably kill any ordinary person.

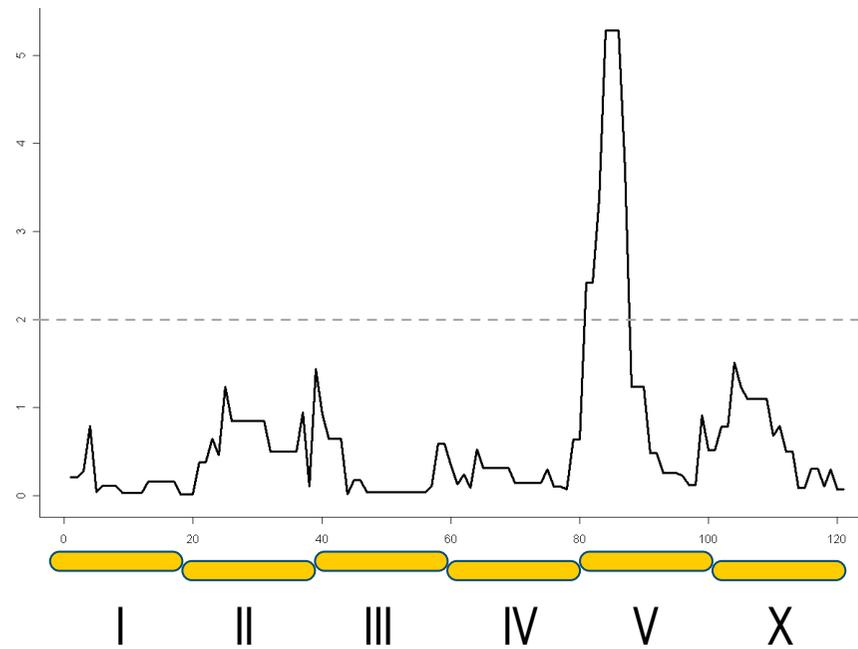
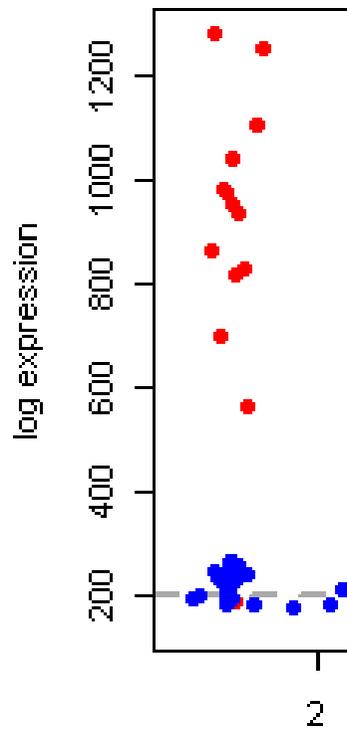
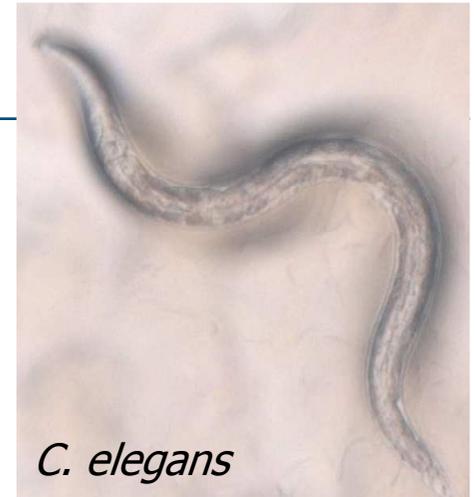
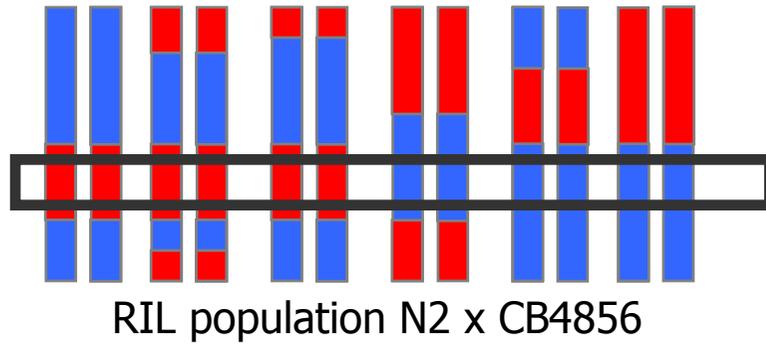
Even the singer himself cannot understand how he has survived this long, recently describing himself as a "medical miracle" after going on a "bender" for "40 years".

Aging

- **Aging is a complex process characterized by a decay of biological functions**
- **Gene expression changes with age in all the species studied**
- **Aging is assumed to be a consequence of lack of regulation on essential genes for survival (Lu, *et al.* 2004; McCarroll, *et al.* 2004)**

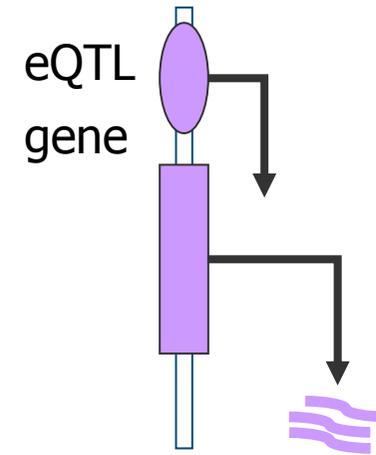
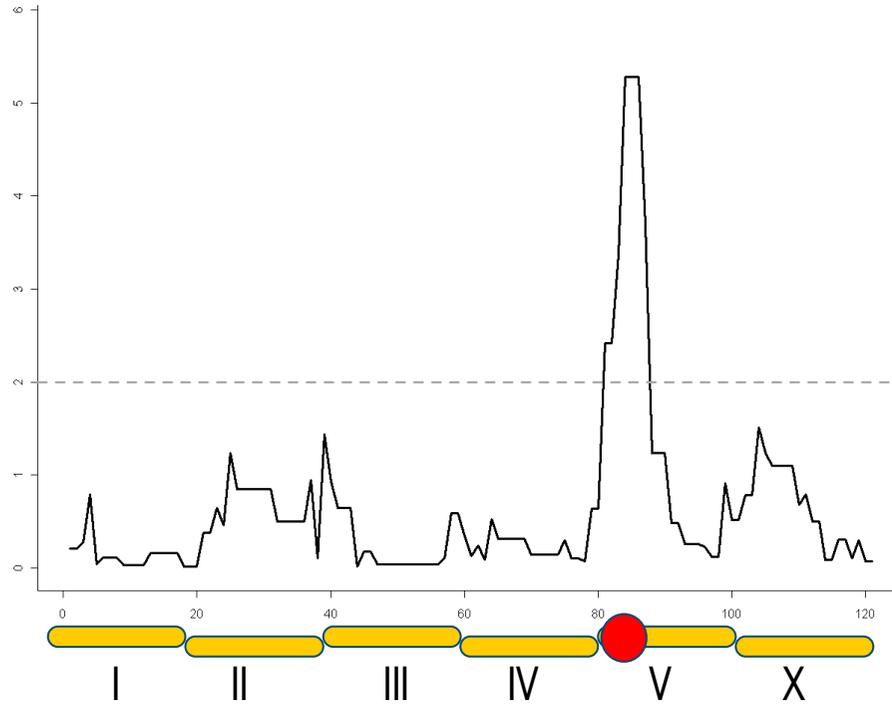
Gene expression regulation & Age

Mapping gene expression variation (eQTL)



eQTL (cis and trans)

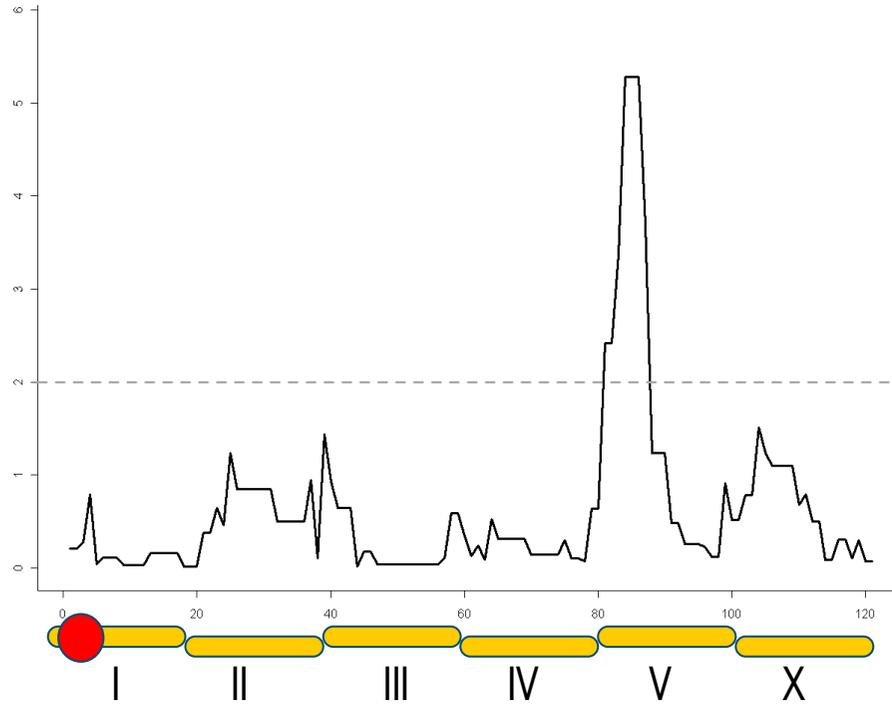
cis-acting eQTL



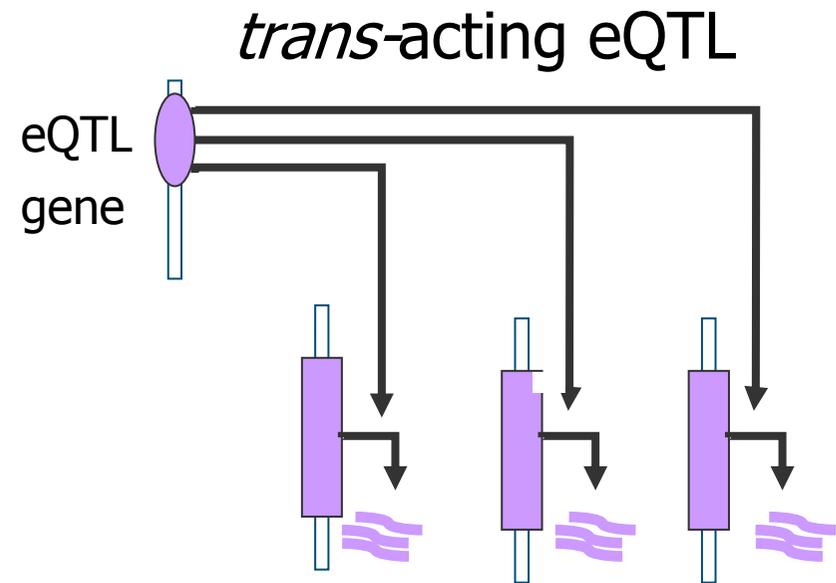
Allele a **ACTGG**GATCGTTCGA

Allele b **ACTGC**GATCGTTCGA

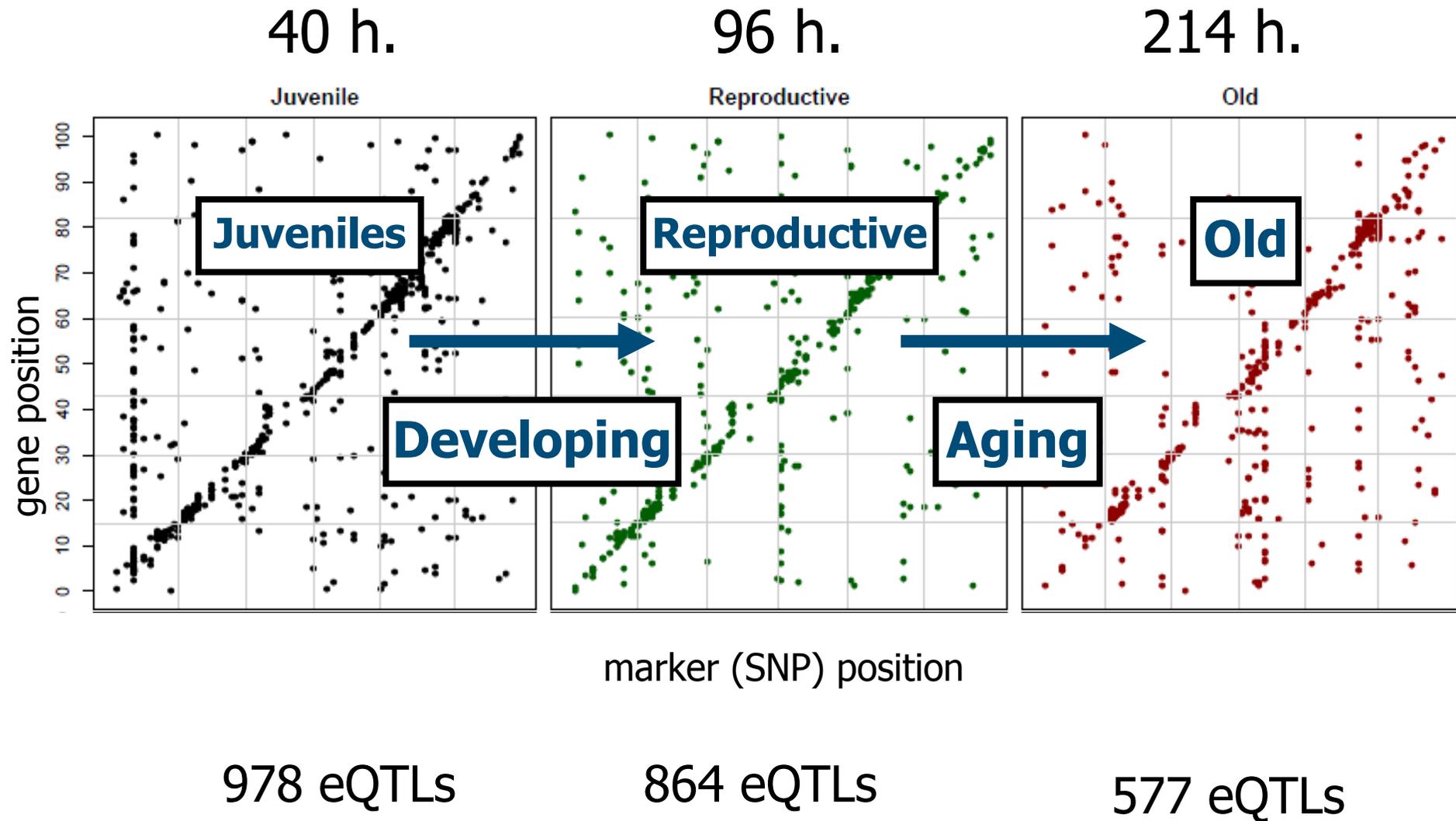
eQTL (cis and trans)



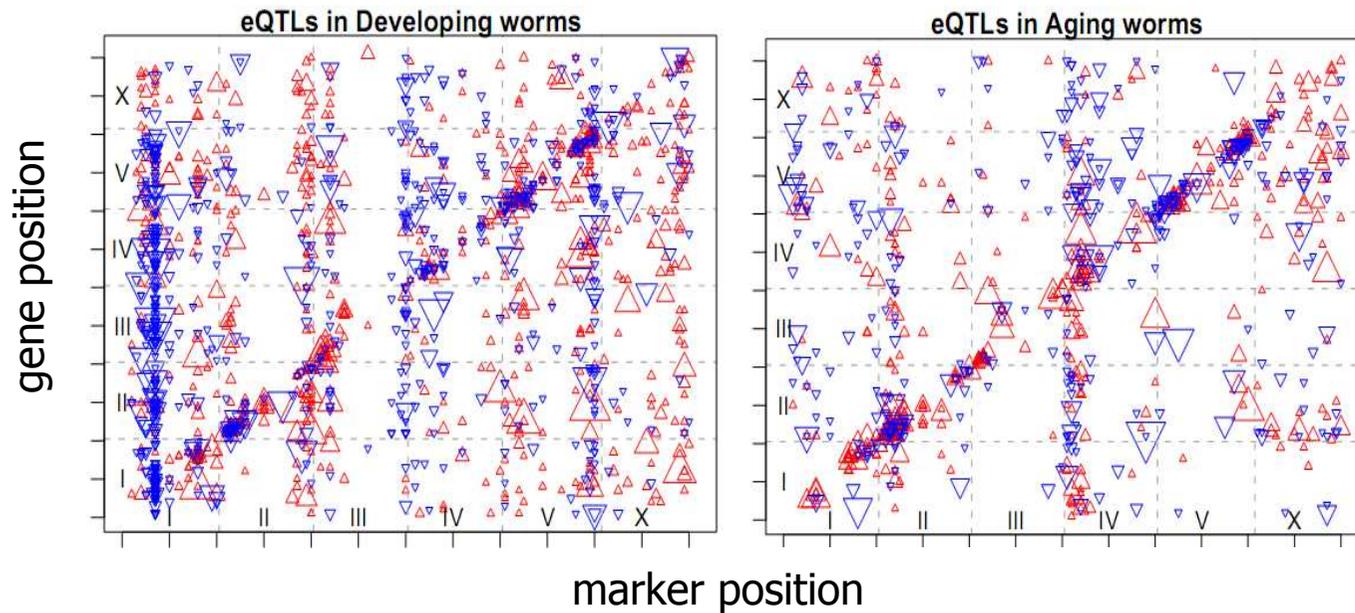
Allele a	ACTG G GATCGTTCGA
Allele b	ACTG C GATCGTTCGA



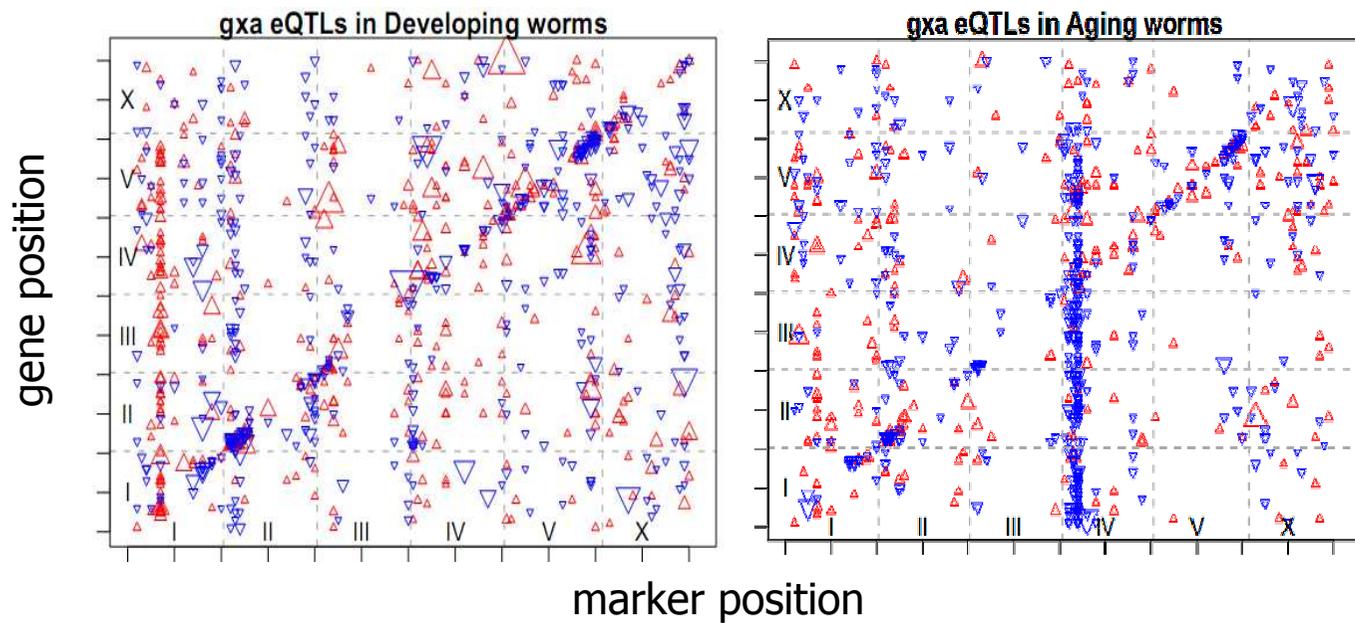
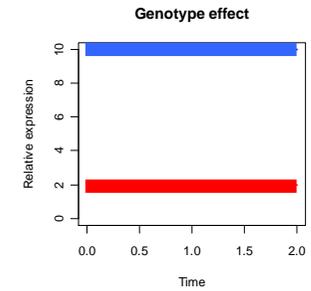
eQTLs at different ages



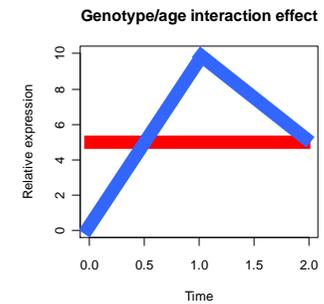
Age & Genotype effect



Age independent eQTLs

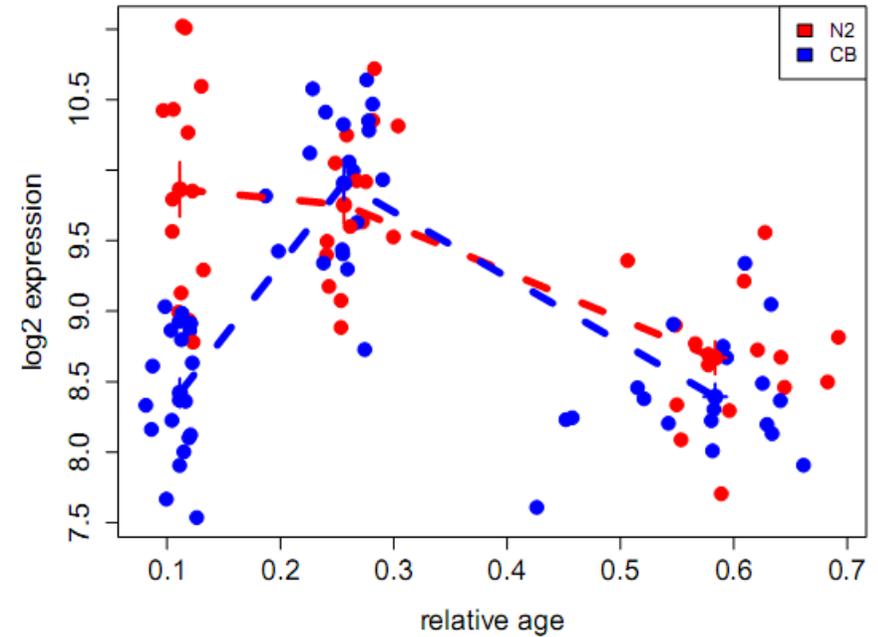
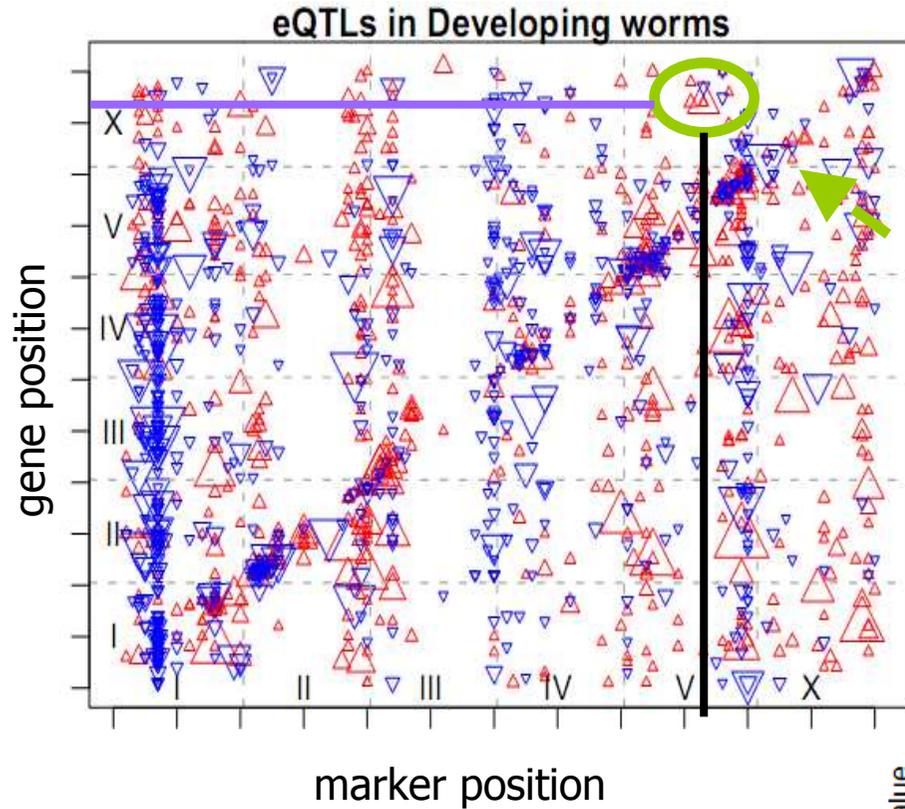


Genotype-by-age eQTLs

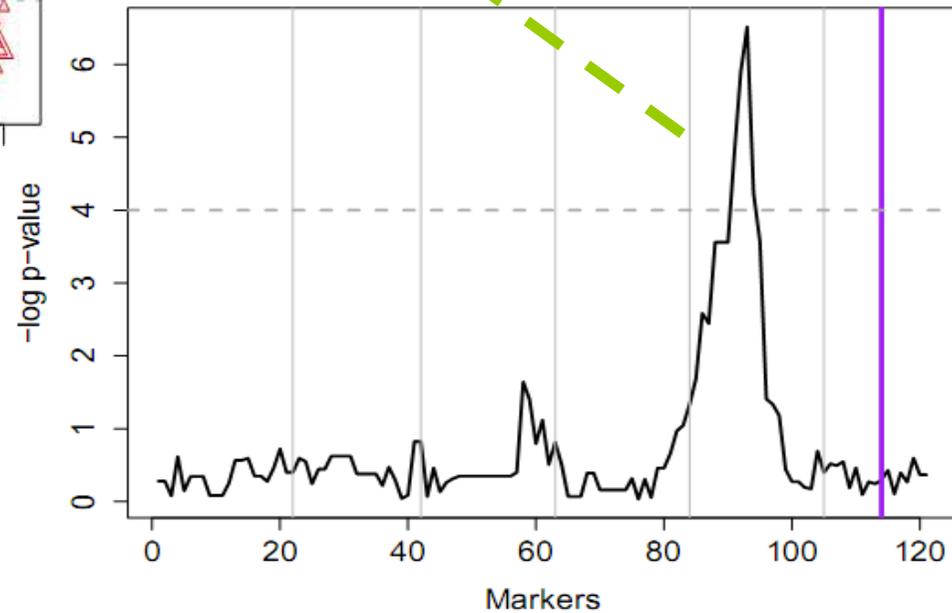


$-\log_{10} p\text{-value} > 3$

Example: *pgp-6*



pgp-6 encodes an ATP-binding protein that is a member of the P-glycoprotein subclass of the ATP-binding cassette (ABC) transporter superfamily



Conclusions from Viñuela & Snoek, *et al.* (2010)

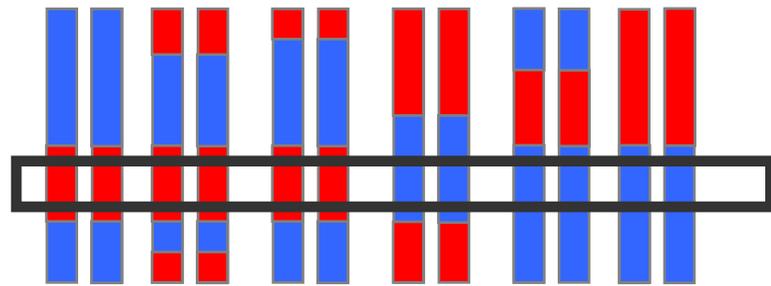
- **Gene expression regulation changes with age**
- **Variation in gene expression patterns can be heritable → gxaeQTLs**
- **The number of detected eQTLs decreased with age**

Why?

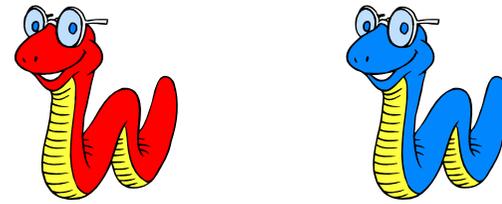
Lack of regulation

Lack of large effect regulatory loci in old worms

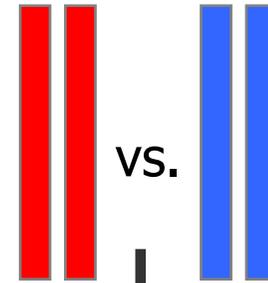
Parental



RILs



N₂

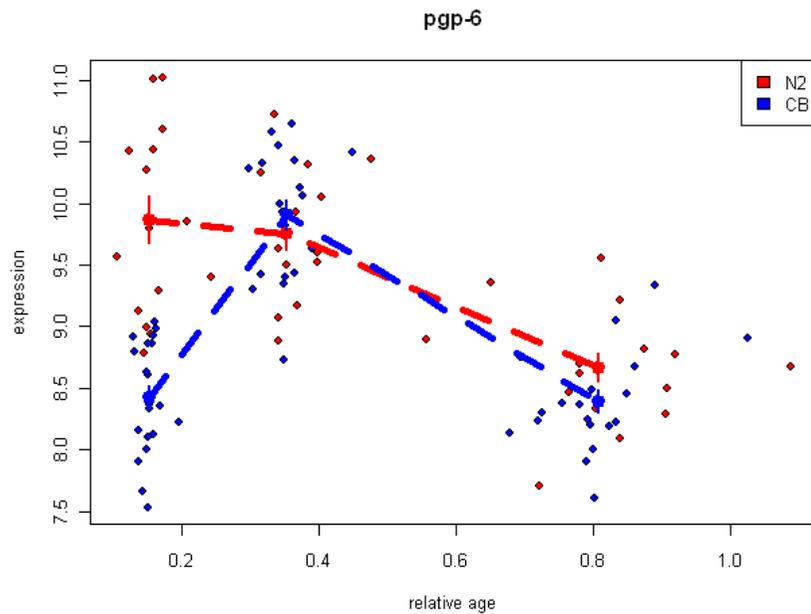
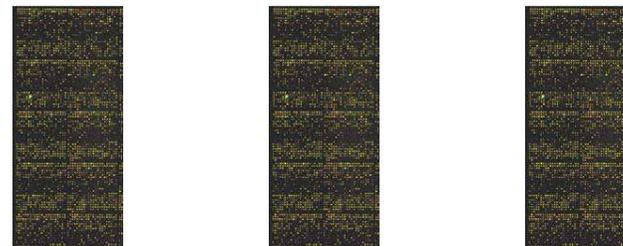
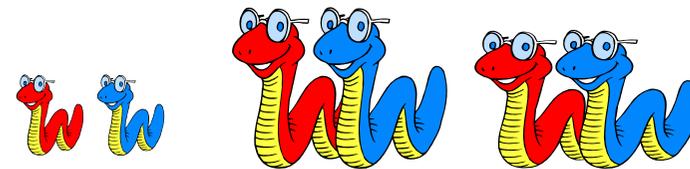


CB

40 h.

96 h.

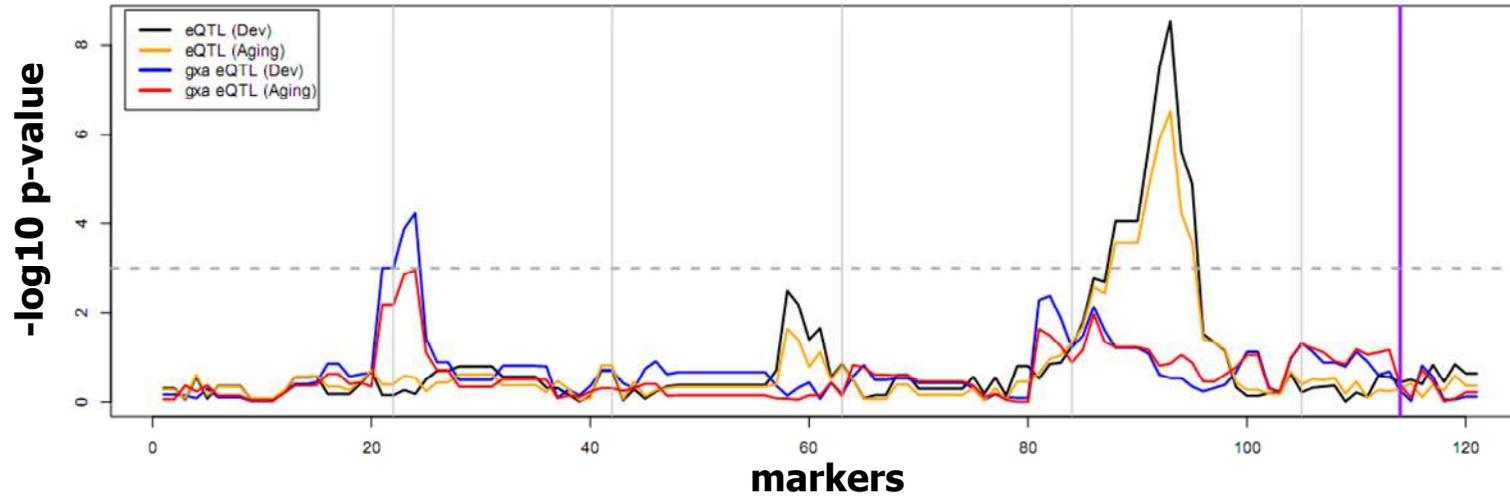
214 h.



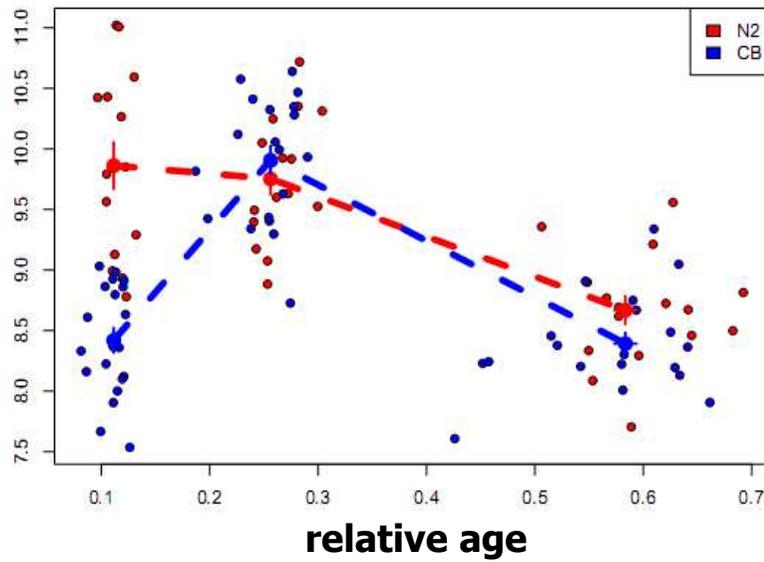
Viñuela, *et al.* (in preparation)

Gene expression and recombination

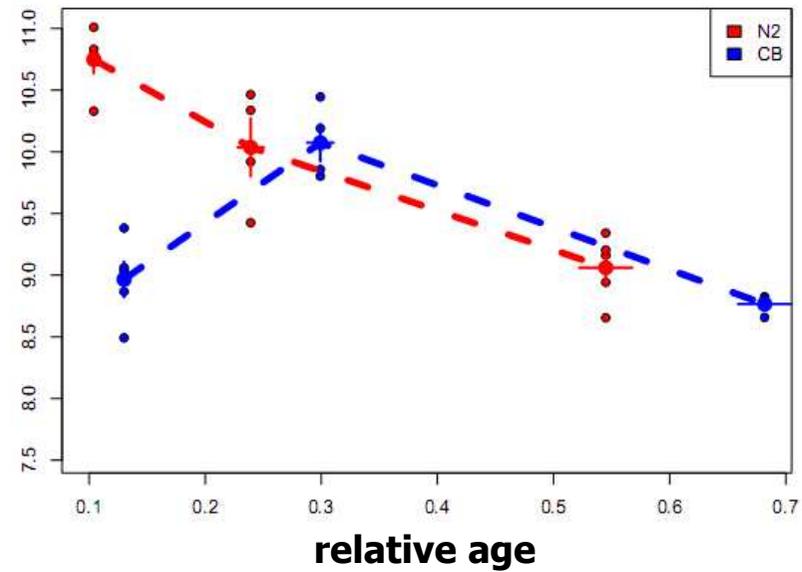
pgp-6



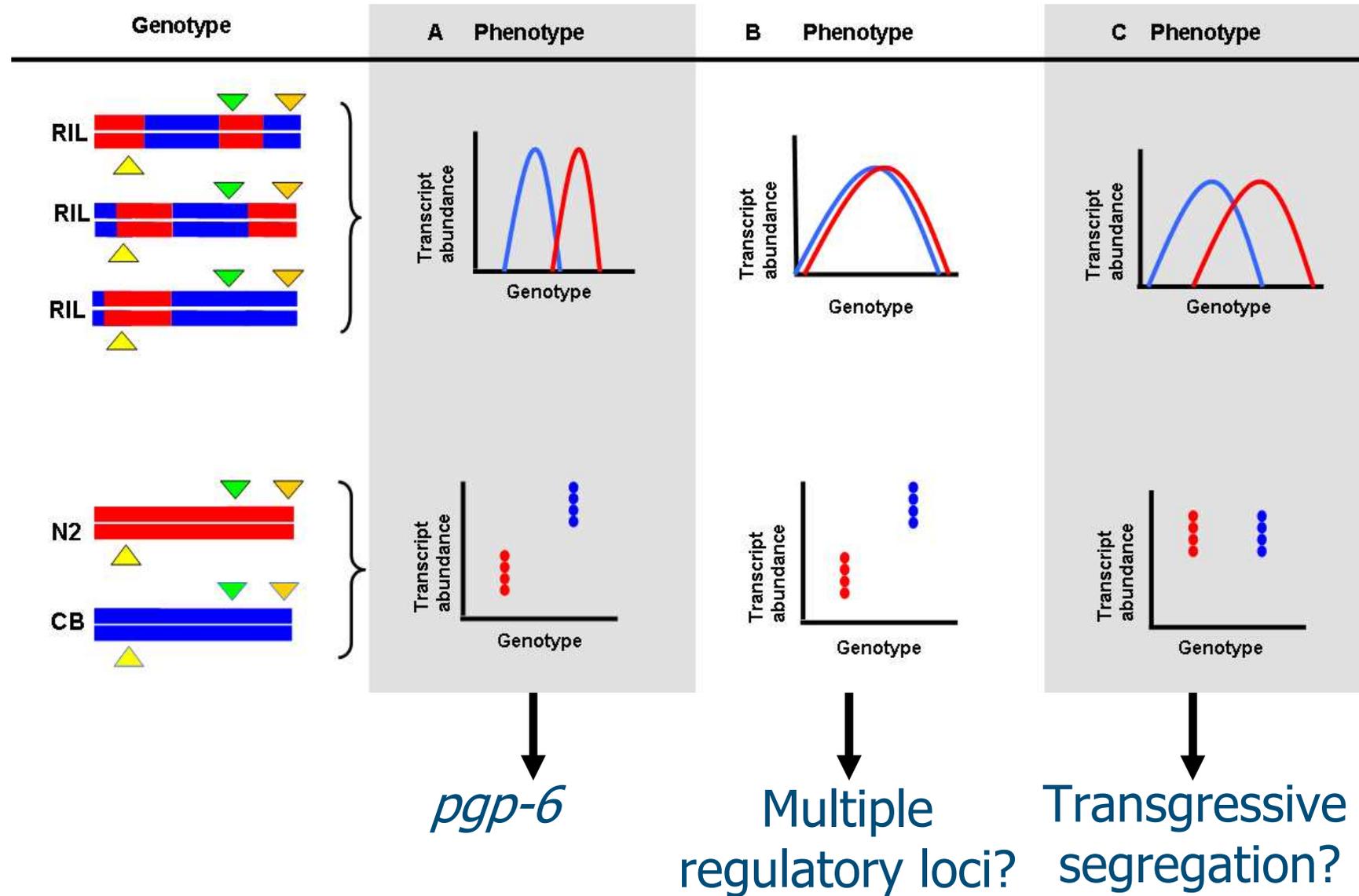
RILs



N2 & CB4856

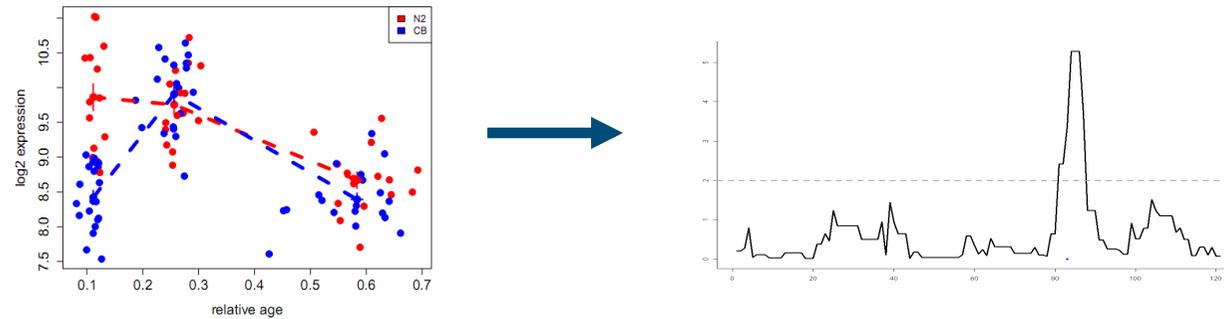


Gene expression and recombination



Phenotype (p) = Genotype (g) + Environment (e)

VAR (p) = VAR (g) + VAR (e)



Heritability is the proportion of phenotypic variation in a population that is attributable to genetic variation among individuals.

VAR(p) ~ VAR(e)

$0 < H^2 > 1$

VAR(p) ~ VAR(g)

$0 \% < H^2 > 100\%$

$H^2 = (VAR_{RIL} - VAR_P) / VAR_{RIL}$

Missing eQTLs?

- **Brem and Kruglyak (2005)**



Yeast

Highly heritable genes



59% eQTL

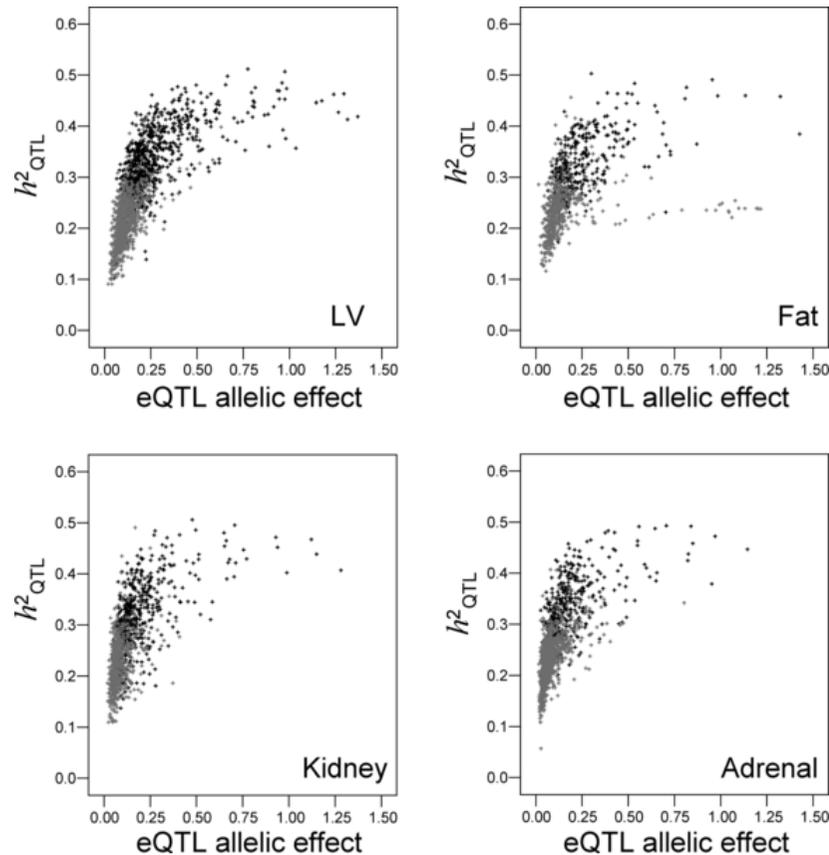
**Small additive or small
interacting effects**

Missing eQTLs?

- **Brem and Kruglyak (2005)**
- **Petretto, *et al.* (2006)**



Rats



**Fat, kidney, adrenal
and heart tissues**

**Filter for $h^2 < 20\%$
resulted in 65%-80%
less *trans*-acting eQTL
detected**

**Multiple loci with
small effects**

Missing eQTLs?

- **Brem and Kruglyak (2005)**
- **Petretto, *et al.* (2006)**
- **Keurentjes, *et al.* (2007)**



Arabidopsis

**65.6% of differentially
expressed genes
between the parents
had an eQTL**

**Highly complex
regulation on
gene expression**

Conclusion

- **Gene expression regulation changes with age**
- **Variation in gene expression patterns can be heritable → gxaeQTLs**
- **Heritability gene expression changes with age**
- **The decreased number of eQTLs suggest:**
 - **Lack of large effect regulatory loci in old worms**

Acknowledgments:

Jan Kammenga's group

