

Genetics of Global Gene Expression

Matthew Rockman, Leonid Kruglyak

2006

Megan Zerez

How can we study evolution?

Genome:
~23,000 genes

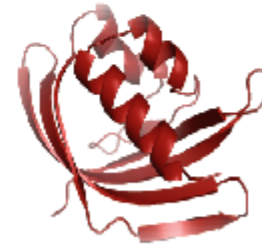


Genotype



Proteome &
Regulatory mechanisms

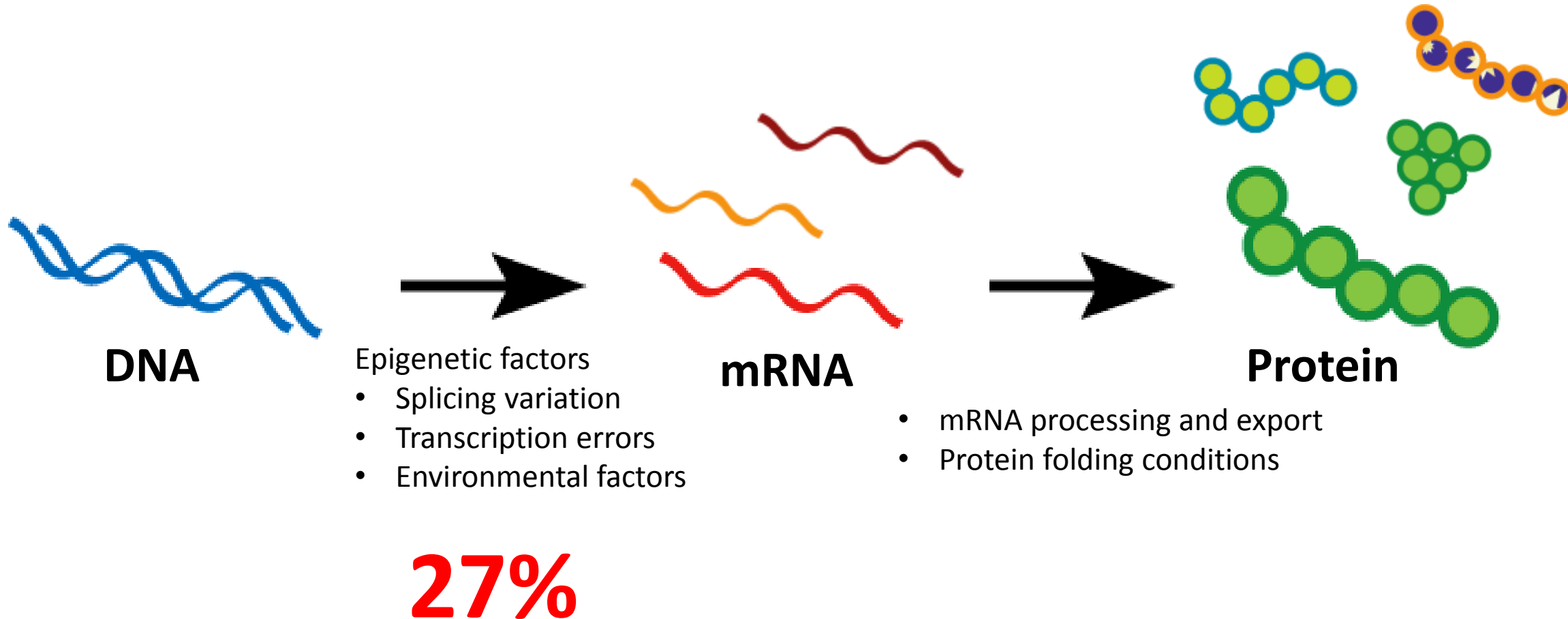
Phenotype



Est. Proteome:
>1,000,000

From genome to proteome

- An estimated 2 orders of magnitude increase in complexity– how?



Phenotype: global gene expression

- Method: quantify mRNA transcripts, correlate with genome data

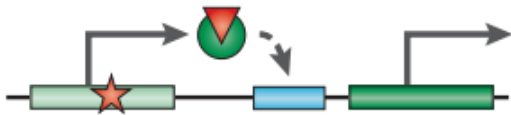
Measuring Gene Expression

- **Quantitative Trait Locus:** Section of the genome influencing some quantifiable phenotype
- Only linked to 27-29% of phenotypic effects
 - ~~Fisher (1930): Infinite genes each contributing a tiny (often undetectable) effect to phenotype~~
 - Orr (1998): Genes influence phenotype on an exponential scale
 - QTLs themselves encode genes which can also have variant expression
 - Non-additive interactions between QTLs may account for other effects
 - Distal acting QTLs are more difficult to identify than local QTLs

Distal QTLs vs Local

a Local regulatory variation

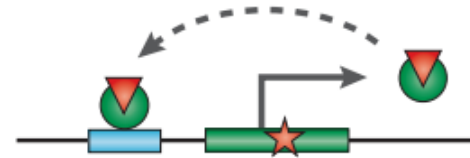
Neighbouring gene



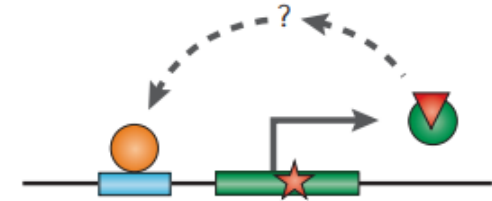
Cis-regulatory
(allele-specific)



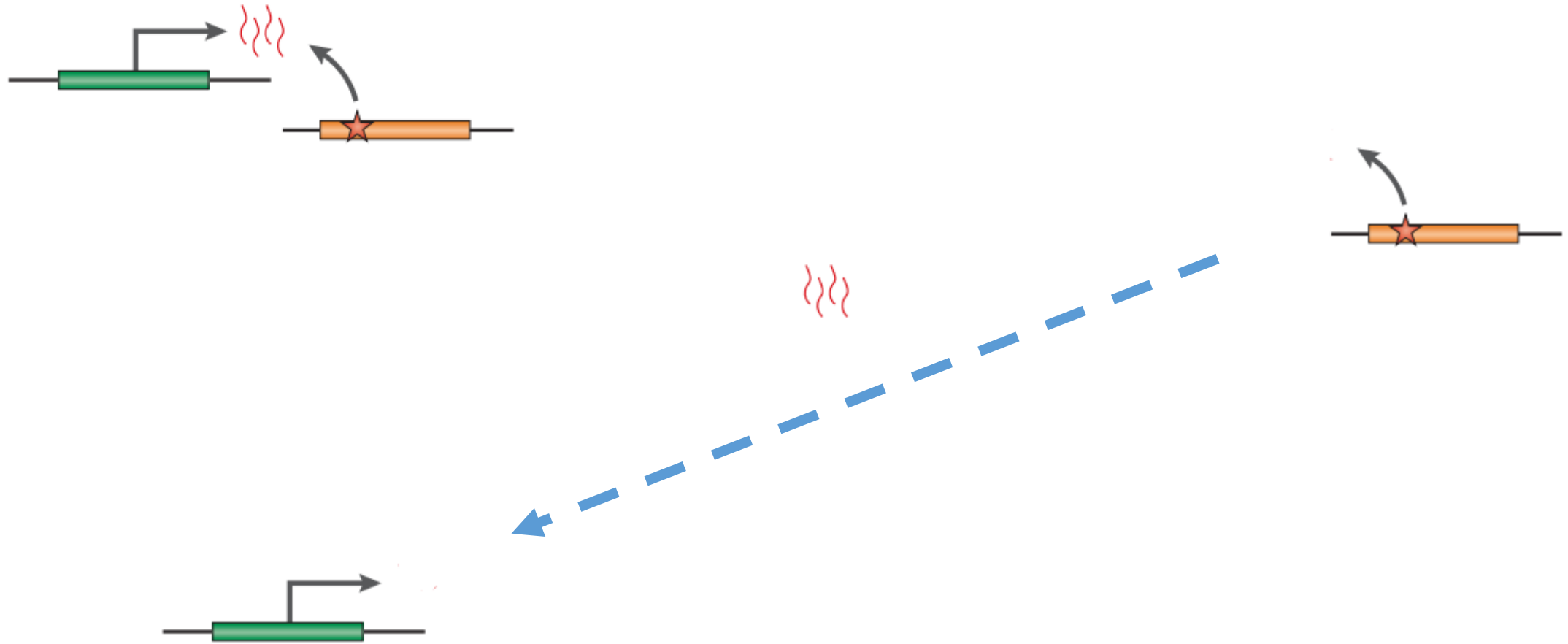
Autoregulatory



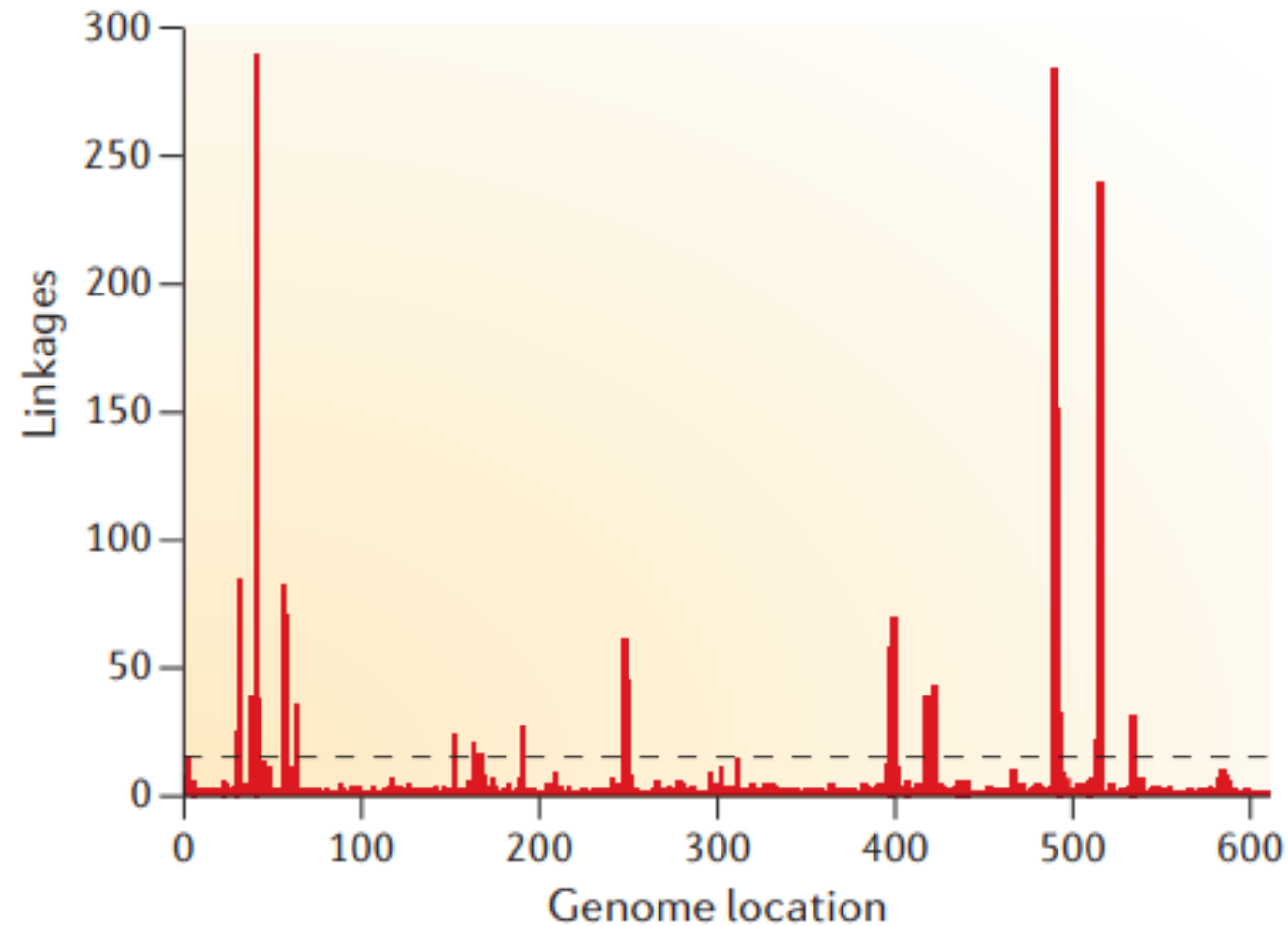
Feedback



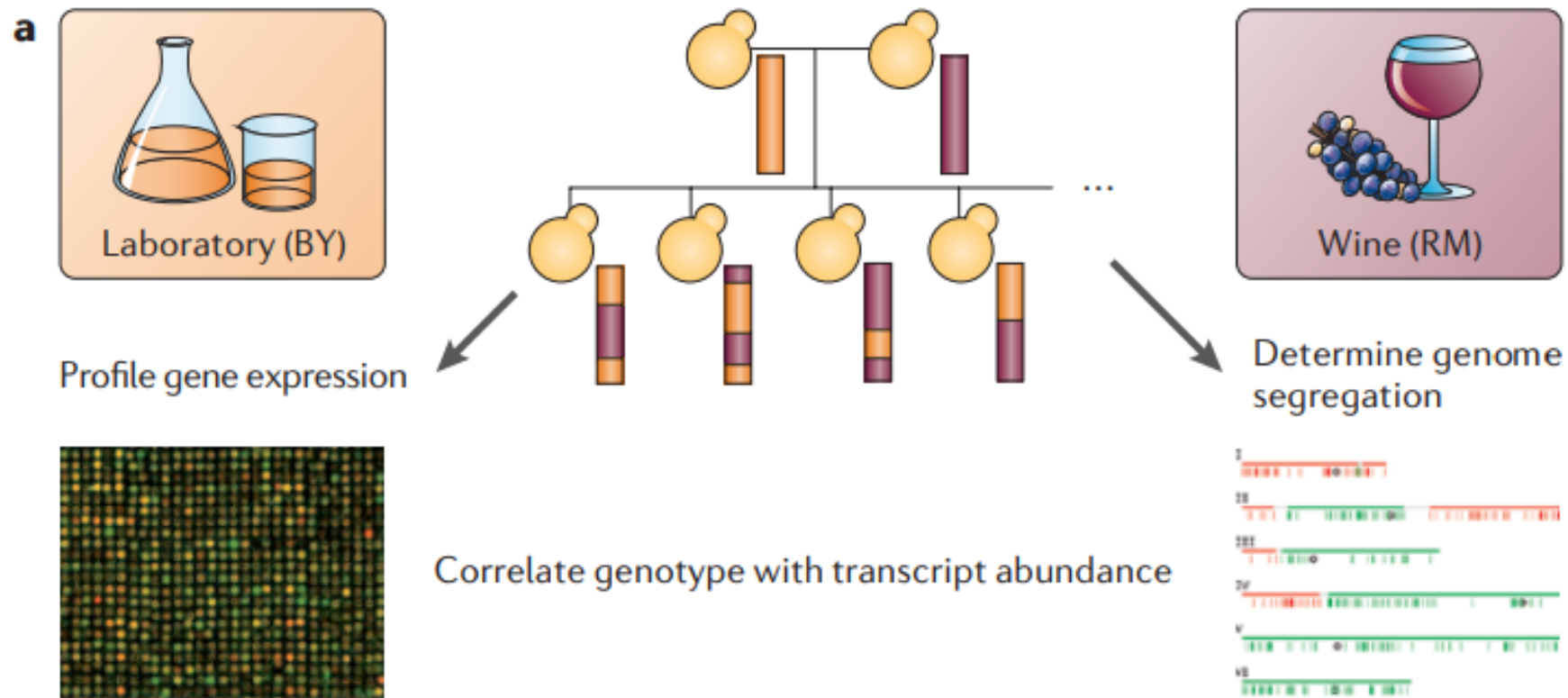
Distal QTLs vs Local



Distant QTL 'hotspots' for yeast



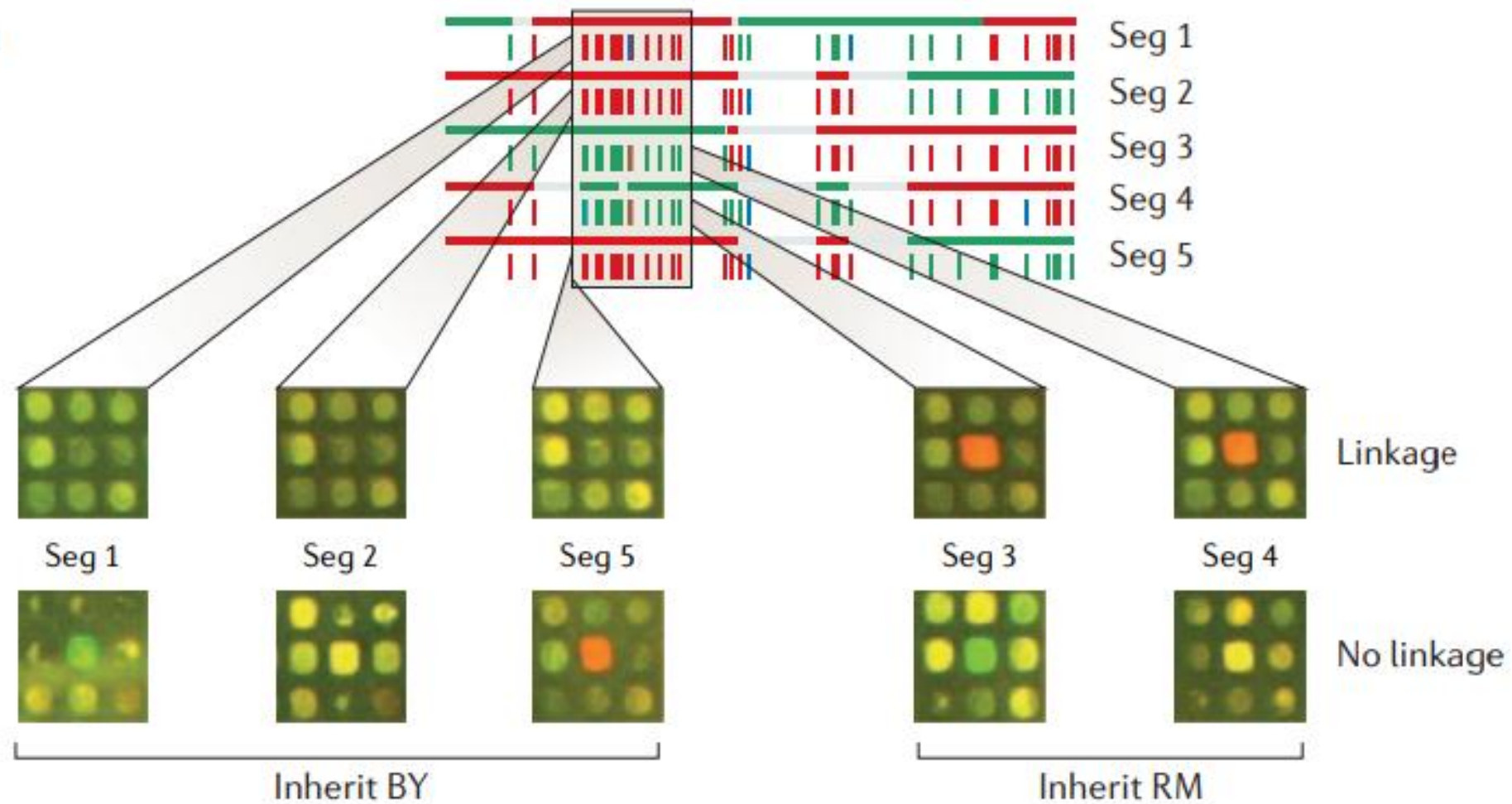
Experimental Design to compare expression of wine yeast vs laboratory yeast

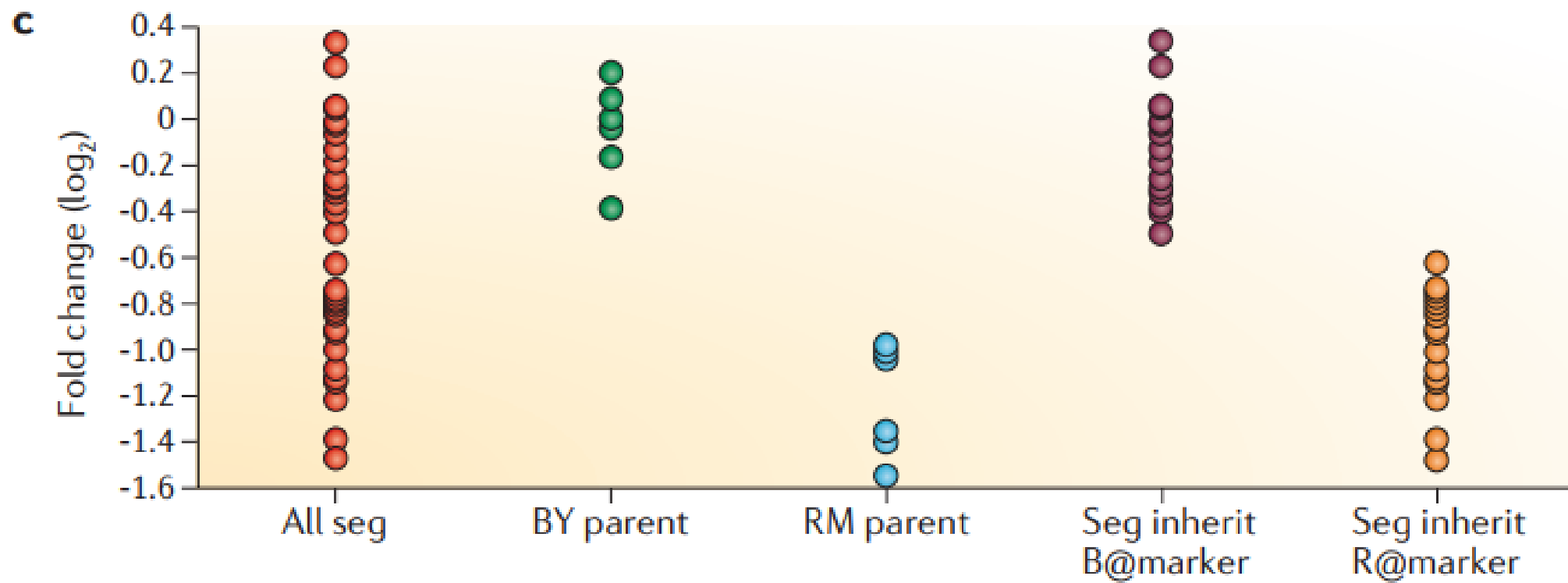


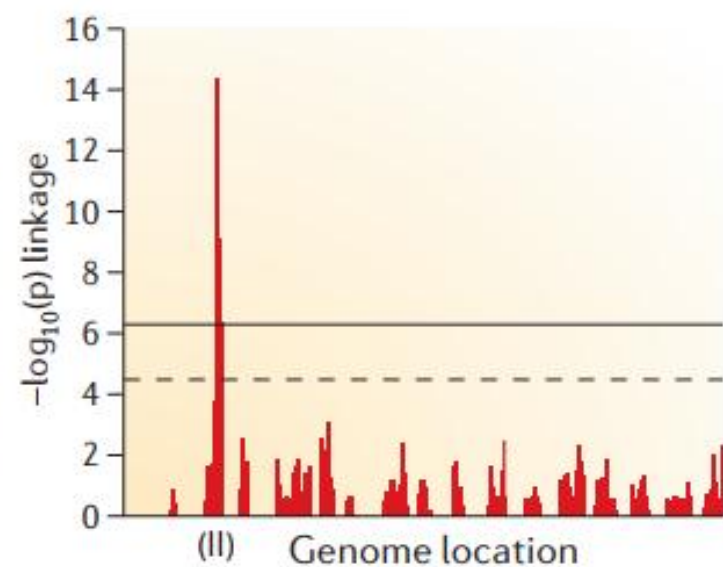
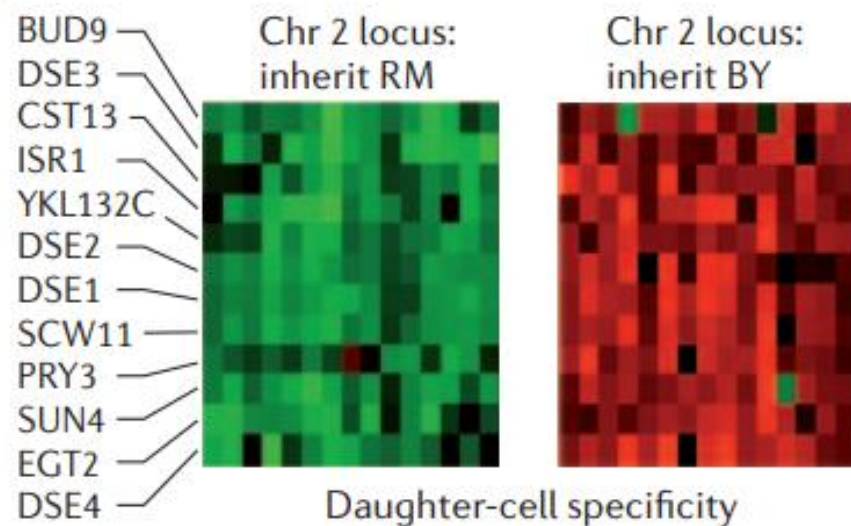
Note: microarrays can be used to compare two samples of cDNA, each dot corresponding to a gene.

Red indicates the gene is strongly expressed, **yellow** indicates no change, **green** indicates strong repression

b

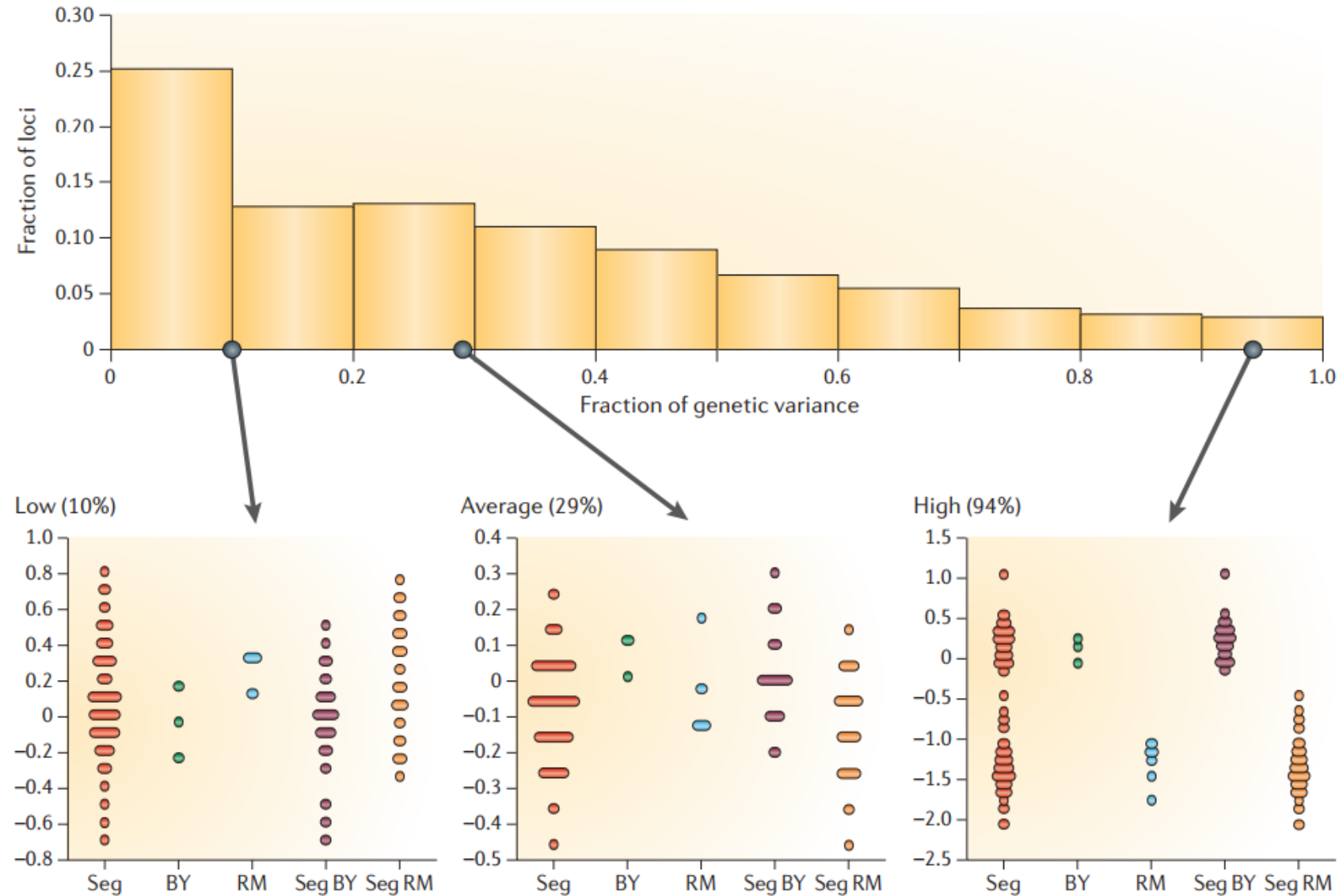




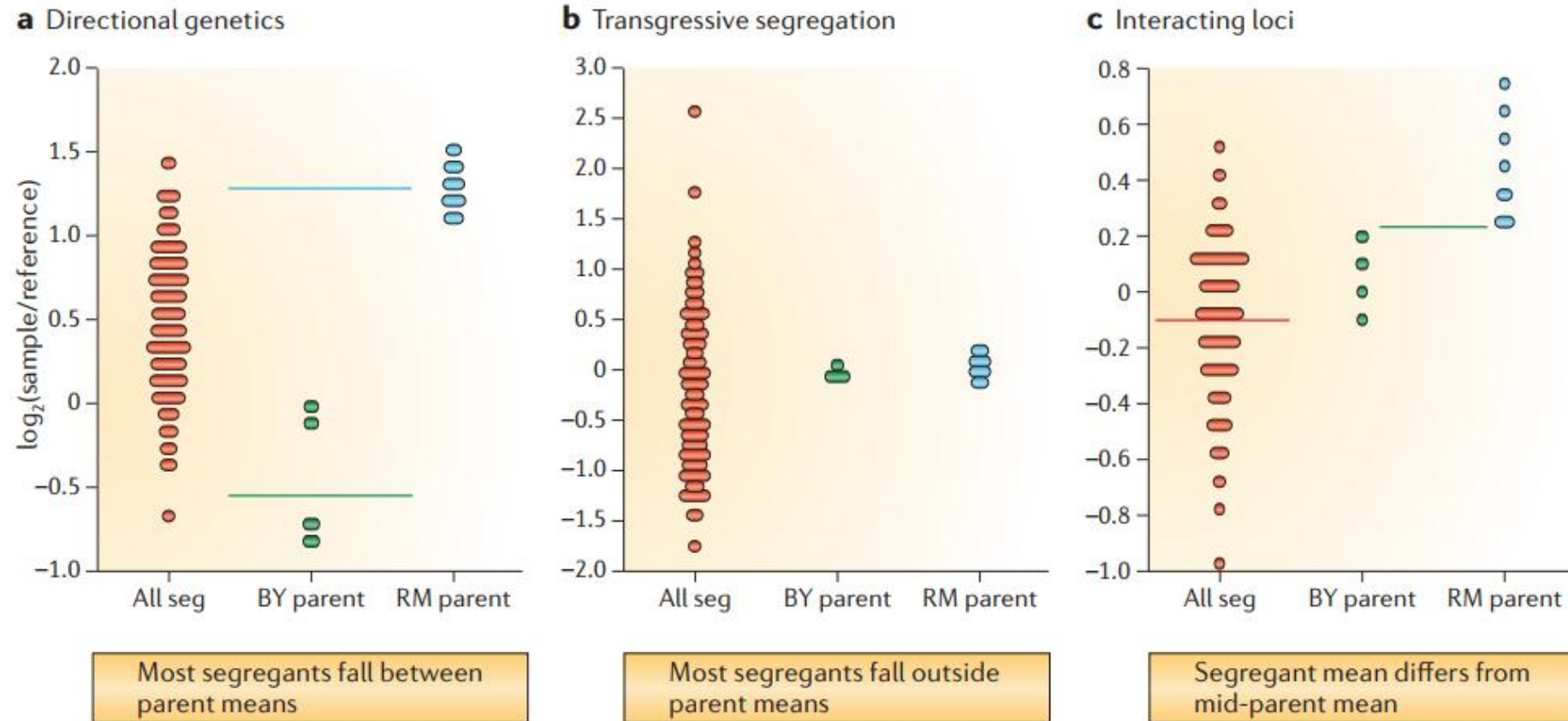
d

| | | | | | | | | |
|---------------------------------|----|------------|---------|---|-----|------------|------------|------------|
| | RM | DNFLLRLSQS | IPNLKHL | D | DLR | ACDNVSDSGV | VCIALNCPKL | KTFNIGRHRR |
| | BY | DNFLLRLSQS | IPNLKHL | V | LR | ACDNVSDSGV | VCIALNCPKL | KTFNIGRHRR |
| <i>Saccharomyces paradoxus</i> | | | | D | | | | |
| <i>Saccharomyces mikatae</i> | | | | D | | | | |
| <i>Saccharomyces bayanus</i> | | | | D | | | | |
| <i>Saccharomyces servazzii</i> | | | | D | | | | |
| <i>Zygosaccharomyces rouxii</i> | | | | D | | | | |
| <i>Kluyveromyces lactis</i> | | | | D | | | | |
| <i>Pichia angusta</i> | | | | D | | | | |

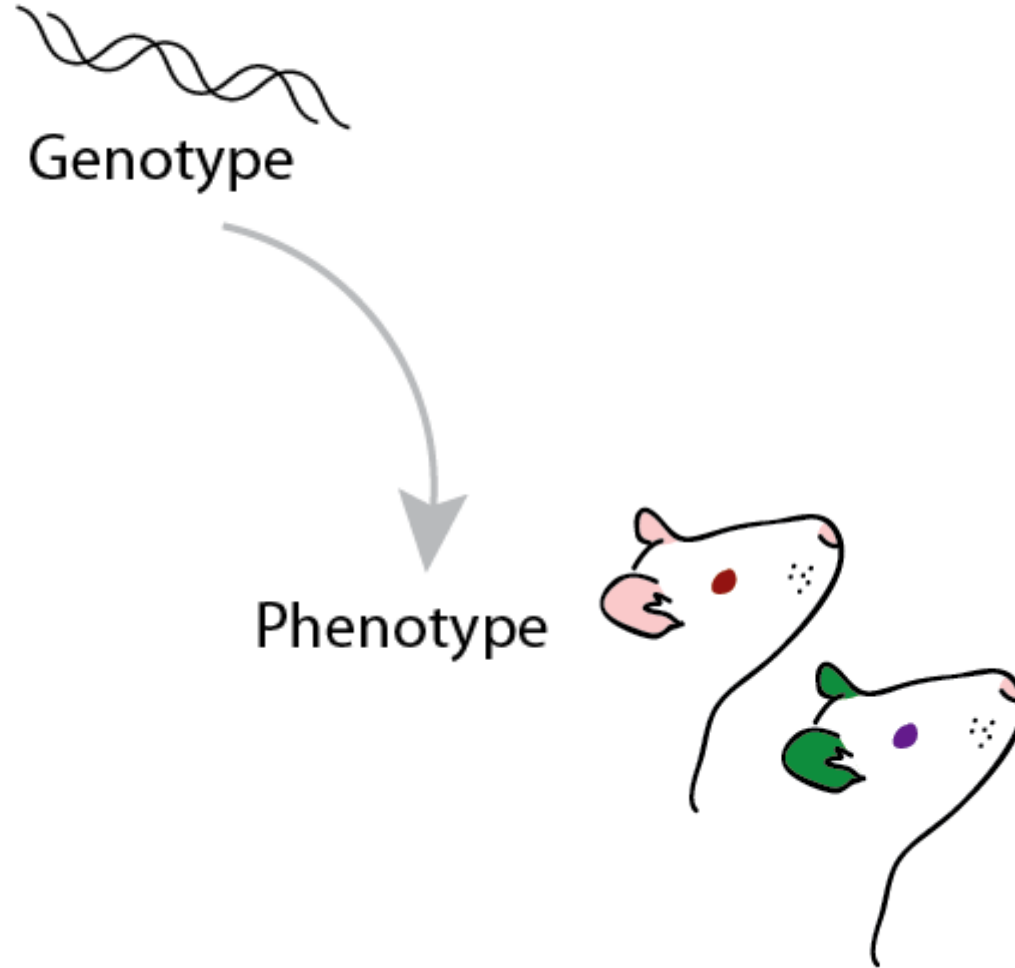
Most genes affected by fewer loci



Examples of Complex inheritance of transcript level phenotype



Where have we left off?



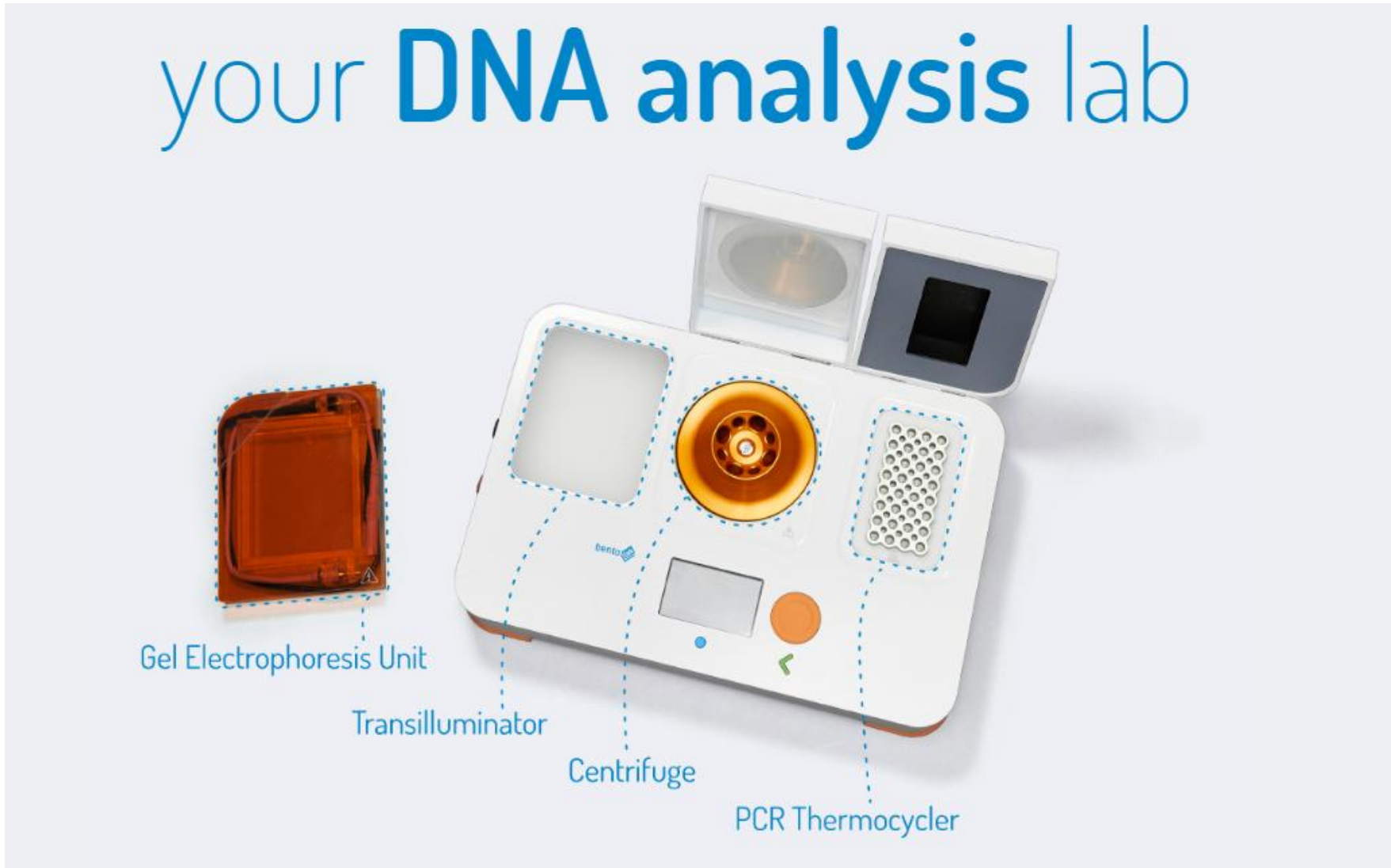
Where are we today?

- Improved technologies:
 - Faster/more accessible sequencing (RNA-seq, ~2005)
 - Large scale ChIP-seq: analysis of protein/DNA interaction
 - Increased sensitivity for transcriptome
 - Larger databases to reference (ENCyclopedia of DNA Elements– ENCODE database)
- New challenges
 - Growth stage of cells have different expression profiles
 - Trans-QTLs (distal) might rather act upon transcription factors from cis-QTLs

Mapping QTLs to disease

| Disease/trait study | Implicated eQTL genes | Expression source | Refs |
|---|--|--|-----------------------|
| Asthma | <i>ORMDL3</i> | EBV-transformed LCLs | 24 |
| Blood lipid levels | <i>SORT1, PPP1R3B, TTC39B</i> | Liver | 53,54 |
| Body mass index | <i>NEGR1, ZC3H4, TMEM160, MTCH2, NDUFS3, GTF3A, ADCY3, APOB48R, SH2B1, TUFM, GPRC5B, IQCK, SLC39A8, SULT1A1, SULT1A2</i> | Blood, brain, liver, lymphocytes, subcutaneous and visceral adipose tissue | 48 |
| Breast cancer | <i>RRP1B</i> | PyMT-induced primary tumours | 55 |
| Coeliac disease | <i>MMEL1, NSF, PARK7, PLEK, TAGAP, RRP1, UBE2L3, ZMIZ1</i> | Blood | 47 |
| Crohn's disease | <i>PTGER4, CARD9, ERAP2, TNFSF11</i> | EBV-transformed LCLs | 56 |
| Fat distribution | <i>GRB14, TBX15, PIGC, ZNRF3, STAB1, AA553656</i> | Blood, lymphocytes, omental fat, subcutaneous adipose tissue | 57 |
| Height | Multiple genes implicated | EBV-transformed LCLs, lymphocytes | 58,59 |
| Kidney-ageing | <i>MMP20</i> | Kidney | 60 |
| Migraine | <i>MTDH</i> | EBV-transformed LCLs | 49 |
| Multiple diseases | <i>CDKN2A, CDKN2B, CDKN2B-AS1</i> | Blood | 61 |
| Osteoporosis-related | <i>WLS, MEF2C, FOXC2, IBSP, TBC1D8, OSBPL1A, RAP1A, TNFRSF11B</i> | Liver, lymphocytes, primary osteoblasts | 62,63 |
| Parkinson's disease | <i>MAPT, LRRC37A, HLA-DRA, HLA-DQA2, HLA-DRB5</i> | EBV-transformed LCLs, frontal cortex | 64,65 |
| Psoriasis | <i>SDC4, SYS1, DBNDD2, PIGT, RPS26*</i> | Lesional psoriatic skin | 66 |
| QRS duration and cardiac ventricular conduction | <i>TKT, CDKN1A, C6orf204</i> | Blood | 67 |
| Type 2 diabetes | <i>FADS1, FADS2, KLF14, CCNE2, IRS1, JAZF1, CAMK1D</i> | Blood, EBV-transformed LCLs, liver, subcutaneous adipose tissue | 68,69 |

Addendum: Bentolab– \$1200



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