imb Institute of Molecular Biology

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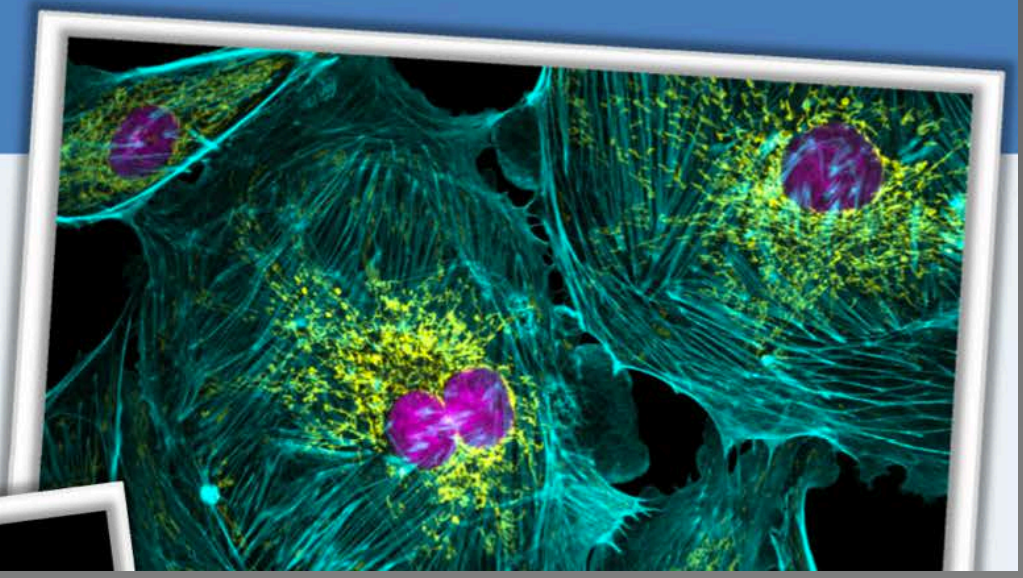


Winter Semester 2013/2014

Tuesday, 8:15-9:45 am

Institute of Molecular Biology
2nd Floor Seminar Room
Ackermannweg 4
Johannes Gutenberg University Campus

Introduction to epigenetics

1. Introduction

2. Phylogeny of DNA methylation

3. Nutrigenomics

4. Transgenerational *effects*
   Imprinting and erasure

5. Transgenerational *inheritance*

frontiers article alert

Thu, 13 September 2018

New articles in the field of

GENETICS

FRONTIERS IN GENETICS

Section "Epigenomics and Epigenetics"

Epigenome-Wide Analyses Identify Two Novel Associations With Recurrent Stroke in the Vitamin Intervention for Stroke Prevention Clinical Trial
Nicole M. Davis Armstrong, Wei-Min Chen, Michael S. Brewer, Stephen R. Williams, Michèle M. Sale, Bradford B. Worrall, and Keith L. Keene

Identification of Hyper-Methylated Tumor Suppressor Genes-Based Diagnostic Panel for Esophageal Squamous Cell Carcinoma (ESCC) in a Chinese Han Population
Chenji Wang, Weilin Pu, Dunmei Zhao, Yinghui Zhou, Ting Lu, Sidi Chen, Zhenglei He, Xulong Feng, Ying Wang, Caihua Li, Shilin Li, Li Jin, Shicheng Guo, Jiucun Wang, and Minghua Wang

The Lysine Demethylase dKDM2 Is Non-essential for Viability, but Regulates Circadian Rhythms in Drosophila
Yani Zheng, Yongbo Xue, Xingjie Ren, Mengmeng Liu, Xiao Li, Yu Jia, Ye Niu, Jian-Quan Ni, Yong Zhang, and Jun-Yuan Ji

FRONTIERS IN GENETICS

Section "Livestock Genomics"

Comparative Transcriptome Profiling of mRNA and lncRNA Related to Tail Adipose Tissues of Sheep
Lin Ma, Meng Zhang, Yunyun Jin, Sarantsetseg Erdenee, Linyong Hu, Hong Chen, Yong Cai, and Xianyong Lan

Genomic Prediction of Complex Phenotypes Using Genic Similarity Based Relatedness Matrix
Ning Gao, Jinyan Teng, Shaopan Ye, Xiaolong Yuan, Shuwen Huang, Hao Zhang, Xiquan Zhang, Jiaqi Li, and

frontiers
The world's 4th most-cited open-access Genetics & Heredity journal
See 2018 impact metrics

FRONTIERS IN GENETICS (Continued)

Section "Bioinformatics and Computational Biology"

Bioinformatics Analysis Identifies p53 as a Candidate Prognostic Biomarker for Neuropathic Pain
Yibo Gao, Na Sun, Lieju Wang, Ying Wu, Longfei Ma, Juncong Hong, Jinxuan Ren, Bin Zhu, Lina Yu, and Min Yan

DECtp: Calling Differential Gene Expression Between Cancer and Normal Samples by Integrating Tumor Purity Information
Weiwei Zhang, Haixia Long, Binsheng He, and Jialiang Yang

Identification and Analysis of Blood Gene Expression Signature for Osteoarthritis With Advanced Feature Selection Methods
Jing Li, Chun-Na Lan, Ying Kong, Song-Shan Feng, and Tao Huang

FRONTIERS IN GENETICS

Section "Behavioral and Psychiatric Genetics"

Binge Ethanol Drinking Produces Sexually Divergent and Distinct Changes in Nucleus Accumbens Signaling Cascades and Pathways in Adult C57BL/6J Mice
Deborah A. Finn, Joel G. Hashimoto, Debra K. Cozzoli, Melinda L. Helms, Michelle A. Nipper, Moriah N. Kaufman, Kristine M. Wiren, and Marina Guizzetti

Genetics research areas
Frontiers in Genetics 2018

"Applied Genetic Epidemiology"
"Behavioral and Psychiatric Genetics"
"Bioinformatics and Computational Biology"
"Cancer Genetics"
"Epigenomics and Epigenetics"
"Evolutionary and Genomic Microbiology"
"Evolutionary and Population Genetics"
"Genetic Disorders"
"Genetics of Aging"
"Genomic Assay Technology"
"Livestock Genomics"
"Nutrigenomics"
"RNA"
"Statistical Genetics and Methodology"
"Stem Cell Research"
"Toxicogenomics"

epigenetics: definitions

sensu strictu: environmentally induced transgenerational phenotypic change without change of the DNA sequence (but with changes of epigenetic marks)

and many others

	Epigenetics definition	Focus of definition	Interpretation
1	Regulation of gene expression	Mechanistic view of the epigenome	• Uses the literal etymology of 'above' or 'beyond' genetics • No particular focus on transgenerational transfer
2	Stable changes in gene function without changes in DNA sequence	Gene function	• Narrows definition of epigenetics to consider modification of chromatin • No particular focus on transgenerational transfer
3	Non-genetic causes of a phenotype	Phenotype	• Focuses on linkage of mechanism to outcome (phenotype) • Transgenerational transfer is part of a larger suite of outcomes, including developmental plasticity
4	Study of heritable changes in gene function that occur without a change in the DNA sequence	Transgenerational transfer of gene function	• Explicit focus on transgenerational transfer (inheritance) of gene function • Focuses on mechanism with lesser focus on phenotypic outcome or evolutionary implications
5	Study of heritable phenotype without a change in the DNA sequence	Transgenerational transfer of phenotype	• Explicit focus on transgenerational transfer (inheritance) • Focuses on phenotypic outcome and evolutionary implications, with minor focus on mechanism
6	Study of processes that give rise to developmental plasticity and canalization	Persistent phenotype as a result of events that occur during development	• Distinction among 'epigenetics', 'epigenetic inheritance' and 'cellular epigenetic inheritance' • Focuses on cellular phenotypic outcome and evolutionary implications, with major focus on mechanism • Focuses on transgenerational transfer *via* gametic transmission
7	Alteration of gene expression by modification of chromatin	Strict inheritance of epigenetic marks such as imprinted genes	• Focuses on the overlap between transgenerational non-genomic transgenerational inheritance and epigenetic inheritance • Distinction between indirect and direct epigenetic inheritance

Kovalchuk (2012) Frontiers in Genetics 3, 1 Transgenerational epigenetic inheritance in animals

Ho and Burggren (2010) J. Exp. Biol. 213, 3 Epigenetics and transgenerational transfer: a physiological perspective

in short:

‘Epigenetics is a useful word if you don’t know what’s going on – if you do, you use something else’

(quote attributed to Adrian Bird)

Introduction to epigenetics 2018/19

Lecturer	Title	Date	Slides
Gert Pflugfelder	Introduction to epigenetics	16.10.2018	Coming soon
Christof Niehrs	DNA methylation & demethylation	23.10.2018	Coming soon
René Ketting	Small non-coding RNAs	30.10.2018	Coming soon
Natalia Soshnikova	Histone variants	06.11.2018	Coming soon
Mark Helm / Jean-Yves Roignant	Nucleic acid modifications / Mechanisms and functions of RNA modifications	13.11.2018	Coming soon
Eva Wolf	Circadian clocks as gene regulatory systems	20.11.2018	Coming soon
Holger Richly	ncRNAs & the regulation of gene expression	27.11.2018	Coming soon
Anton Khmelinskii*	Prions: Epigenetics, evolution and disease	04.12.2018	Coming soon
Peter Baumann	The epigenetic clock	11.12.2018	Coming soon
Julian König	Genomic views of splicing regulation	18.12.2018	Coming soon
Falk Butter	Quantitative proteomics	08.01.2019	Coming soon
Christoph Cremer	Imaging the cell nucleus: Genome architecture & gene regulation	15.01.2019	Coming soon
Leszek Wojnowski	Epigenetics in the context of health & medicine	22.01.2019	Coming soon
Miguel Andrade / Stefan Legewie **	Data mining approaches to the prediction of gene and protein function / Epigenetics: Quantitative approaches & theoretical models	29.01.2019	Coming soon
David Rosenkranz	Epigenetic Mechanisms in Evolution	05.02.2019	Coming soon

BOOK REVIEW ARTICLE

Front. Genet., 26 October 2015 | http://dx.doi.org/10.3389/fgene.2015.00315

Book review: Epigenetics (second edition, eds. Allis, Caparros, Jenuwein, Reinberg)

Krassimir Yankulov*

Department of Molecular and Cellular Biology, University of Guelph, Guelph, ON, Canada

A book review on Epigenetics, second edition

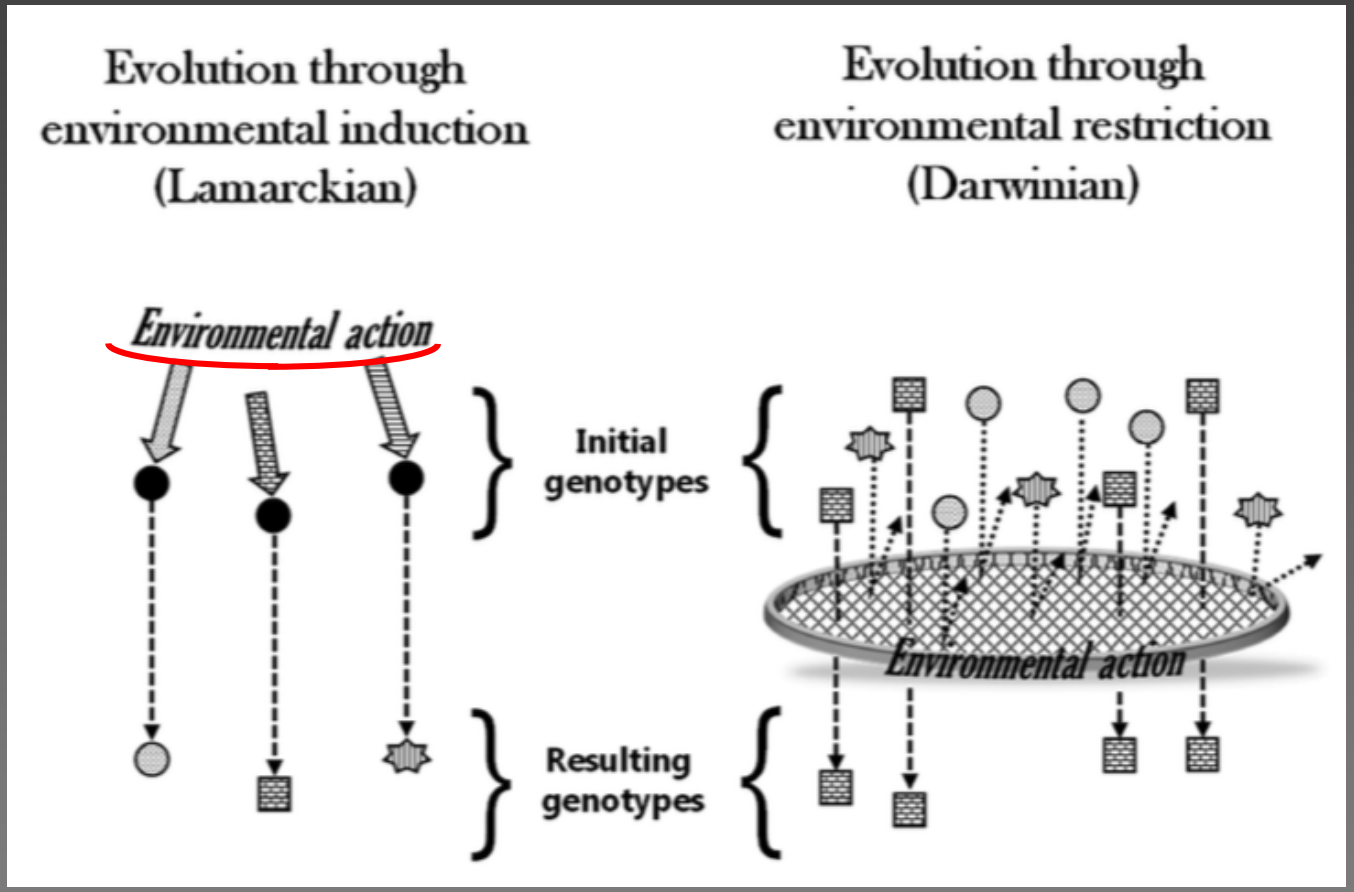
Edited by C. David Allis, Marie-Laure Caparros, Thomas Jenuwein, and Danny Reinberg. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 2015

Epigenetics is a dynamic and well-established branch of genetics. It deals with heritable traits, which are not transmitted by the sequence of DNA but rather by the state of chromatin. The evolving landscape of epigenetic research has been reviewed in many excellent books and monographs. Amongst these, the second edition of *Epigenetics* by Cold Spring Harbor Laboratory Press (Allis et al., 2015) stands out as one of the most comprehensive references for all major developments and perspectives in the field. Built upon the foundation of the first edition (published in 2007), this new edition continues to deliver a solid basic knowledge of various epigenetic processes in model organisms (including yeasts, ciliates, plants, insects, and mammals), of gene imprinting, of dosage compensation, of DNA methylation, and histone modifications. Twelve new chapters track the recent developments in epigenetic processes in cancer, neuronal development, and mental illness, in responses to the environment and in long-range chromatin interactions. All chapters are written by prestigious researchers and are nicely organized to start with a brisk summary followed by a short overview and heavily and richly illustrated main text. In this respect, the book targets a broad audience and can easily serve as an educational resource in specialized higher level undergraduate and graduate university courses or as a reference for advanced level scientists. Its breadth of topics makes it a compulsory item on the shelf of every lab that is closely or remotely involved in epigenetic studies.

Was man schwarz
auf weiß besitzt,
kann man getrost
nach Hause tragen.

Goethe Faust 1

The Lamarckian flavour of epigenetics



with phenotype

with adaptive phenotype

Guerrero-Bosagna 2017

Jean Baptiste de Lamarck (1744-1829)

Flore française (1778)
Dictionnaire de botanique (1783-1796)
Philosophie zoologique (1809)
Système des animaux sans vertèbres (1815-1822)

Jardin des Plantes

Epigenetic inheritance systems

epigenetic marks

DNA methylation

versus

chromatin remodeling
histone modification
ncRNAs

Self-sustaining loops (involving DNA)
(auto-regulation of gene activity via their protein products)

structural inheritance (not involving genomic DNA)
(membrane features, mitochondria, cilia, prions, viruses, RNA, proteins etc.)

cultural/socioeconomic inheritance

Ho and Burggren (2010) J. Exp. Biol. 213, 3
Epigenetics and transgenerational transfer: a physiological perspective

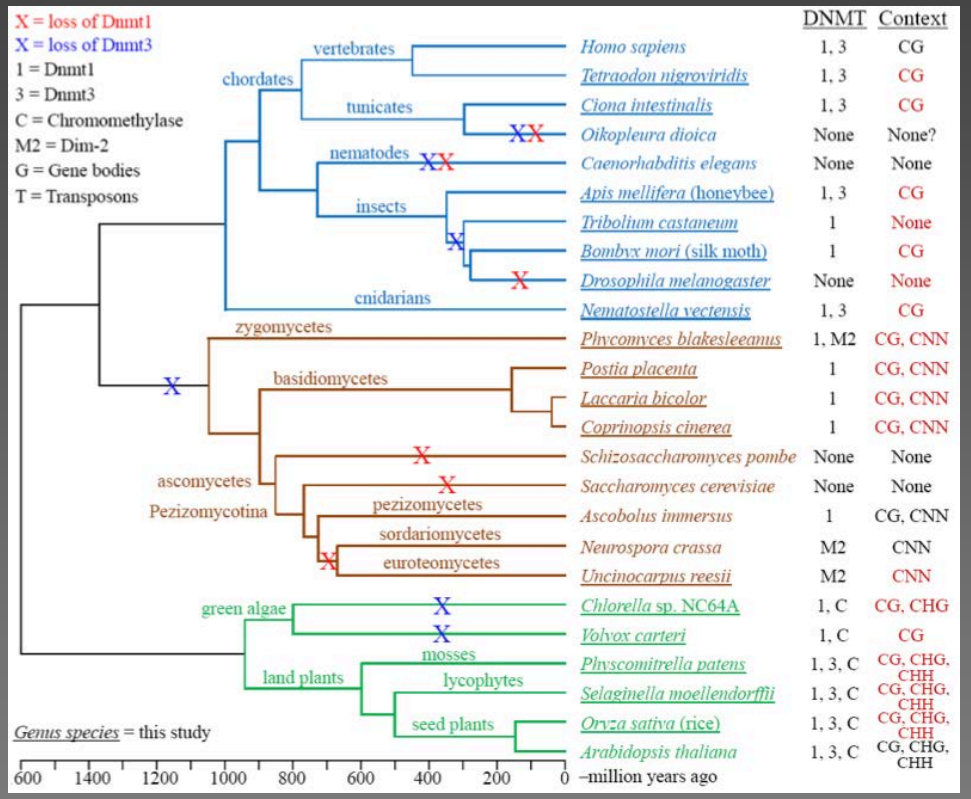
Phylogeny of DNA methylation

DNA *versus* chromatin modification: many species do fine without Dnmt3 or Dnmt1

DNA cytosine methyltransfereases in selected species

Organism	Dnmt1 'maintenance'	Dnmt2	Dnmt3 'de novo'	CpG methylation
Nematode worm				No
Flies, mosquitoes		●		No
Silk worm	●	●		?
Flour beetle	●	●		?
Honey bee	●●	●	●	Yes
Solitary wasp	●●●	●	●	Yes
Aphid	●●	●	●	Yes
Louse	●●	●		?
Daphnia	●	●	●	?
Mammals	●	●	●●●	Yes

Weaver (2012) BioTechniques 06/27/2012



Zemach et al. (2010) Science 328, 916

CpG DNA methylation in *Drosophila* is not required for epigenetic phenomena

DNMTs have little intrinsic regional specificity, therefore, need to be guided to specific sites by factors with DNA/chromatin recognition abililty (possibly by H3K9me which binds HP1 which in turn recruits DNMTs).

No preferential CpG methylation in *Drosophila*, a Dnmt2-only organisms

Methylation rare in space

EVIDENCE OF CYTOSINE METHYLATION IN *DROSOPHILA MELANOGASTER*

Genomic location of mC	Developmental timing of mC	mC/C (%)	Sequence context of mC	Methods used	References
n.d.	Embryos and larvae	n.d.	n.d.	DB	1 (1983)
n.d.	Early embryo (0–4 h)	0.35 (2D-TLC), 0.25 (BS)	CpN with preference for CpT	BS, 2D-TLC, HPLC	7
n.d.	All stages, less abundant in adults	0.08	n.d.	2D-TLC, HPLC	8
IC: ubiquitous	Embryos	CE: 0.37 ± 0.07	n.d.	CE, IC, SB	9
Gag ORF of rover	Adults	n.d.	insignificant	AC, BS	10
IC: ubiquituous	Embryos	n.d.	n.d.	IC	11
DNAREP1_DM	Germ line	n.d.	CpN	NSP	12
Rbf promoter and exon 1, pathogenic	Eye disc	n.d.	CpN, with preference for CpG	BS, MSRE	13
Retrotransposons	Germ line	n.d.	CpN	NSP	14
Ftz enhancer, pathogenic	Germ line, embryos, adults	BS: 8.4	CpN	BS, MSRE, SB	15
Invader 4 LTR	Embryos	BS: up to 57.9	CpN	BS, MSRE	16
Gene promoters (e.g., Rb, Antp, CG2316) and retrotransposons (HeT-A and Rt1b{})	Soma	BS: 7.0/8.0 (Rb promoter/exon1 in S2 cell expressing transgenic SETDB)	CpN	BS, ChIP, MSRE	17
Genome-wide	0–3 h embryos	0.11	CpN	BS	18 (2010)

not detectable

n.d., not determined; AC, affinity chromatography; BS, bisulfite sequencing; CE, capillary electrophoresis; ChIP, chromatin immunoprecipitation using mC antibodies; 2D-TLC, 2D thin layer chromatography; DB, dot blot; HPLC, high pressure liquid chromatography; IC, immunocytology; MSRE, methylation-sensitive restriction endonucleases; NSP, nucleotide substitution pattern; SB, slot blot.

Krauss and Reuter (2011) Progr. Mol. Biol. Translat. Sci 101, 177

Epigenetic Enigmas

Methylation rare in time

Overturning previous studies, a peculiar protozoan mysteriously uses a DNA-markup system to take out the genetic trash.

By Beth Marie Mole | October 17, 2012

1 Comments Like 0 Pin it +1 3 Link this Stumble Tweet this

Wikimedia, Unknown Source

While most organisms use methyl marks on the genome to stake out gene expression, the fresh-water protozoan *Oxytricha trifallax* use the tags to kick junk DNA—95 percent of its genome—to the curb, according to a new study in *Genome Biology* published today (October 17). The finding refutes previous studies that concluded the ciliated single-cell critters—which usually carry four nuclei—have methylation-free DNA.

"It's actually surprising that there is methylation, because it wasn't reported to be there—a lot of studies in the 80s and 90s looked for it and didn't find it," said John R. Bracht, a postdoctoral researcher at Princeton University, and lead author of the study. "And what's kind of fun about this, is that it's the exact same modification that you'll find in humans," he added, "but it may be playing a different role."

Elimination of 95% of micronuclear DNA
Fragmentation of genome to create ~ 16,000 nanochromosomes
~ 2000-fold amplification of nanochromosomal DNA (polytene)

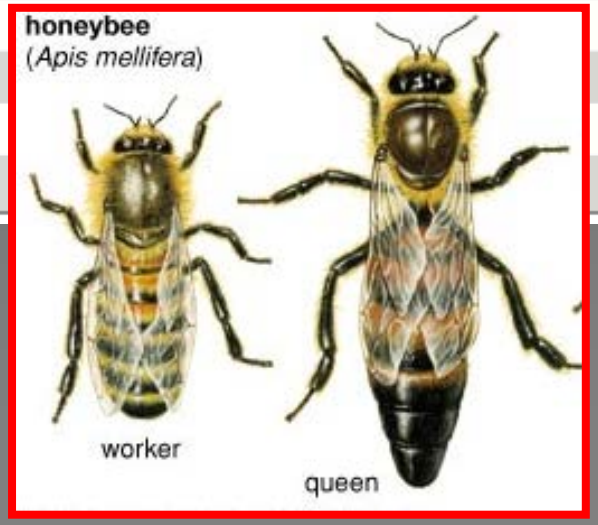
JR Bracht, DH Perlman and LF Landweber (2012) *Genome Biology,* doi:10.1186/gb-2012-13-10-r100,
JR Bracht (2014) BioEssays 36, 346

Nutri-epigenomics

What food (royal jelly) can do to a bee by postembryonic epigenetic reprogramming

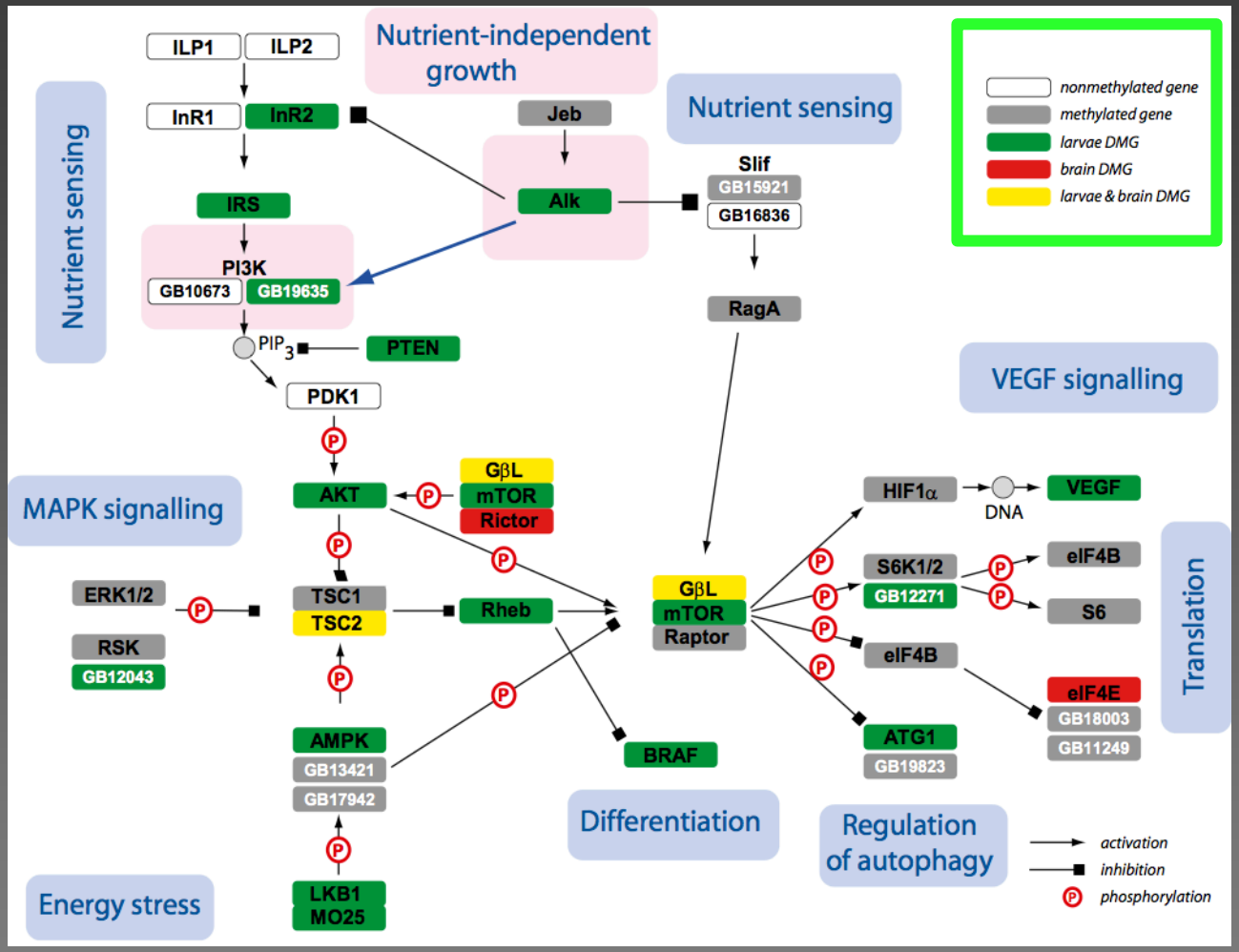
	Worker	Queen
Mass at emergence	81–151mg	178–292mg
Development egg->adult	16–24 days	14–17 days
Age	15–38 days (summer bees) 140 days (winter bees)	1–3 years normally (up to 8 yrs in some cases)
Facets in compound eye	5,000–6,000	3,500
Placoid olfactory sensillae	2,700	1,600
Pollen basket	Yes	No
Wax glands	Yes	No
Spermatheca	Rudimentary	Large
Ovarioles	2–12	150–180
Sting barbs	Yes	Rudimentary
Mandibular glands	Large	Very large
Nasonov glands	Yes	No
Dance communication	Yes	No

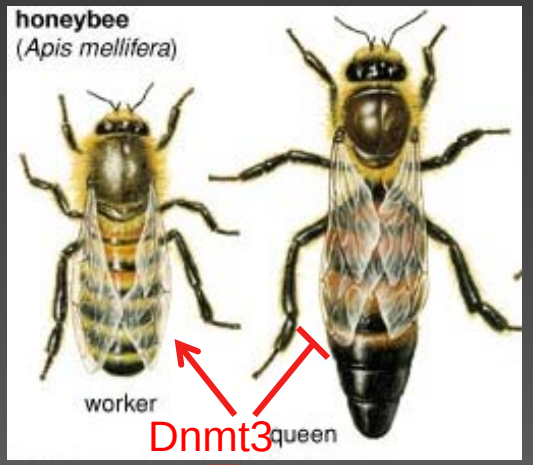
dancing worker



Chittka and Chittka (2010)
Epigenetics of Royalty.
PLoS Biol 8, 1

Nutri-epigenomics





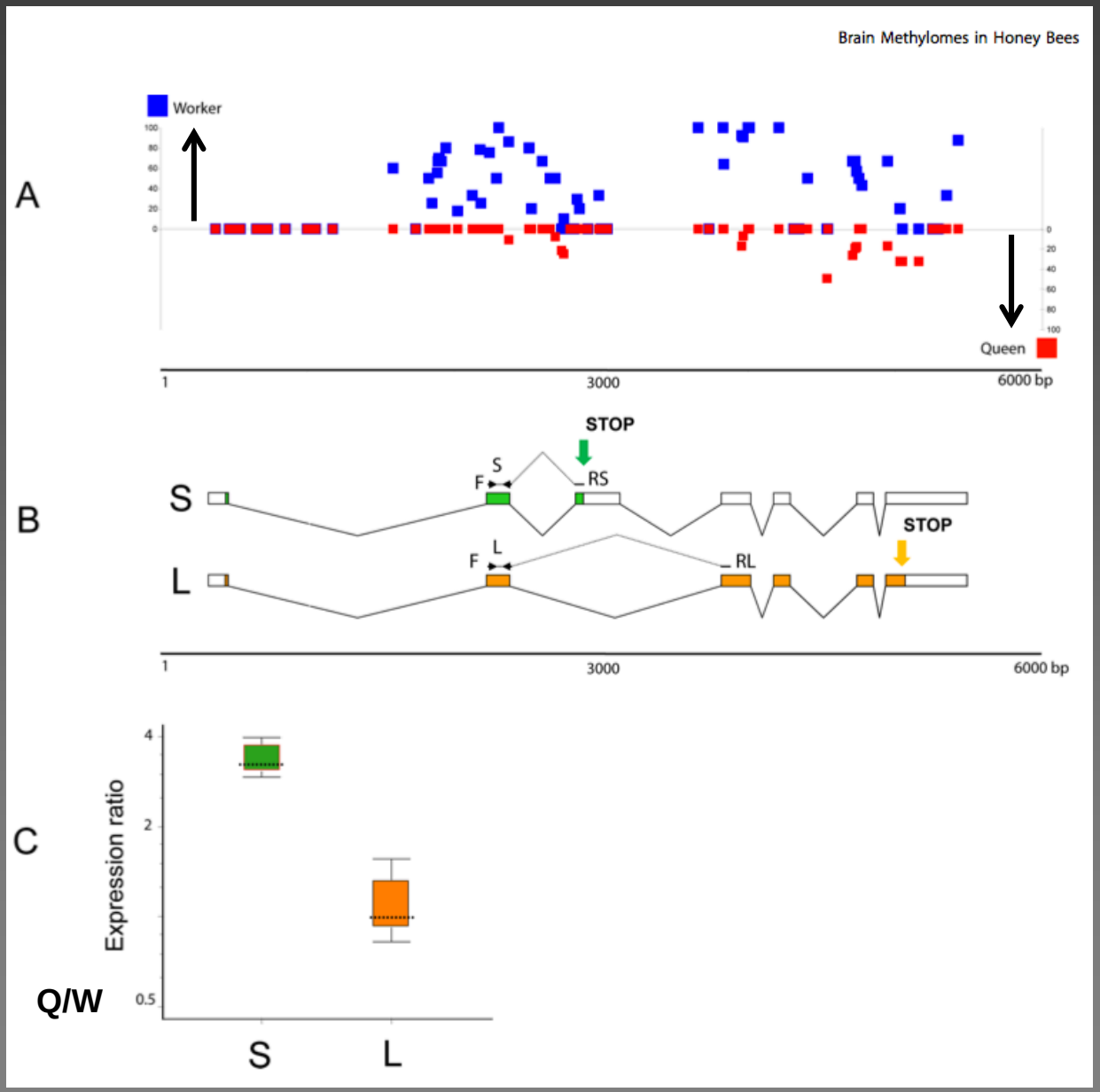
bee bread royal jelly

Silencing *Dnmt3* in larvae generates adult bees with queen characteristics, i.e. is equivalent to royal jelly.

Kucharski et al. (2008) Science 319, 1827
Foret et al. (2012) PNAS 109, 4968

Food quality/quantity can affect gene expression via DNA methylation: splicing

In honey bee only 7x 10[4] of 10[7] CpGs are methylated, many of them differentially (queen *vs* worker). (561 genes with differential on splicing)



gene GB18602

methylation represses the formation of the short splice form

Lyko et al. (2010) PLOS Biol. The honey bee epigenomes: differential methylation of brain DNA in queens and workers

Shayevitch et al. (2018) RNA 24, 1351

Nutri-epigenomics

What food (beebread) can do to a bee by postembryonic gene regulation

ENTOMOLOGY

A dietary phytochemical alters caste-associated gene expression in honey bees

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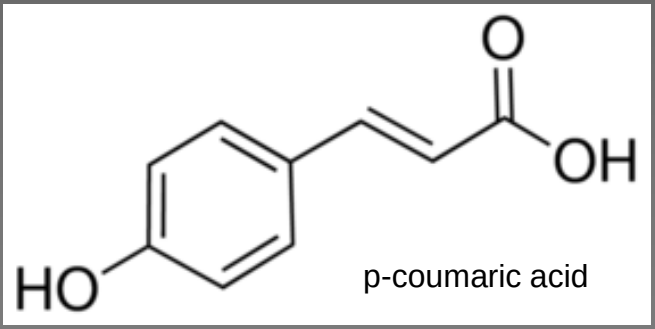
10.1126/sciadv

Wenfu Mao,[1] Mary A. Schuler,[2] May R. Berenbaum[1]*

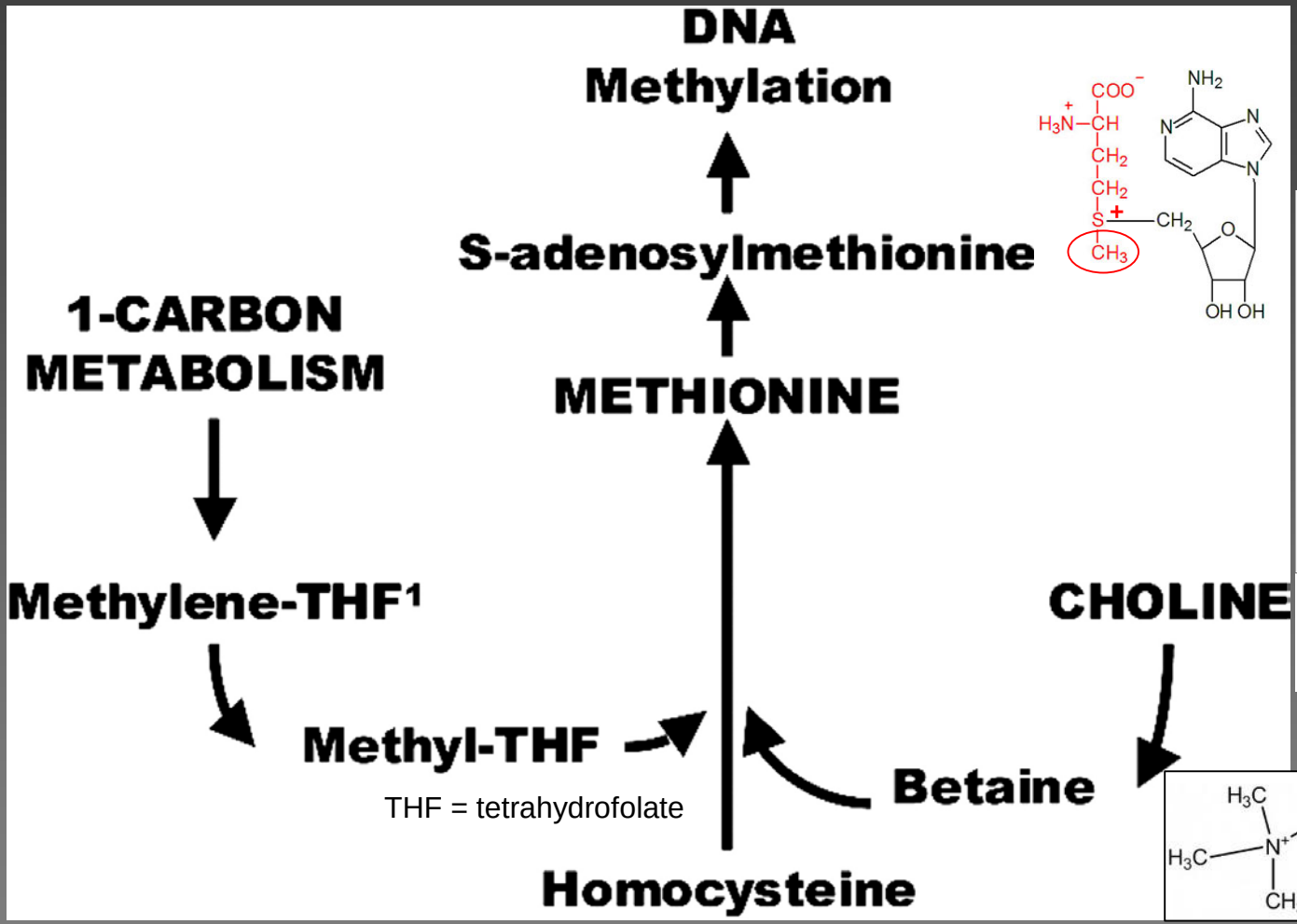
In the eusocial honey bee *Apis mellifera*, with reproductive queens and sterile workers, a female larva's developmental fate depends on its diet; nurse bees feed queen-destined larvae exclusively royal jelly, a glandular secretion, but worker-destined larvae receive royal jelly for 3 days and subsequently jelly to which honey and beebread are added. RNA-Seq analysis demonstrated that *p*-coumaric acid, which is ubiquitous in honey and beebread, differentially regulates genes involved in caste determination. Rearing larvae in vitro on a royal jelly diet to which *p*-coumaric acid has been added produces adults with reduced ovary development. Thus, consuming royal jelly exclusively not only enriches the diet of queen-destined larvae but also may protect them from inhibitory effects of phytochemicals present in the honey and beebread fed to worker-destined larvae.

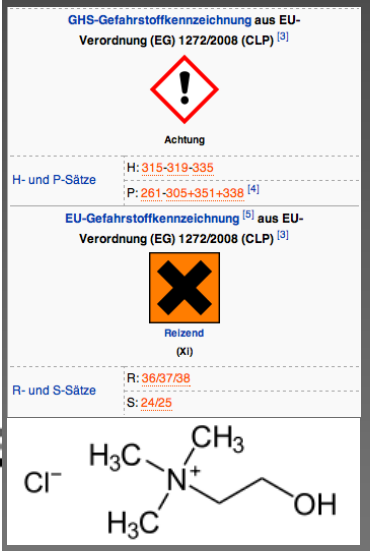


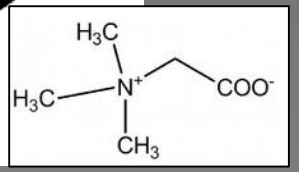
p-coumaric acid

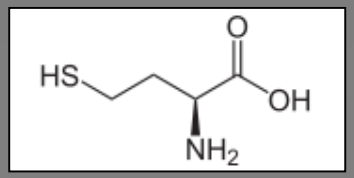
Mao, Schuler, Berenbaum Sci. Adv. 2015;1:e1500795 28 August 2015

Nutri-epigenomics: nutrition and DNA-methylation









Niculescu M D , Zeisel S H J. Nutr. 2002;132:2333S-2335S
Diet, Methyl Donors and DNA Methylation: Interactions between Dietary Folate, Methionine and Choline

transgenerational effects: imprinting

imprinting: differential gene expression from maternal and paternal alleles.
differential expression NOT caused by differences in **sequence** (genetic)
but by differences in DNA and/or histone **modification** (epigenetic)

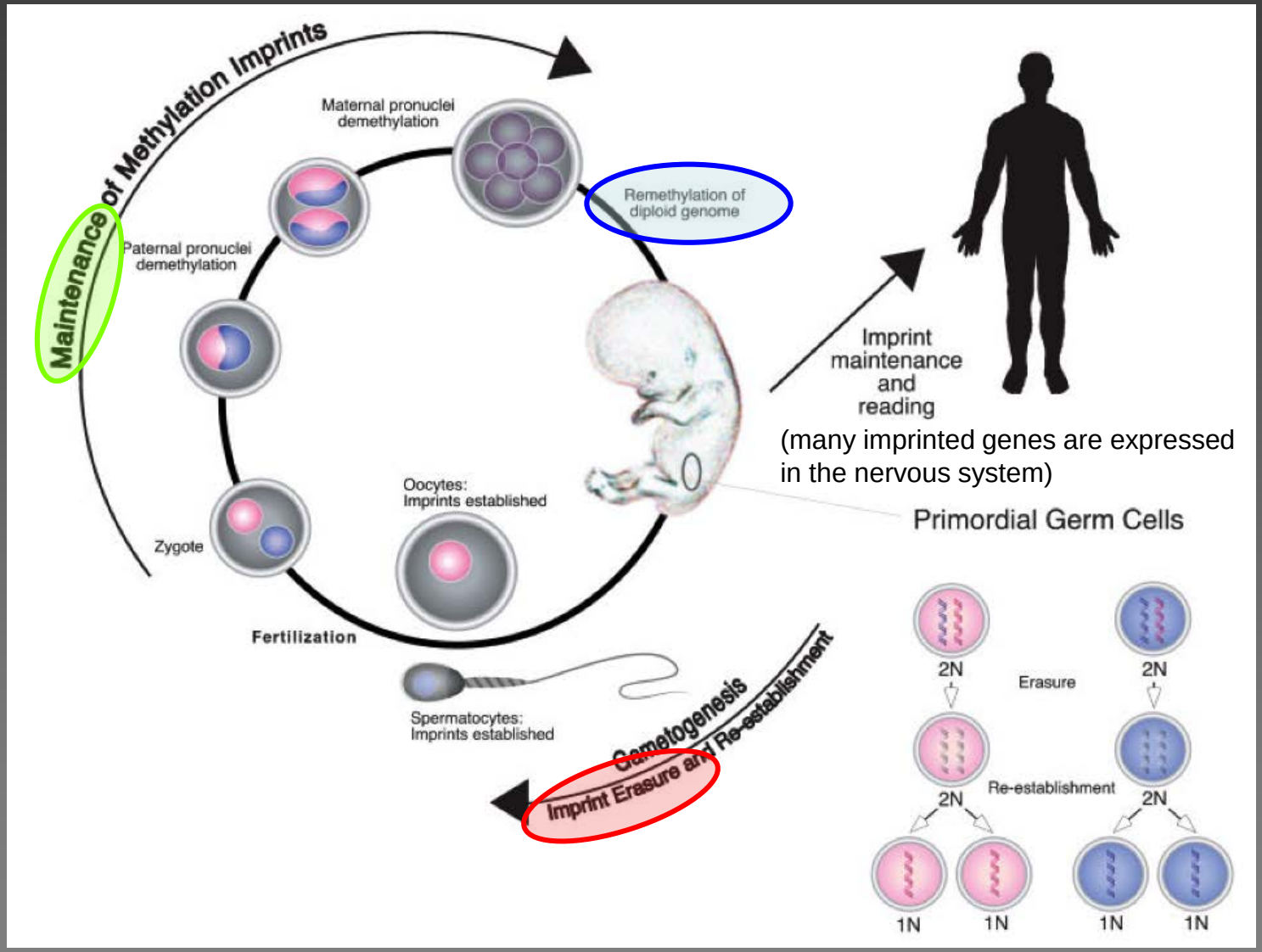
up to 200 genes are expected to be imprinted in human (156 genes identified by 2010)

Some imprinted genes are expressed from paternal, others from maternal genome; I. e. paternal and maternal genomes are functionally NOT equivalent (bi-parental requirement). Gynogenetic and androgenetic mouse embryos (generated by pronuclear transplantation) die during embryogenesis. Gynogenetic embryos have under-developed placentae, androgenetic embryos *vice versa*. Imprinted genes not only control fetus and placental development but also maternal care of offspring.
parental conflict hypothesis: War of the sexes at genome level.

In the mouse, > 85% of imprinted genes cluster to 11 chromosomal regions. Embryos that are uniparentally disomic for these regions do not thrive.
Clusters can be up to 4 Mb.
Clusters can contain genes with reciprocal imprints.
Imprinting control region (ICR) can control imprinted expression of several genes in one cluster.
ICRs of different imprint clusters differ in sequence but share a high level of CpG dinucleotides.
Clustering of imprinted genes is conserved between mouse and human (functional significance)
Imprinting is caused by modification of histones and DNA.
Either the active or the inactive allele can be methylated.

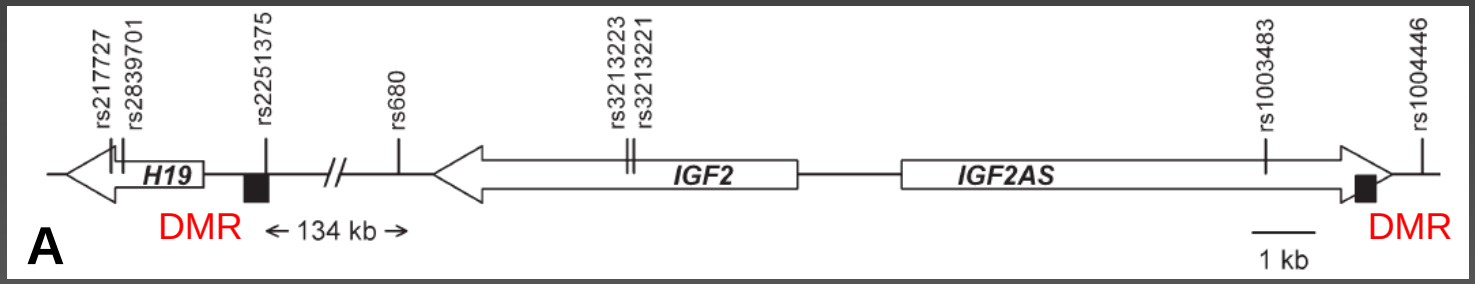
Imprinting is a transgenerational effect but imprints generally are not inherited across meiosis [?!]

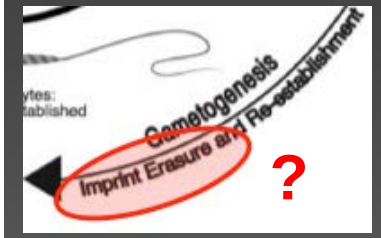
Genomic imprinting and erasure through the mammalian life cycle: (temporally remote) epigenetic control of development

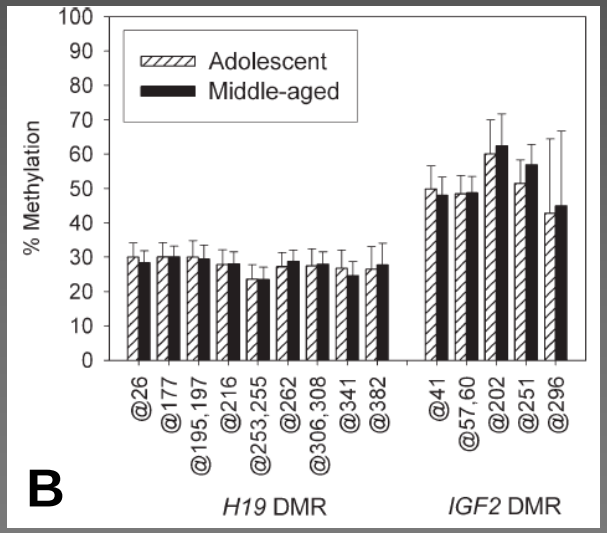


Murphy (2003) BioEssays 25, 577. Imprinting evolution and the price of silence

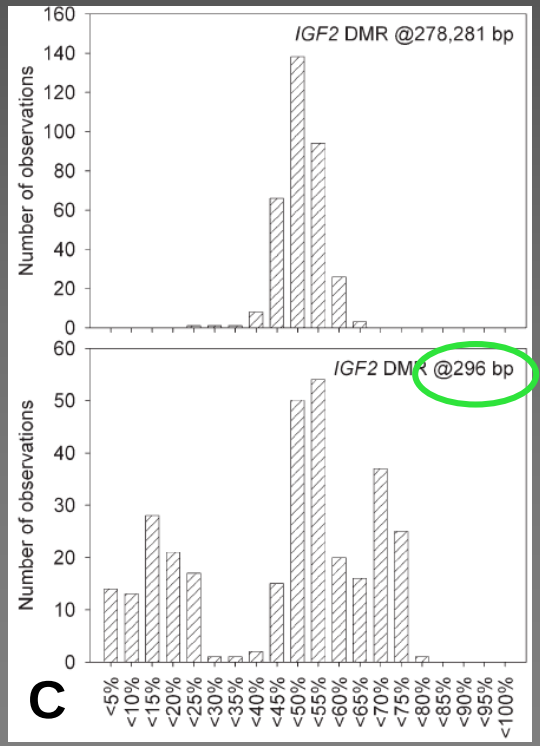
Heritability of the degree of methylation at particular CpGs in the differentially methylated regions (DMRs) of imprinted genes: genotype dependent remethylation **OR** incomplete erasure



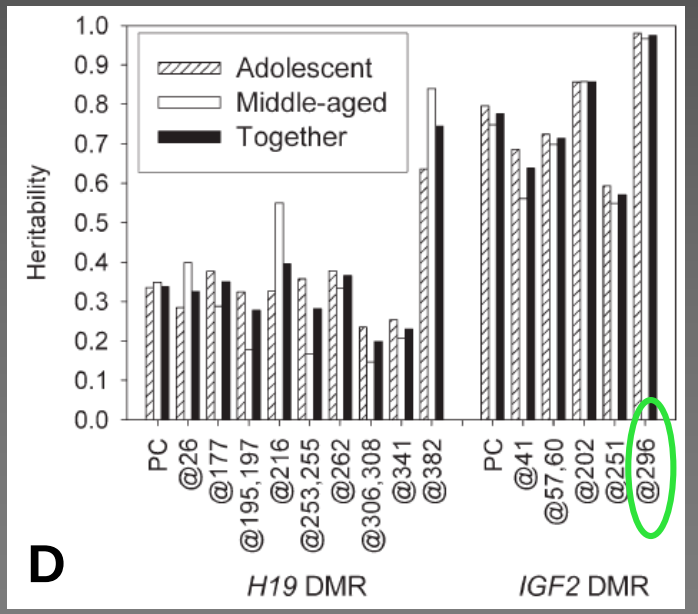




mean methylation (whole blood) is site-specifc and independent of age (372 individuals).



inter-individual variation of the extent of methylation at particular sites



Characteristic heritability of the degree of methylation at particular CpGs in the H19/IGF2-DMRs

Hejmans et al. (2007) Hum Mol Genet 16, 547

Transient environmental influences can produce persistent changes in epigenetic marks that can have life-long phenotypic consequences

Hejmans et al (2008): Persistent epigenetic differences associated with prenatial exposure to famine in humans

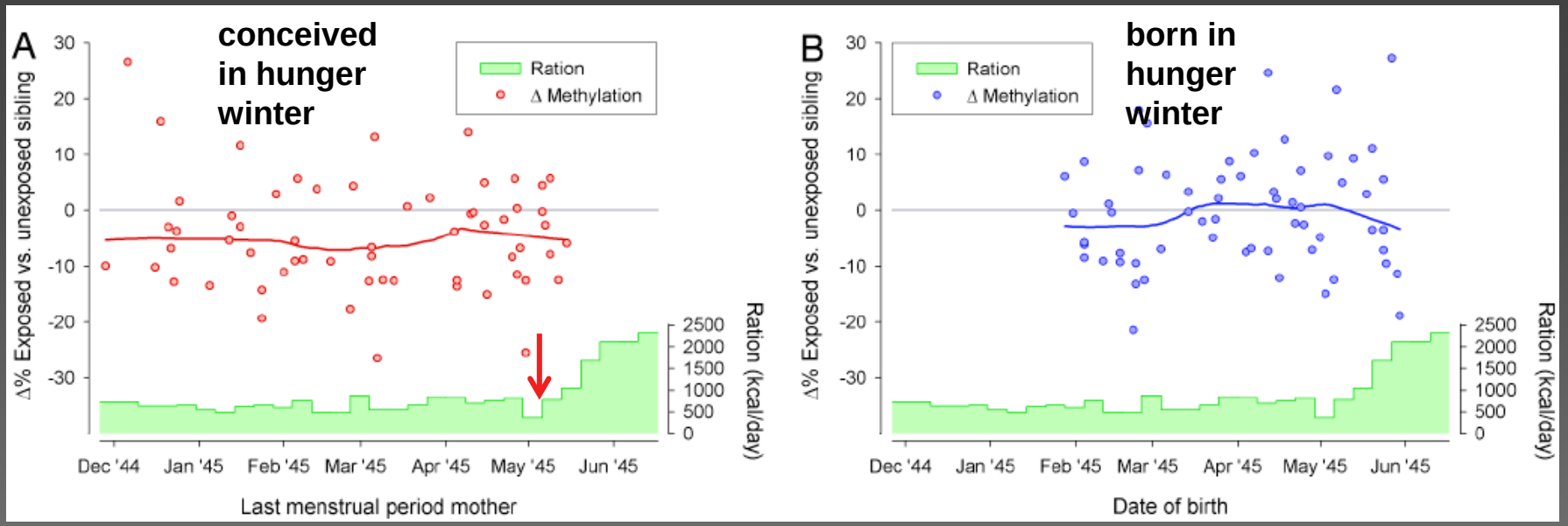


Table 3. Timing of famine exposure during gestation, *IGF2* DMR methylation, and birth weight

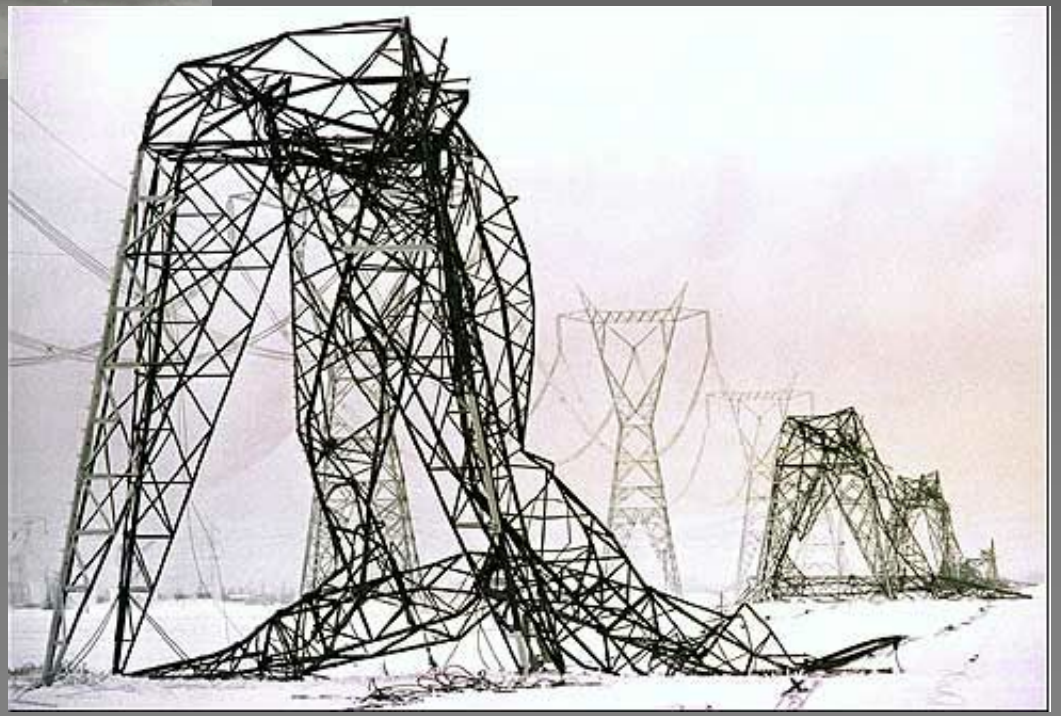
	Periconceptional exposure	Late gestational exposure	All controls
n	60	62	122
Males, %	46.7	45.2	45.9
Mean age, years	58.1 (SD, 0.35)	58.8 (SD, 0.4)	57.1 (SD, 5.5)
Birth weight, g	3612 (SD, 648)	3126 (SD, 408)	—
IGF2 DMR methylation			
Average	0.488 (SD, 0.047)	0.514 (SD, 0.045)	0.517 (SD, 0.047)
$P_{\text{vs all controls}}$	1.5×10^{-5}	.69	
$P_{\text{Interaction}}$			4.7×10^{-3}

P values were obtained using a linear mixed model and adjusted for age.

Analysis (after 58 years) of the *IGF2 DMR (a maternal, repressive imprint)* of males conceived *versus* born during the Dutch Hunger Winter 1944/45 (in comparison with their same-sex siblings born before or after this time).

The Great Icestorm 1998
(Eastern Canada, Northeastern USA)

DNA Methylation Signatures Triggered by Prenatal Maternal Stress Exposure to a Natural Disaster: Project Ice Storm Quebec province, January 6- 9 (1998)



Cao-Lei et al. (2014) PLOS ONE 9, e107653

Transgenerational effects in mammals are difficult to interpret

(are not necessarily evidence for inheritance)

nutrition of the mother affects:

the soma of the mother (1st generation)

the soma of the child (2nd generation)

the germ line in the developing foetus (3rd generation)

Transgenerational inheritance of epigenomic states in plants (?)

1

Cornelis van Haarlem (1562-1638), Two Followers of Cadmus Devoured by a Dragon (1588), oil on canvas on oak, 148.5 x 195.5 cm, The National Gallery (Presented by the Duke of Northumberland, 1838), London. Photo © The National Gallery, London.

2

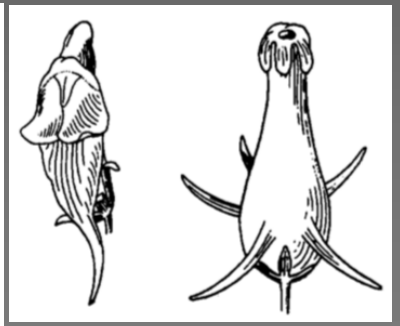
Cadmus and the Dragon, Laconian black-figure kylix C6th B.C., Musée du Louvre

From greek mythology (< 6th c BC) to Linné (1744): The making of the monster Pelor

3

4

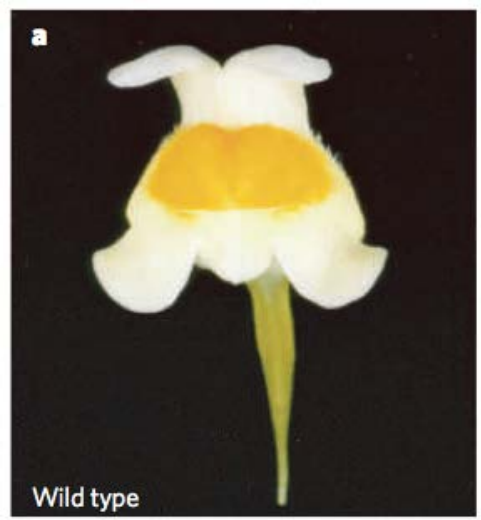
Peter Paul Rubens (workshop of), Cadmus Sowing Dragon's Teeth (1610-90), oil on panel, 27.7 x 43.3 cm, Rijksmuseum Amsterdam, Amsterdam. Wikimedia Commons.

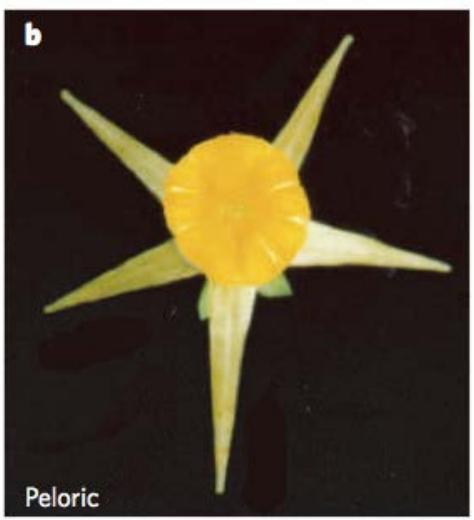


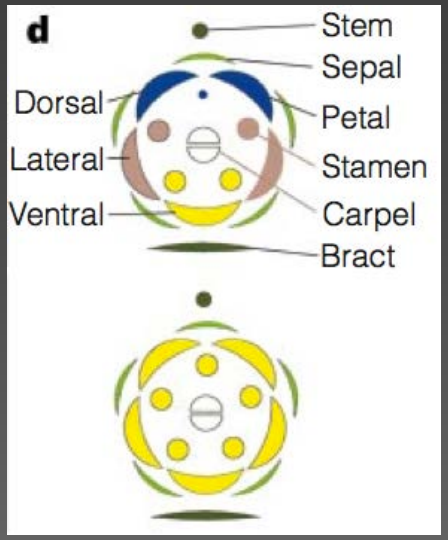
Goethes Morphologische Schriften Jena 1820

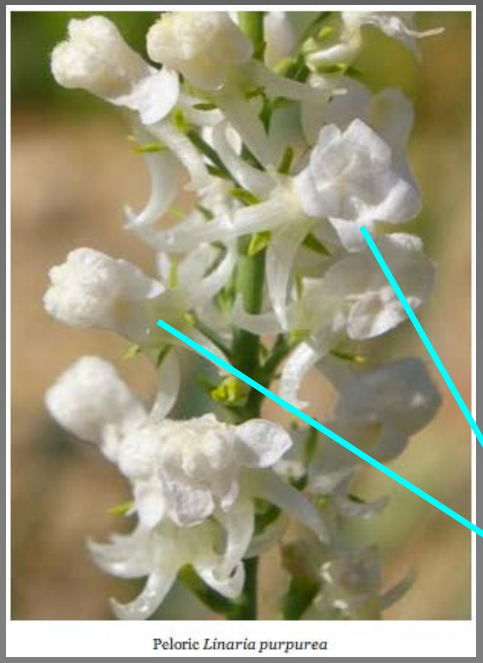
https://eclecticlight.co/2017/03/15/changing-stories-ovids-metamorphoses-on-canvas-10-cadmus-and-the-dragons-teeth/

Transgenerational inheritance of epigenomic states in plants (?)








Peloric *Linaria purpurea*

bilateral symmetry (zygomorphic) vs. radial symmetry (actinomorphic) in *Linaria vulgaris (Echtes Leinkraut, common toadflax)*

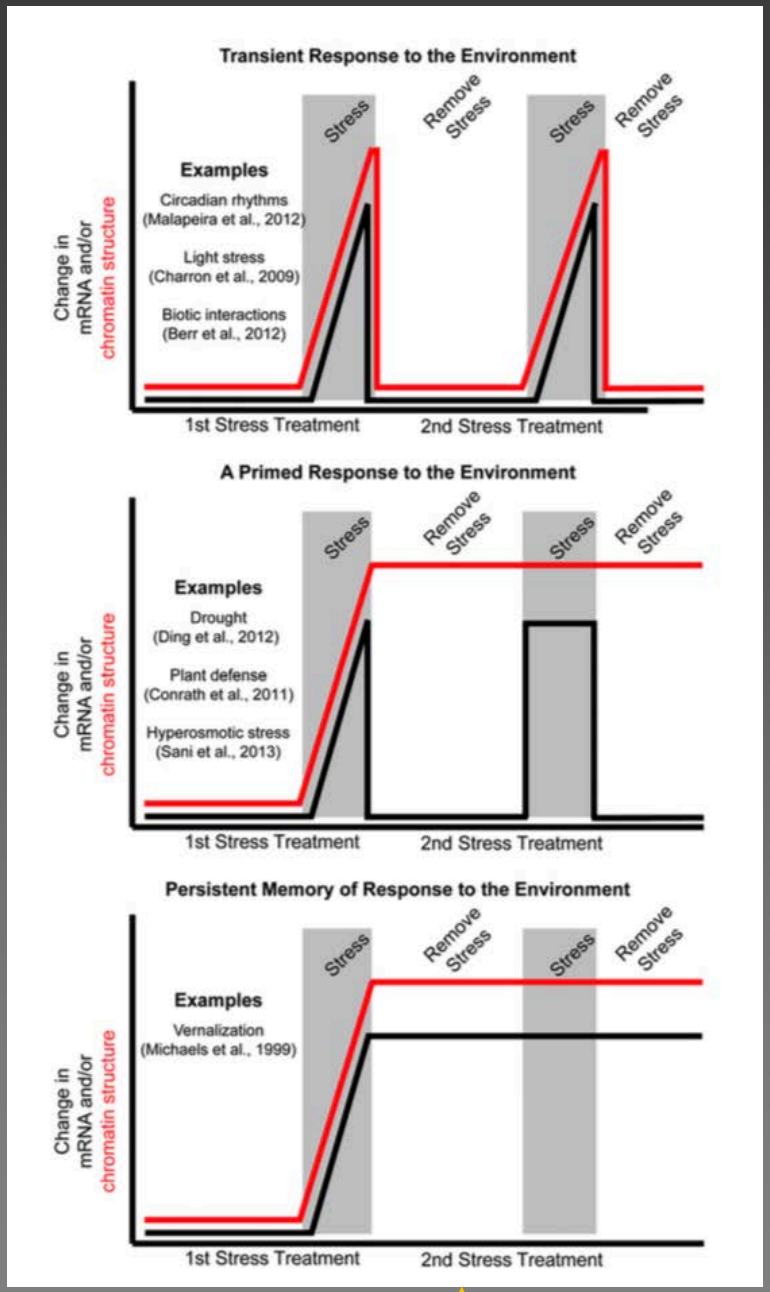
Radial phenotype is caused by (semi-stable) heritable methylation (and inactivation) of the *Linaria cycloidea* gene (*Lcyc*) which is a dorsal determinant.

Peloria is common in zygomorphic flowering plants

same genome [?], different epigenome

Cubas et al. (1999) Nature 401, 157
An epigenetic mutation responsible for natural variation in floral symmetry

Gustafsson (1979) Theor. Appl. Genet. 54, 241



meiosis

No good evidence for transgenerational epigenetic inheritance of selected traits in plants

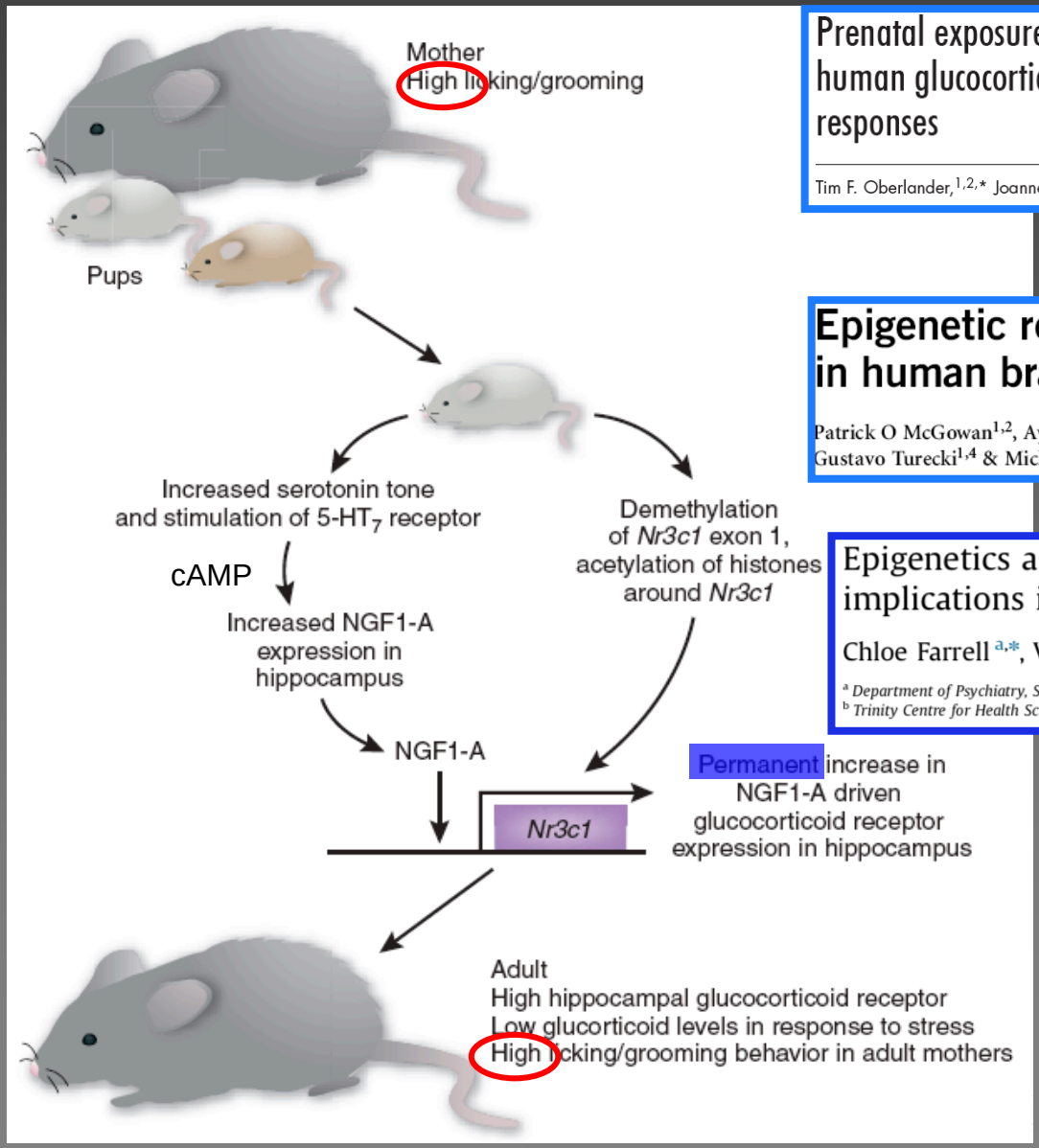
Eichten et al., (2014)
Plant Physiology 165, 933
Epigenetics: Beyond Chromatin Modifications and Complex Genetic Regulation

Verhoeven et al., (2016)
Molecular Ecology 25, 1631
Epigenetics in ecology and evolution: what we know and what we need to know

advanced reading:
https://en.wikipedia.org/wiki/Trofim_Lysenko

Transgenerational effect/inheritance without material transfer: Effects of tenderness.

Prenatal maternal and early developmental influences on adult behavior mediated by „epigenetic“ regulation of *glucocorticoid receptor* expression



Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (*NR3C1*) and infant cortisol stress responses

Epigenetics 3, 97 (2008)

Tim F. Oberlander,[1,2,*] Joanne Weinberg,[2,3] Michael Papsdorf,[1] Ruth Grunau,[1,2] Shaila Misri[4] and Angela M. Devlin[1,2]

Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse

Patrick O McGowan[1,2], Aya Sasaki[1,2], Ana C D'Alessio[3], Sergiy Dymov[3], Benoit Labonté[1,4], Moshe Szyf[2,3], Gustavo Turecki[1,4] & Michael J Meaney[1,2,5]

Nature Neuroscience 12, 342 (2009)

Epigenetics and the glucocorticoid receptor: A review of the implications in depression

Psychiatry Research 242, 349(2016)

Chloe Farrell [a,*], Veronica O'Keane [a,b]

[a] *Department of Psychiatry, School of Medicine, Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin 2, Ireland*
[b] *Trinity Centre for Health Sciences, AMNCH (Tallaght) Hospital, Tallaght, Dublin 24, Ireland*

Hyman (2009) Nature Neuroscience 12, 241.
How adversity gets under the skin

Further examples of non-mendelian inheritance in mammals

Rassoulzadegan, M., V. Grandjean, P. Gounon, S. Vincent, I. Gillot, and F. Cuzin,
RNA-mediated non-mendelian inheritance of an epigenetic change in the mouse.
Nature, 2006. 441(7092): p. 469-74.

Franklin, T.B., H. Russig, I.C. Weiss, J. Graff, N. Linder, A. Michalon, S. Vizi, and I.M. Mansuy,
Epigenetic transmission of the impact of early stress across generations.
Biol Psychiatry, 2010. 68(5): p. 408-15.

Zeybel, M., et al.,
Multigenerational epigenetic adaptation of the hepatic wound-healing response.
Nat Med, 2012. 18(9): p. 1369-77.

Dias, B.G. and K.J. Ressler,
Parental olfactory experience influences behavior and neural structure in subsequent generations.
Nat Neurosci, 2014. 17(1): p. 89-96.

Perspective

Transgenerational epigenetic inheritance: More questions than answers

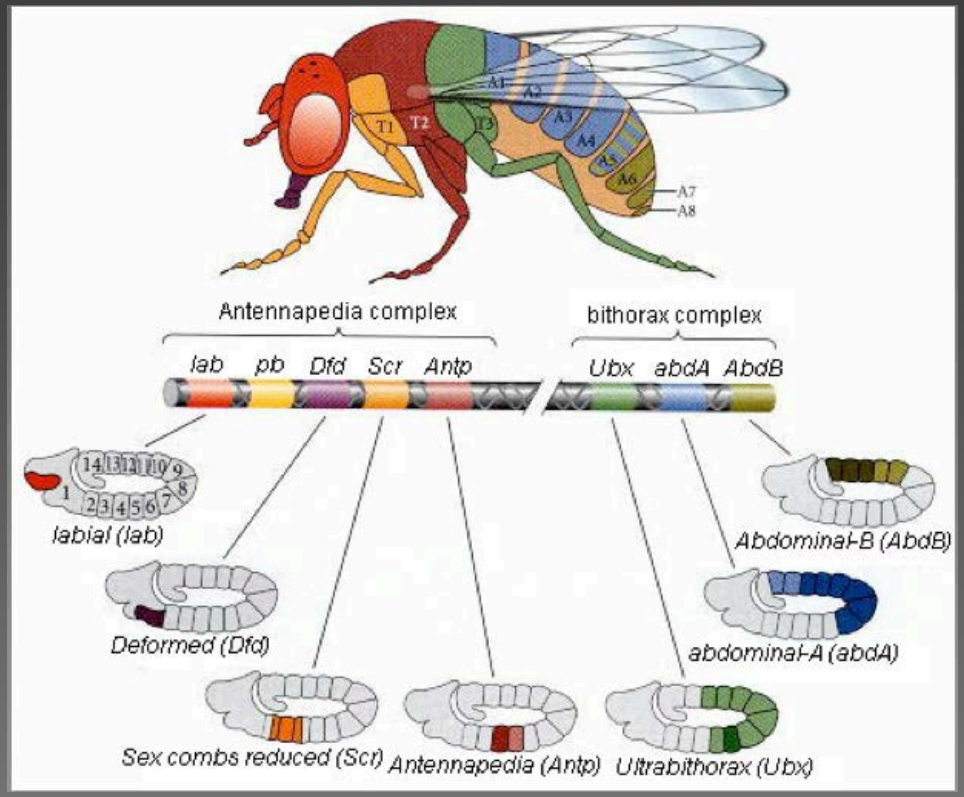
Lucia Daxinger and Emma Whitelaw[1]

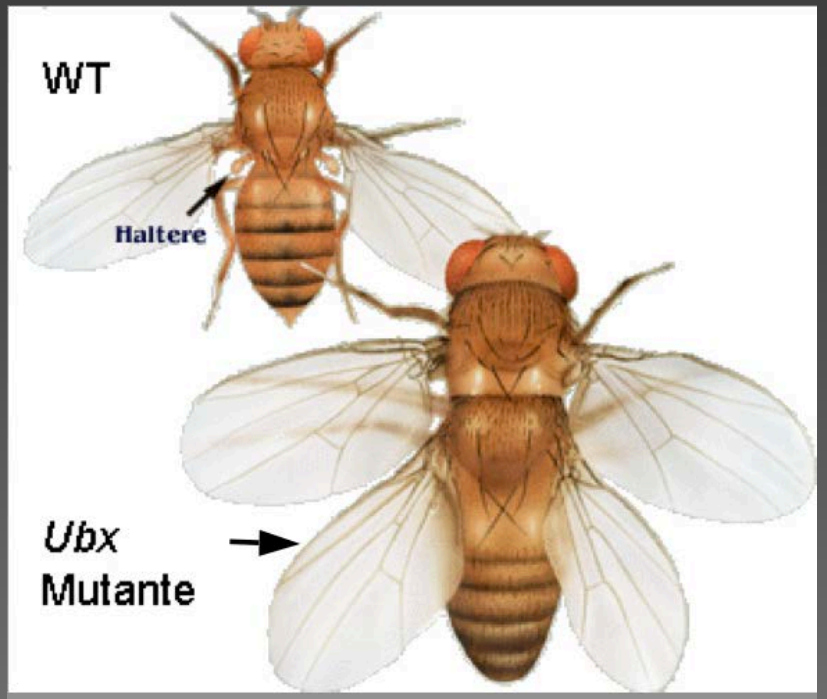
Epigenetics Laboratory, Queensland Institute of Medical Research, Herston, Brisbane, Queensland 4006, Australia

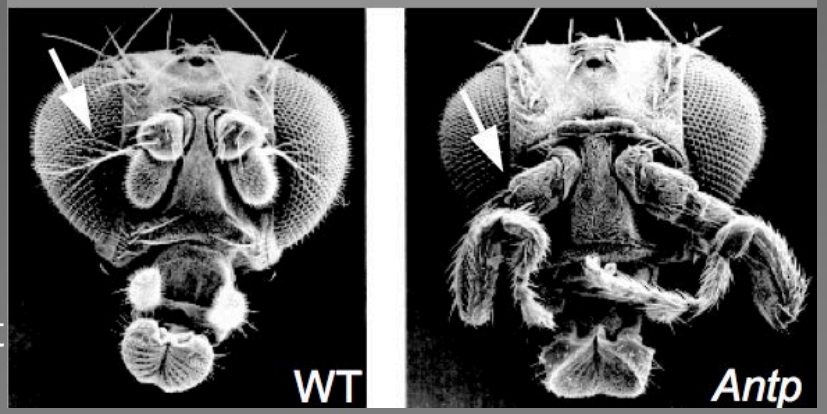
Epigenetics became an established discipline in the 1970s and 1980s as a result of work carried out by geneticists using model organisms such as *Drosophila* (Henikoff 1990). Originally, this research area aimed to understand those instances in which stable changes in genome function could not be explained by changes in DNA sequence. This definition suited Waddington's original purpose, i.e., to explain how a multicellular organism could develop from one genome (Waddington 1942). More recently, with increasing knowledge of the underlying molecular mechanisms, the field has taken on a more biochemical flavor (Bird 2007; Kouzarides 2007).

Daxinger and Whitelaw (2010) Genome Res 20,1623

Homeotic genes and homeotic mutations







The spatially restricted expression of homeotic genes is established in early embryogenesis under the control of maternal and segmentation genes.

How is Hox gene expression maintained throughout development, when the early patterning genes are no longer expressed?

By the action of *Polycomb*-group (*PcG*, repressive) and *trithorax*-group (*trxG*, activating) genes

HOMOEOSIS IN DROSOPHILA: A NEW ENHANCER OF POLYCOMB AND RELATED HOMOEOTIC MUTATIONS

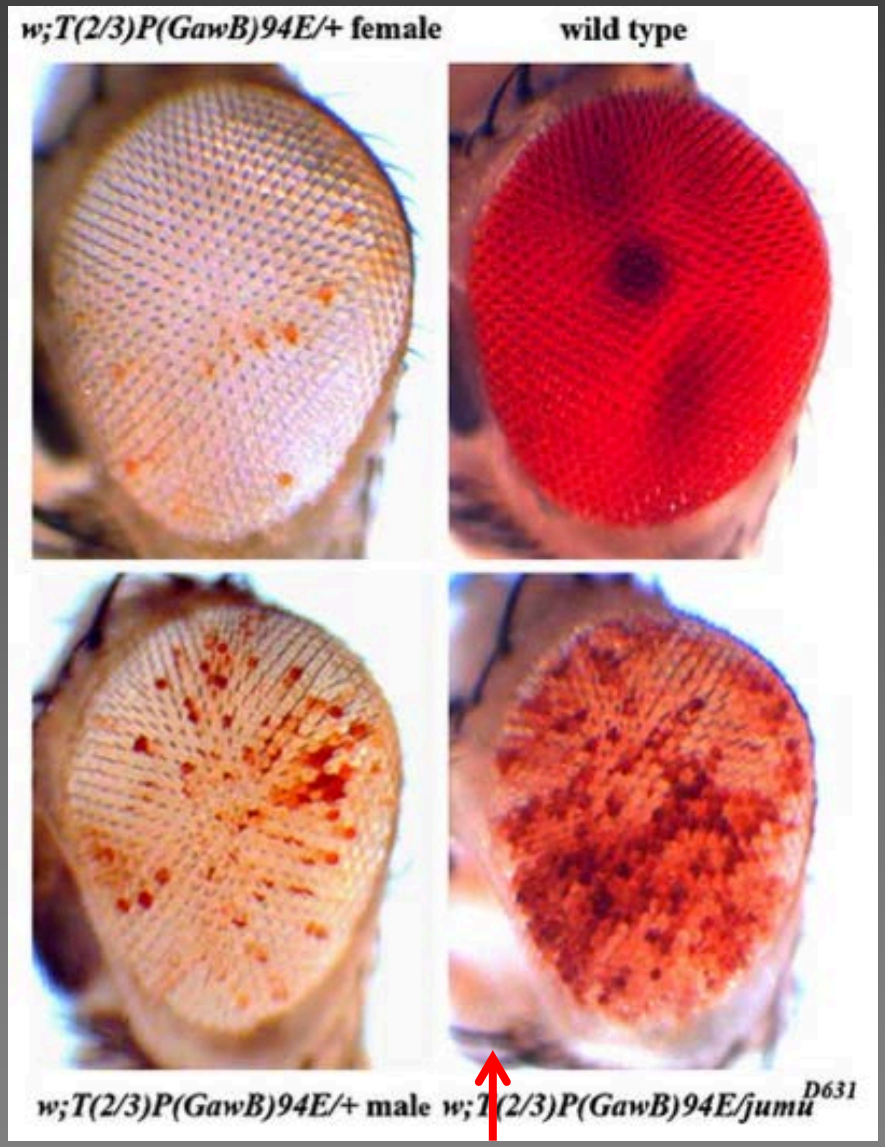
TAKASHI SATO,* MICHAEL A. RUSSELL† AND R. E. DENELL*

Many epigenetically relevant genes were first identified as mutations in *Drosophila* with a homeotic phenotype

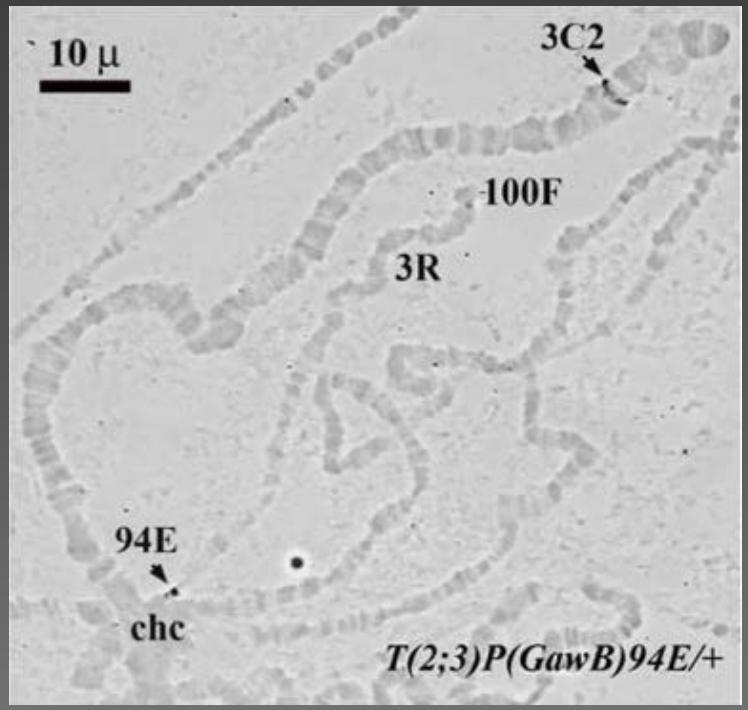
Locus	Location	Variant	Adult phenotype*
Antennapedia	3-47.7	$Antp^{75b}$	Antenna to leg (het)
		$Antp^{Ns}$	Antenna to leg (het and homo)
		$Antp^{EIW15}$	2nd and 3rd to 1st leg (het)
		$Antp^{Scx}$	2nd and 3rd to 1st leg (het)
Contrabithorax	3-58.8	Cbx^{1}	Wing to haltere (het and homo)
engrailed	2-62.0	en^{1}	Posterior to anterior compartment in wing and other structures (homo)
		en^{LA7}	Lethal (homo)
		$Df(2R)en^{28}$	Lethal (homo)
		$Df(2R)en^{50}$	Lethal (homo)
		$Df(2R)en^{A}$	Lethal (homo)
		$Df(2R)en^{B}$	Lethal (homo)
		$Df(2R)en^{SFX51}$	Lethal (homo)
		$T(2;3)en^{SFX57}$	Lethal (homo)
		$T(2;3)Es$	Lethal (homo)
extra sex comb	2-54.9	esc^{1}	2nd and 3rd to 1st leg (homo)
lethal(4)29	4-(within Df(4)G)	$l(4)29$	2nd and 3rd to 1st leg and other effects (homo)
Polycomb	3-48	Pc^{1}, Pc^{3}, Pc^{R1}	2nd and 3rd to 1st leg and other effects (het)
		Pc^{73}	2nd and 3rd to 1st leg (homo)
		$Df(3L)Pc^{MK}$	2nd and 3rd to 1st leg (het)
Polycomblike	2-84	Pcl^{1}, Pcl^{W6}	2nd and 3rd to 1st leg and other effects (het)
		$Df(2R)11B$	2nd and 3rd to 1st leg and other effects (het)
		$Df(2R)Pcl^{W5}$	2nd and 3rd to 1st leg and other effects (het)
		$In(2R)Pcl^{W4}$	2nd and 3rd to 1st leg and other effects (het)
Sex comb reduced	3-47.7	$In(3R)Sre^{Mw}$	1st to 2nd leg, and 2nd and 3rd to 1st leg (het)

Sato et al. (1983) Genetics 105, 357
Ng and Kopp (2008) Behav. Genet. 38, 195

Position effect variegation (PEV): stochastic inactivation of euchromatic genes translocated close to heterochromatin



reduced variegation compared to the isogenic male control (left). *jumu* as haplo-suppressor

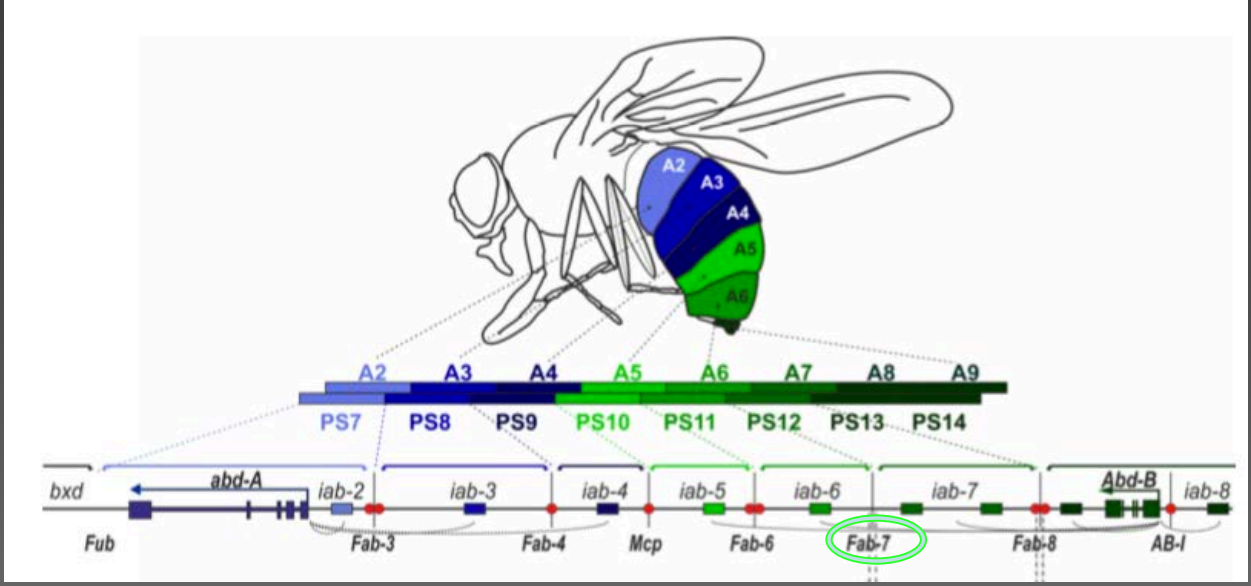


P(GawB) is a white+ marked transposable element translocated close to the chromocenter in this line.

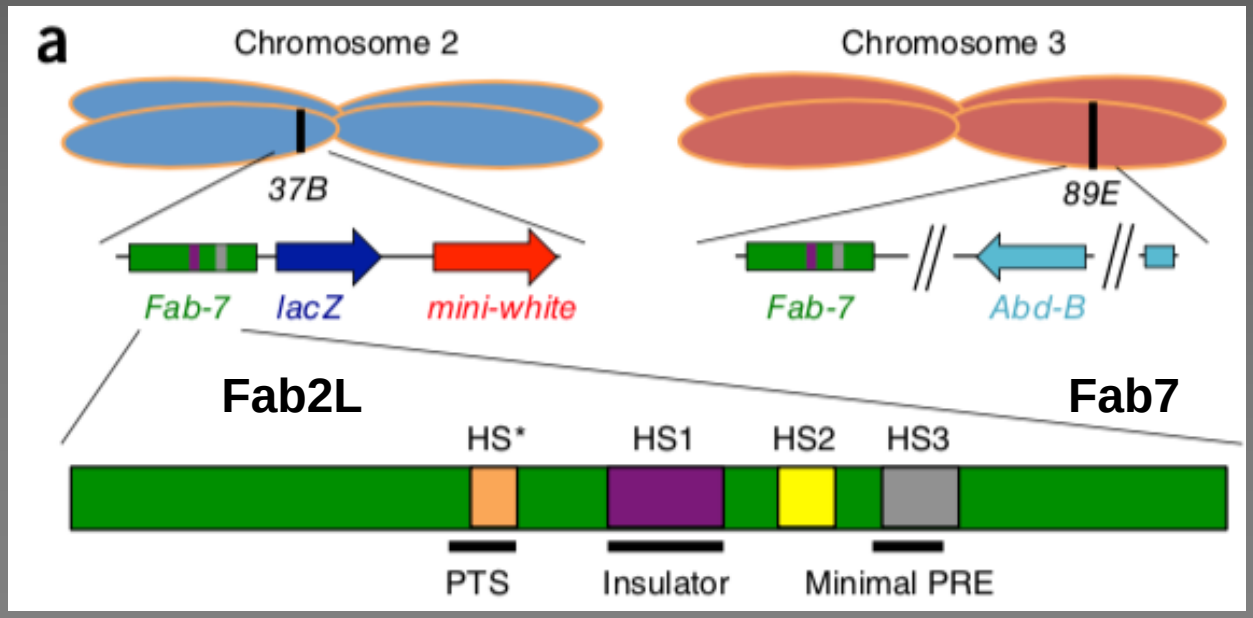
PEV is sensitive to modifiers.
Here: influence of *jumeaux* (*jumu*),
a haplo-suppressor/triplo-enhancer of PEV

Hofmann et al. (2009) Chromosome Res 17, 347

Stable Polycomb-dependent transgenerational inheritance of chromatin states in *Drosophila*



Fab-7: a regulatory element from the AbB region of the *Bithorax* gene complex (Bx-C)

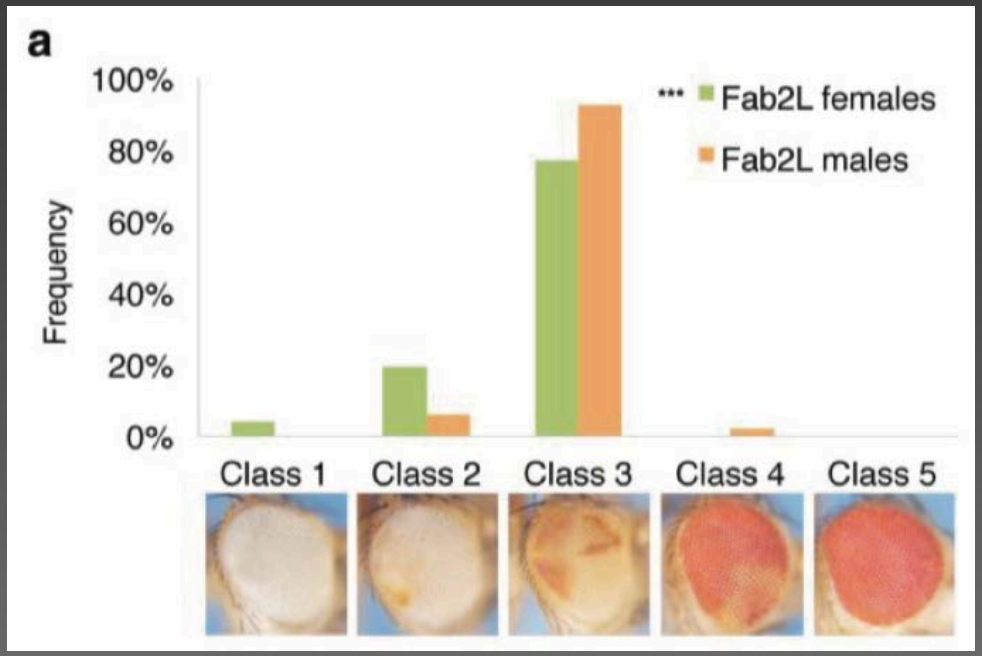


The genetic make-up:
endogenous Fab-7 element on chrs. 3 and Fab-7 containing transgene on chrs. 2

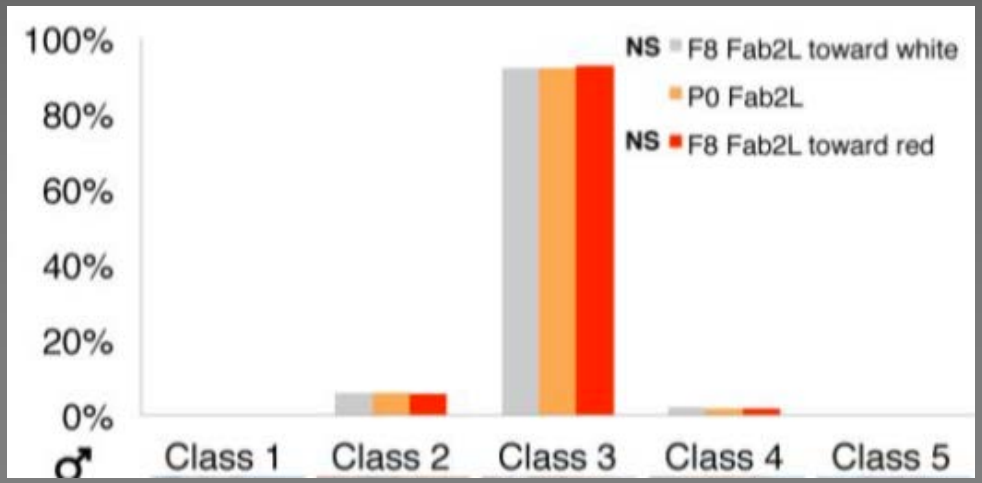
PTS = promoter targeting sequence
PRE = Polycomb response element
HS = nuclease sensitive chromatin regions

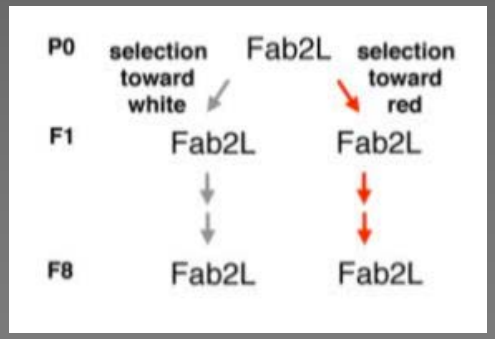
Ciabrelli et al., (2017) Nat. Genet. 49, 876
Kyrchanova et al. (2016) PLOS Genet.

Stable Polycomb-dependent transgenerational inheritance of chromatin states in *Drosophila*



The starting situation: Fab2L/Fab2L; +/+ flies (with four copies of Fab element) show standard position effect variegation (controlled by Pc and Trx group genes)

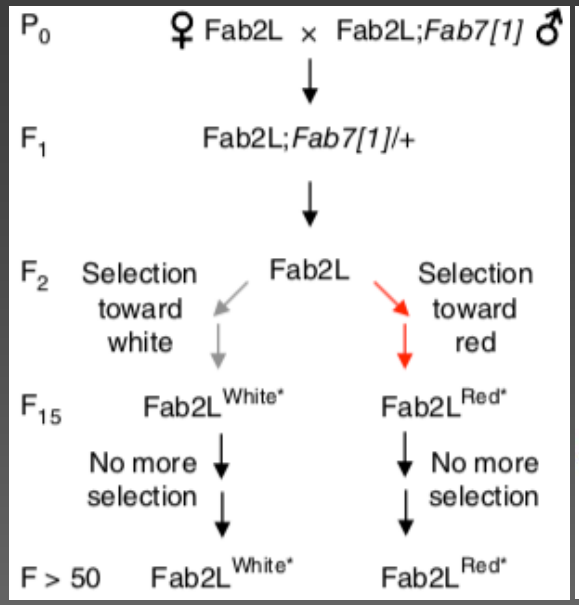


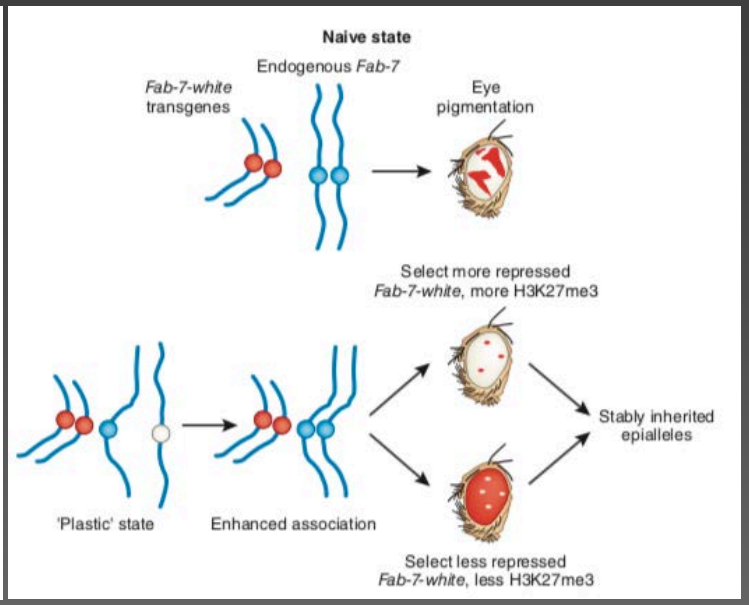


The distribution of pigmentation does not change by selection for low or high pigmentation (after eight generations)

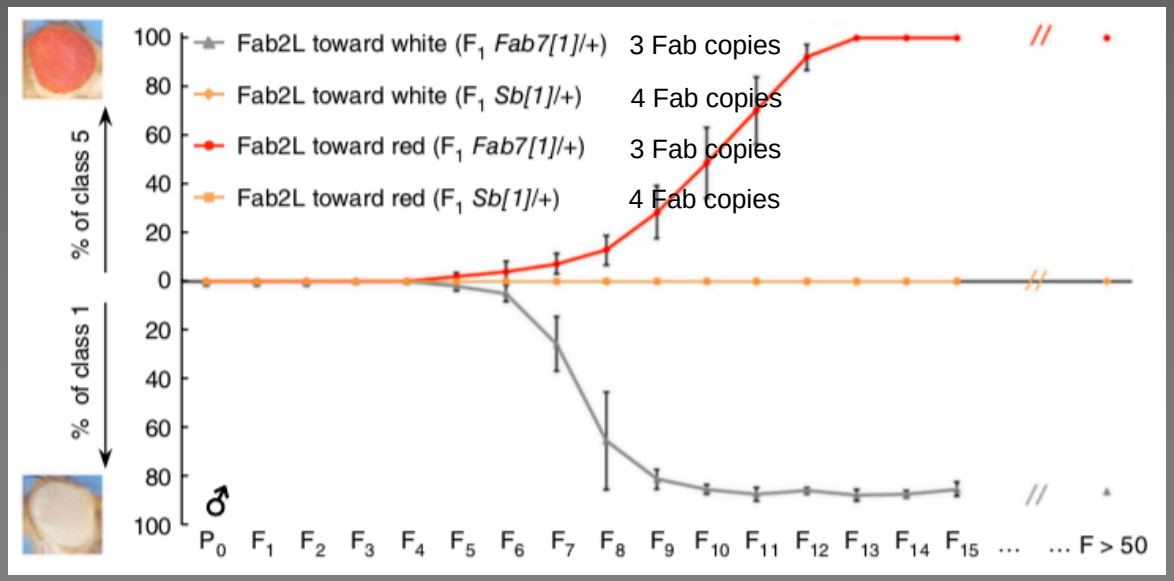
Ciabrelli et al., (2017) Nat. Genet. 49, 876

Stable Polycomb-dependent transgenerational inheritance of chromatin states in *Drosophila*



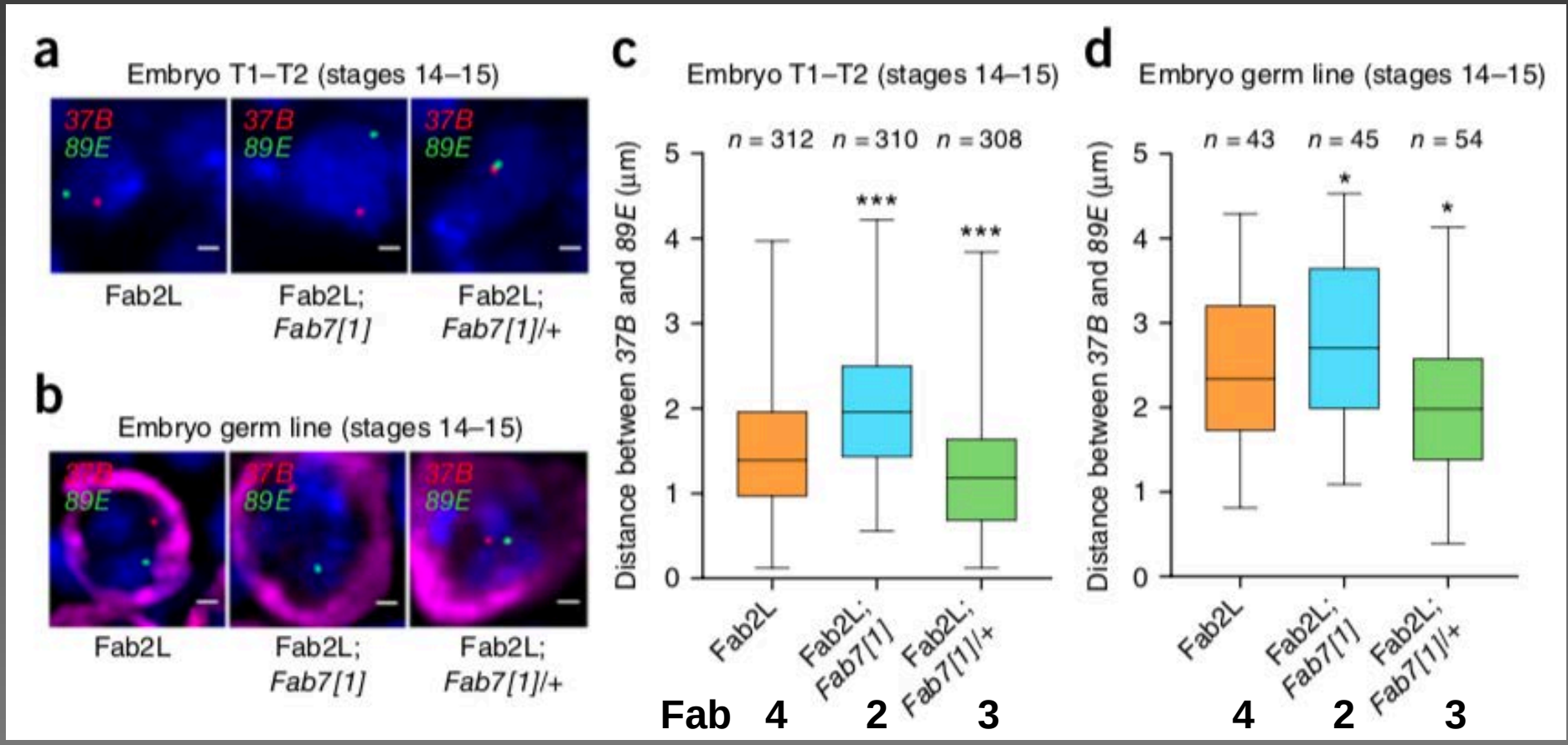


Introduction of transient heterozygosity of the endogenous Fab-7 copy allows the selection of high and low pigmentation epilines, which are identical at the DNA sequence level



Ciabrelli et al., (2017) Nat. Genet. 49, 876
Pirrotta (2017) Nat. Genet. 49, 821

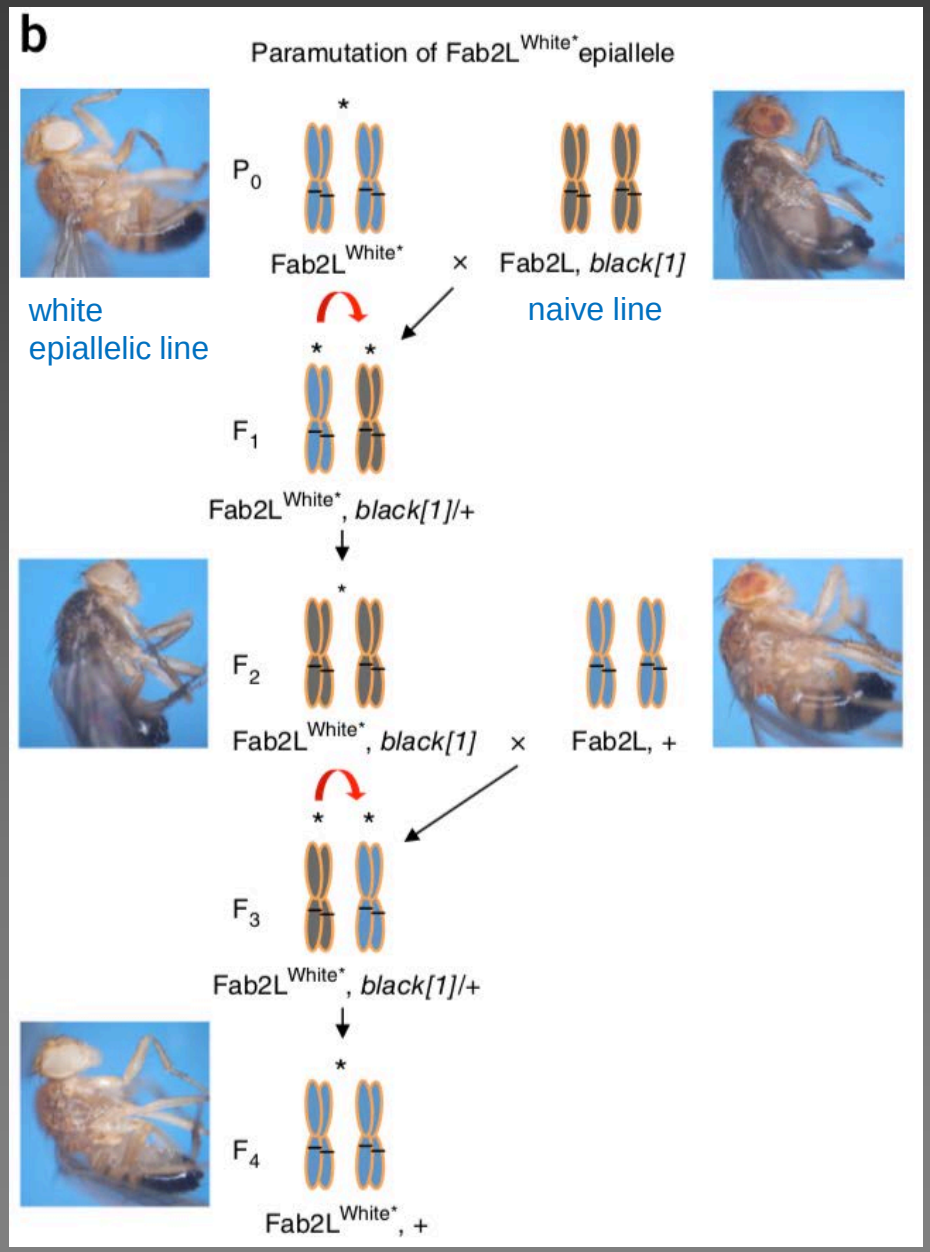
Stable Polycomb-dependent transgenerational inheritance of chromatin states in *Drosophila*



Establishment of epialleles is associated with increased long-range interaction between the chromosomal regions (FISH = fluorescent in situ hybridization)

Ciabrelli et al., (2017) Nat. Genet. 49, 876

Stable Polycomb-dependent transgenerational inheritance of chromatin states in *Drosophila*



The epiallele chromatin state is contagious: it can induce paramutation of "normal" alleles

The originally naive [*black*] chromosome are transformed to the white epiallelic state

The [*black*] white epialleles have gained transforming power

Ciabrelli et al., (2017) Nat. Genet. 49, 876

Transvection: one allele influences the expression of the other allele, if paired

Vol. LXXXVIII, No. 841 The American Naturalist July–August, 1954

THE THEORY AND APPLICATION OF A NEW METHOD OF DETECTING CHROMOSOMAL REARRANGEMENTS IN *DROSOPHILA MELANOGASTER*[1]

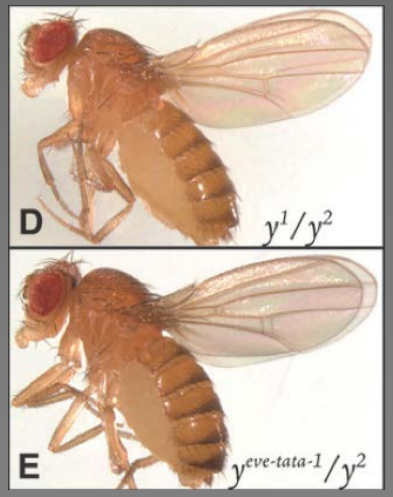
E. B. LEWIS

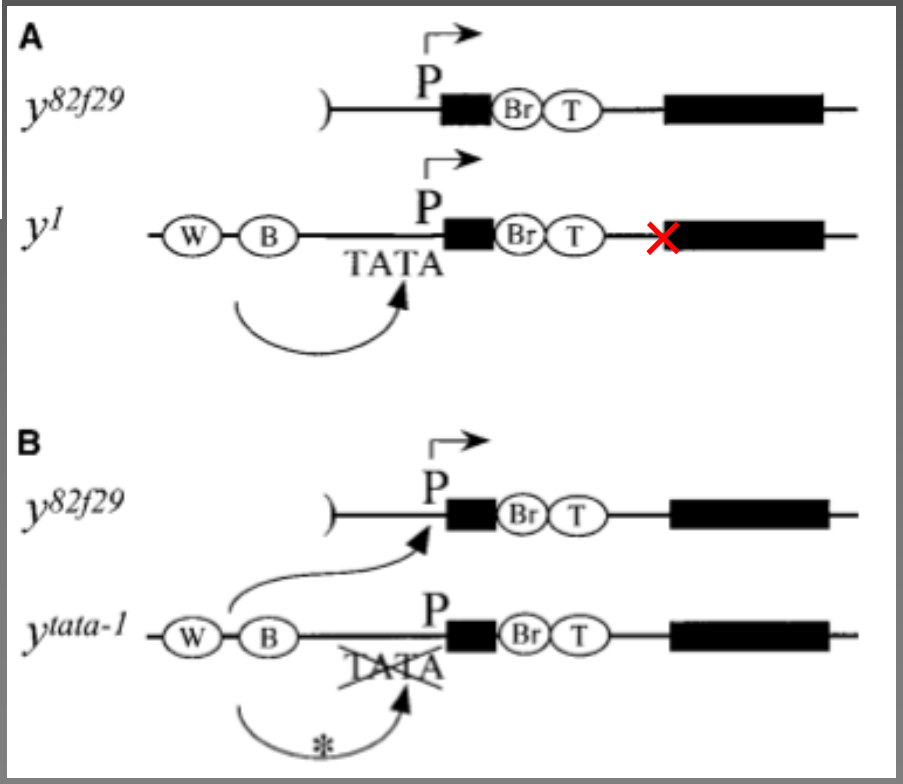
Kerckhoff Laboratories of Biology, California Institute of Technology, Pasadena

A new method of detecting chromosomal rearrangements in *Drosophila melanogaster* has been applied to the problem of measuring the biological effects of ionizing radiations from nuclear detonations. The method, itself, is an outgrowth of studies of the bithorax pseudoallelic genes near the middle of the right arm of the third chromosome (Lewis, 1951). It will be called the "bithorax" method. Results of applying it to the detection of X-ray induced rearrangements will be considered first.

Ed Lewis, Nobel laureate 1995

Pairing can be disrupted by introducing chromosomal rearrangements

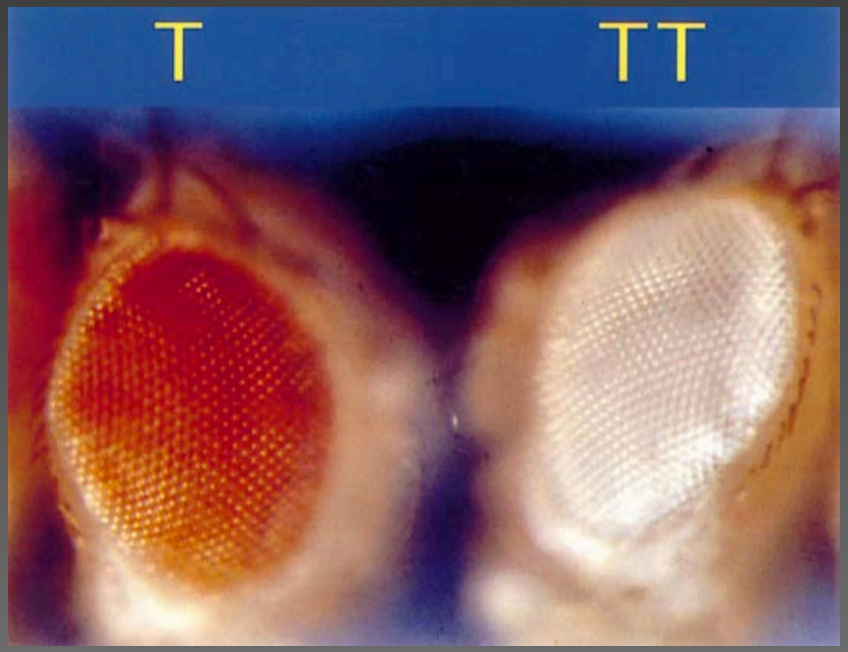




w = wing, b = body, br = bristle, t = tarsi

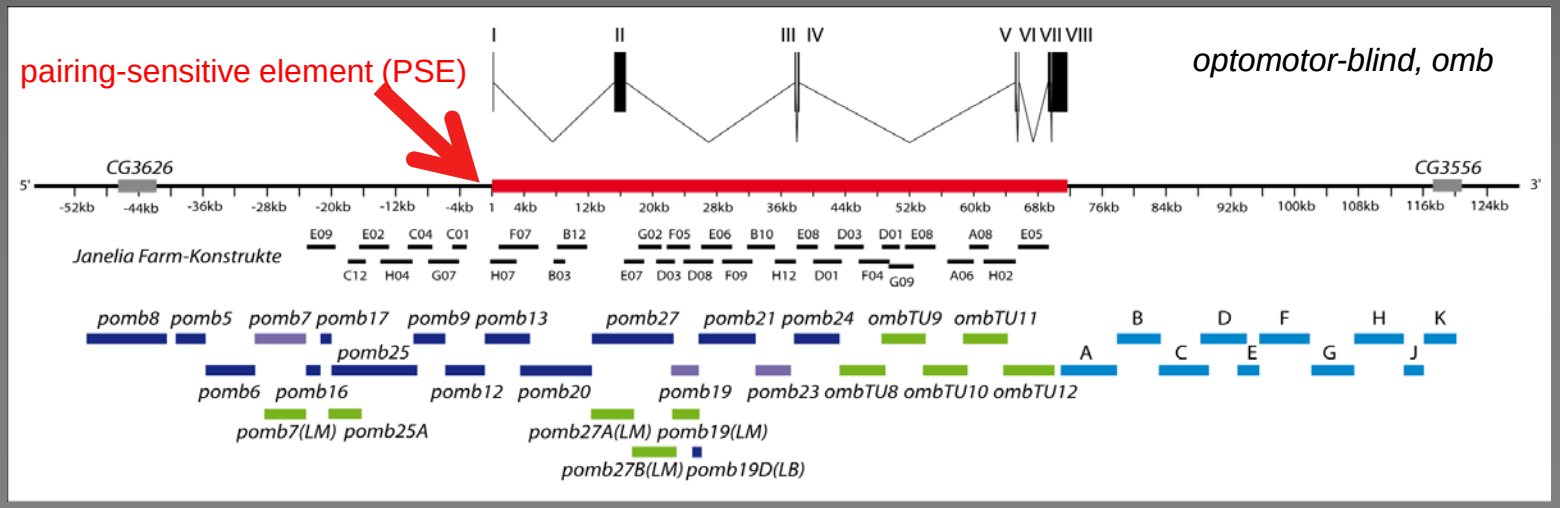
Morris et al. (2004) Genetics 167, 1739

A special case of transvection: Pairing-sensitive silencing (PSS)



T = single copy of transgene construct including marker gene *white* [heterozygous]

TT = two copies of transgene construct including marker gene *white* [homozygous]



Pirrotta (1999) BBA 1424, M1

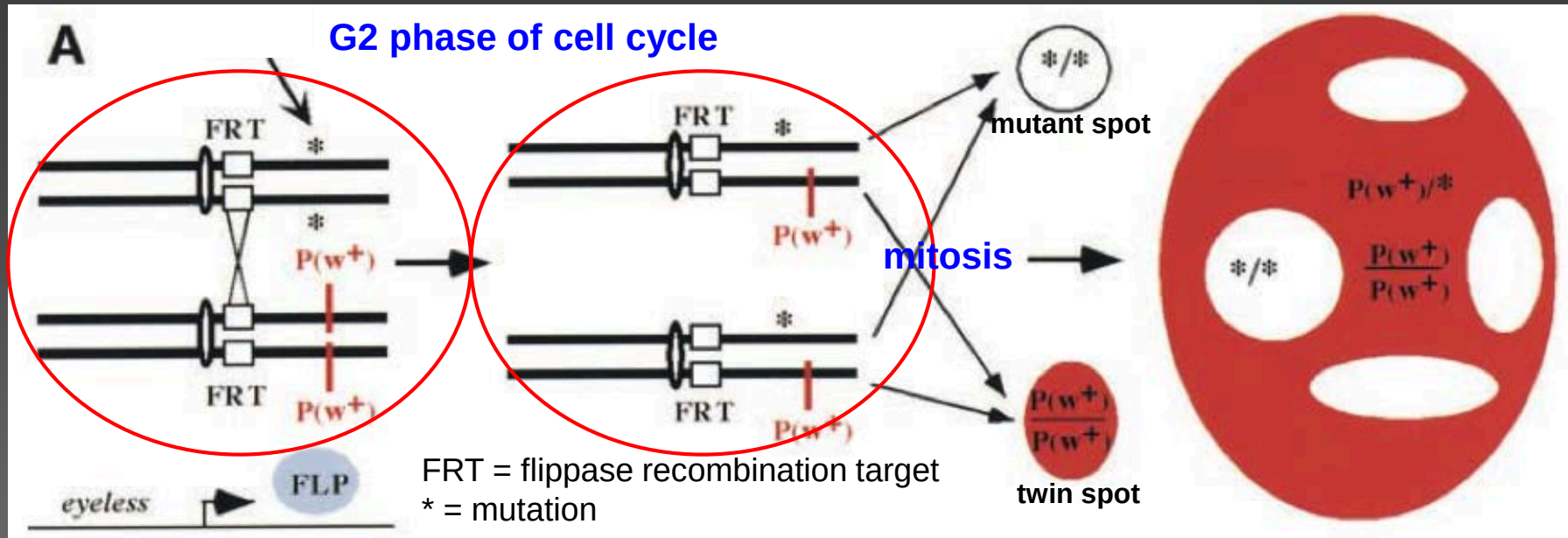
Biochemical composition of PcG and trxG complexes

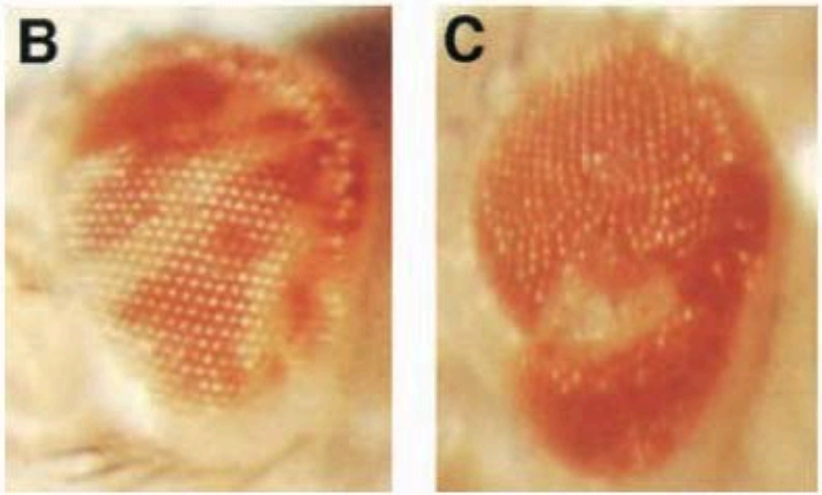
	Drosophila melanogaster	Human
PcG complexes		
PhoRC	dSfmbt Scm-related gene containing four mbt domains	?
	Pho Pleiohomeotic	?
PRC2	E(z) Enhancer of zeste	EZH2
	Esc Extra sex combs	EED
	Su(z)12 Suppressor of zeste	SUZ12
	N55	RpAp48
		RpAp46
PRC1	dRing	RING1A
	Pc Polycomb	HPC1-3
	Ph Polyhomeotic	HPH1-3
	Psc Posterior sex combs	BMI1
	Scm Sex comb on midleg	SCMH1-2
	TBP-associated factors	

	Drosophila melanogaster	Human
trxG complexes		
SWI/SNF	Brm	BRM
	Osa	BAF250
	Moira	BAF170
	Snr1	BAF47
NURF	Iswi	SNF2L
	N38	?
	N301	BPTF
	N55	RpAp46 RpAp48
TAC1	Trx[a] Trithorax	
	dCBP	
	Sbf1	
Ash1	Ash1 absent, small, or homeotic discs 1	
	dCBP	
MLL1-3		MLL1-3[a]
		WDR5
		ASH2L
		RbBP5
		CFP1

Schuettengruber et al. (2007) Cell 128, 735

Technique: Site-specific recombination for the generation of somatic clones

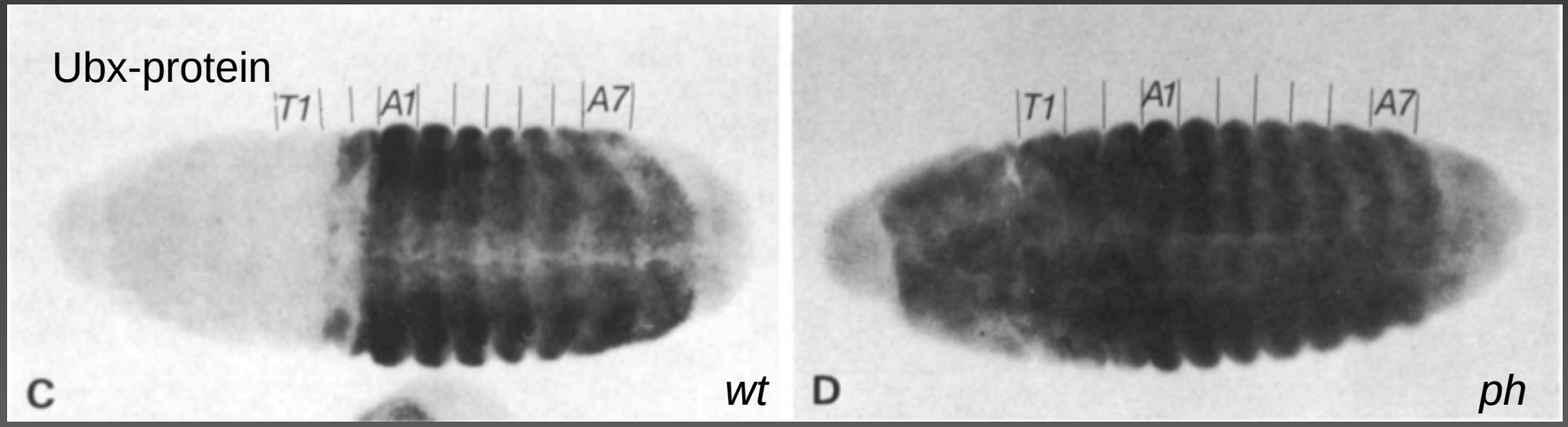




B) control clones
C) *shn* clone (scar formation)

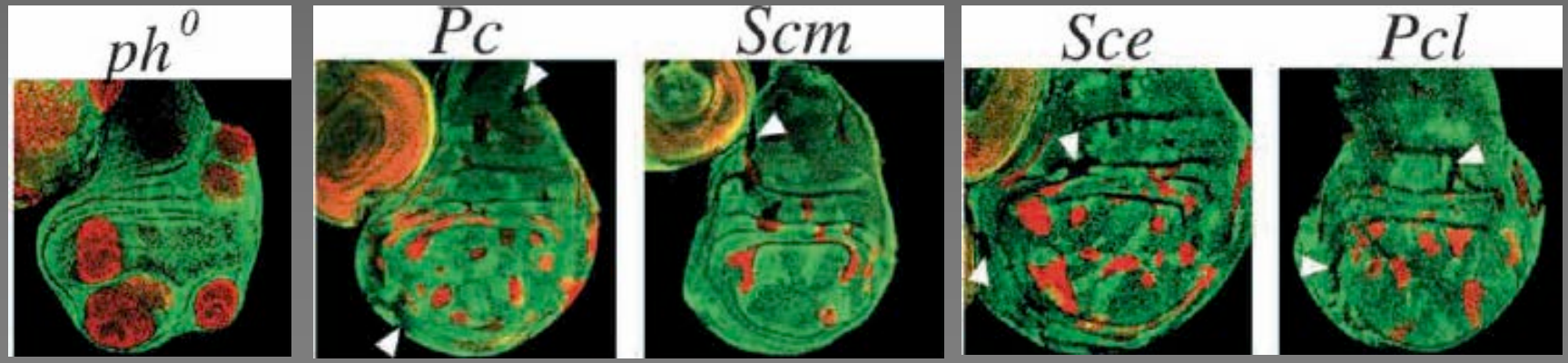
Janody et al. (2004) Genetics 166, 187

Loss of PcG gene activity causes ectopic expression of homeotic genes



Components of the PcG complex are continuously required to maintain repression

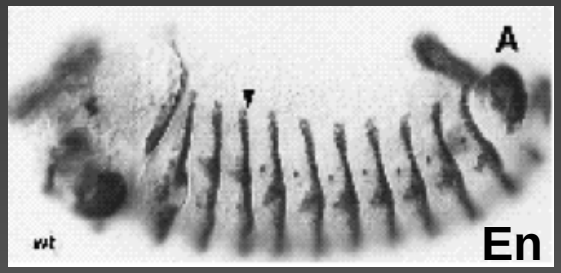
polyhomeotic *Polycomb* *sex combs on midleg* *Sex combs extra* *Polycomb-like*

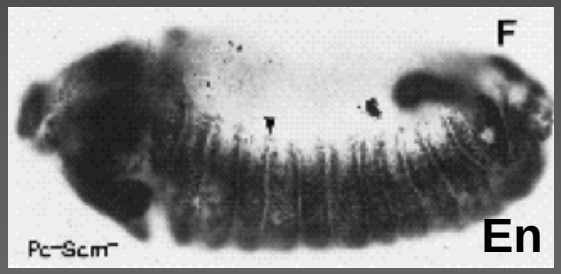


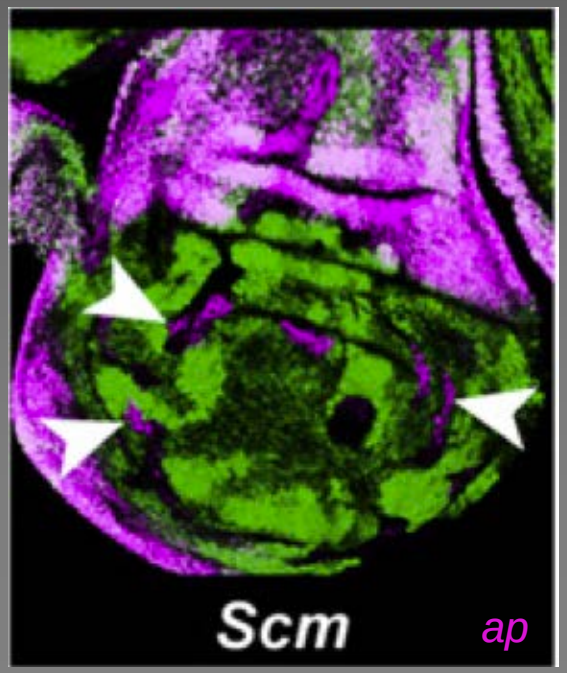
in red: ectopic Abd-B expression in clones induced during larval development in the second thoracic segment (wing disc)

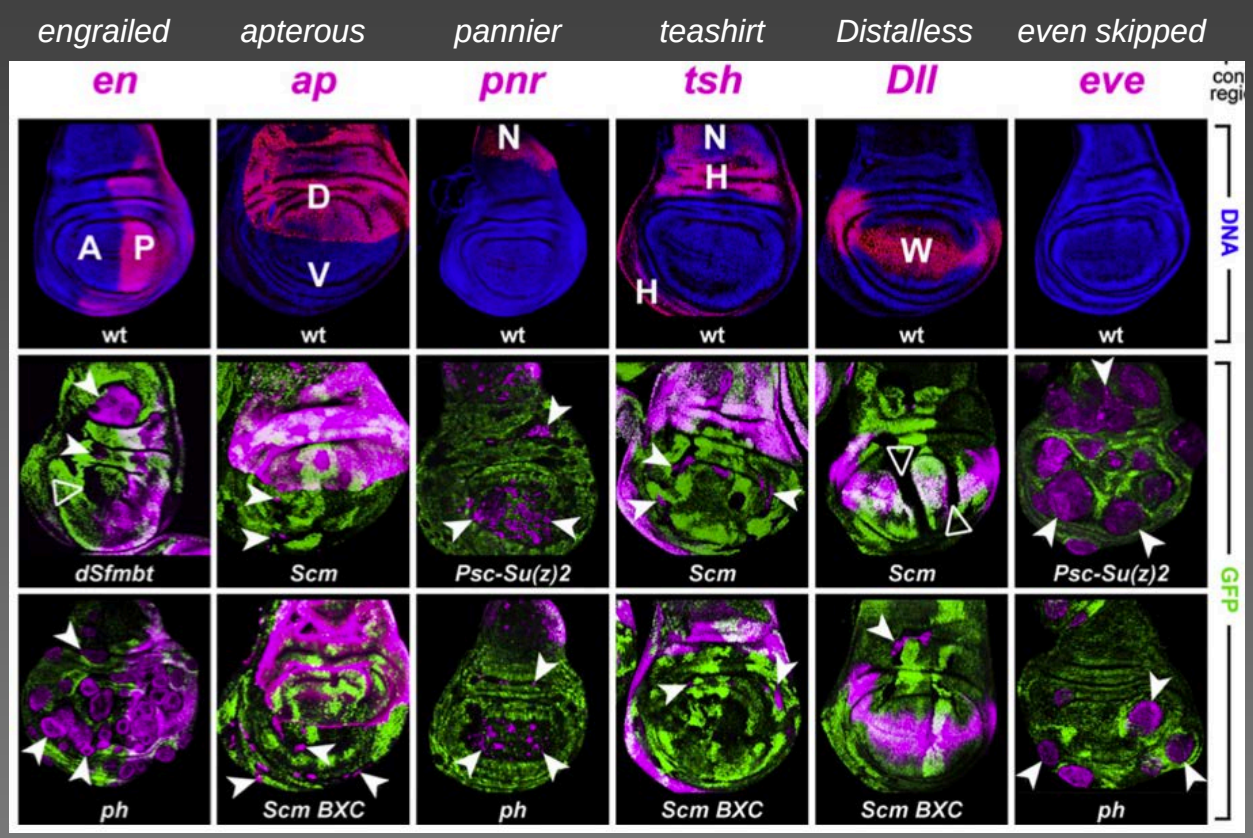
Dura and Ingham (1988) Development 103, 733
Beuchle et al. (2001) Development 128, 993

PcG proteins also prevent the inappropriate expression of non-homeotic developmental genes in both embryonic and imaginal tissues









wing imaginal discs

Moazed and O´Farrell (1992) Development 116, 805
Oktaba et al. (2008) Developmental Cell 15, 877