Déclaration d'intérêts en rapport avec la présentation

➢ **Activités de conseil, fonctions de gouvernance, rédaction de rapports**

Non *Société(s) : ……*

➢ **Essais cliniques, autres travaux, communications de promotion**

Non *Société(s) : ……*

➢ **Intérêts financiers (actions, obligations)**

Non *Société(s) : ……*

➢ **Liens avec des personnes ayant des intérêts financiers ou impliquées dans la gouvernance**

Non *Société(s) : ……*

➢ **Réception de dons sur une association dont je suis responsable**

*Oui ** *Société(s) : ……Blédina……*

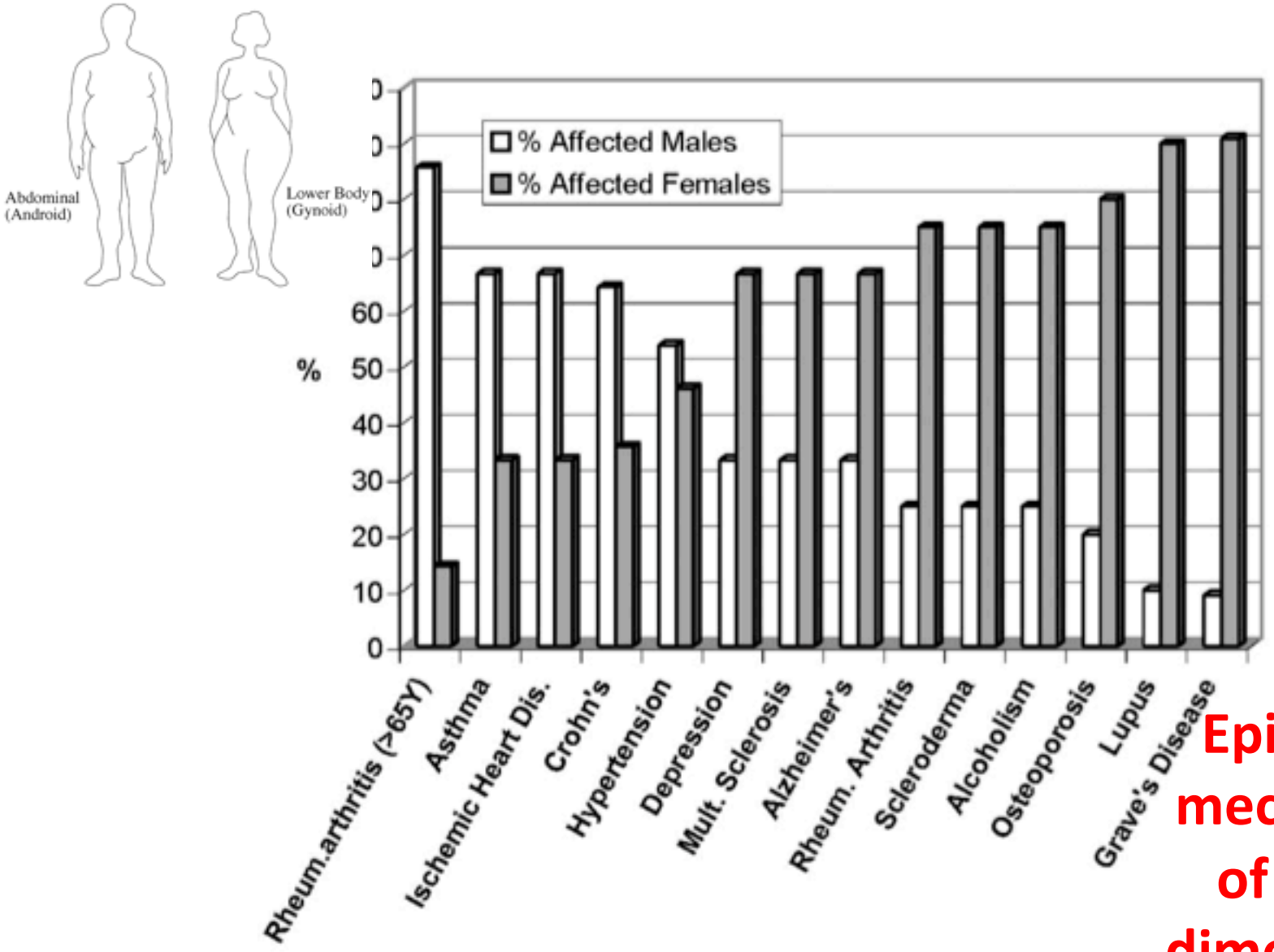
➢ **Détention d'un brevet, rédaction d'un ouvrage utilisé par l'industrie**

Non *Société(s) : ……*

** Effacer l'option inadéquate*

Sex differences and epigenetics

Most complex diseases show sex differences

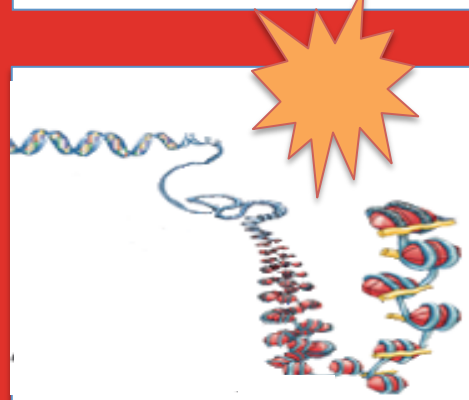


Epigenetic mechanisms of Sexual dimorphism?

3 revolutions

SF DOHaD

Origines Développementales de la SANTÉ

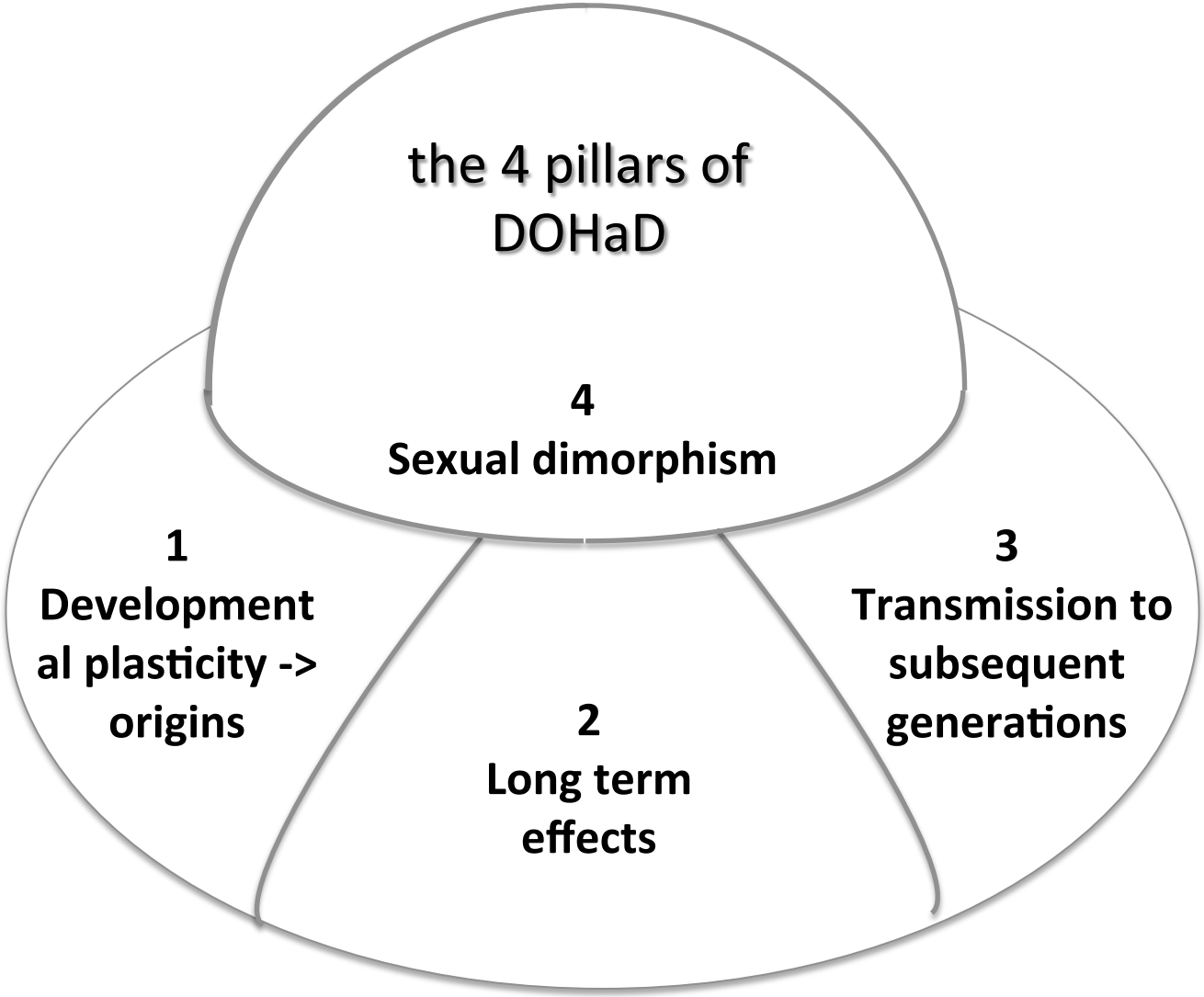


Epigenetics and environment

sexual dimorphism

A change in paradigm!

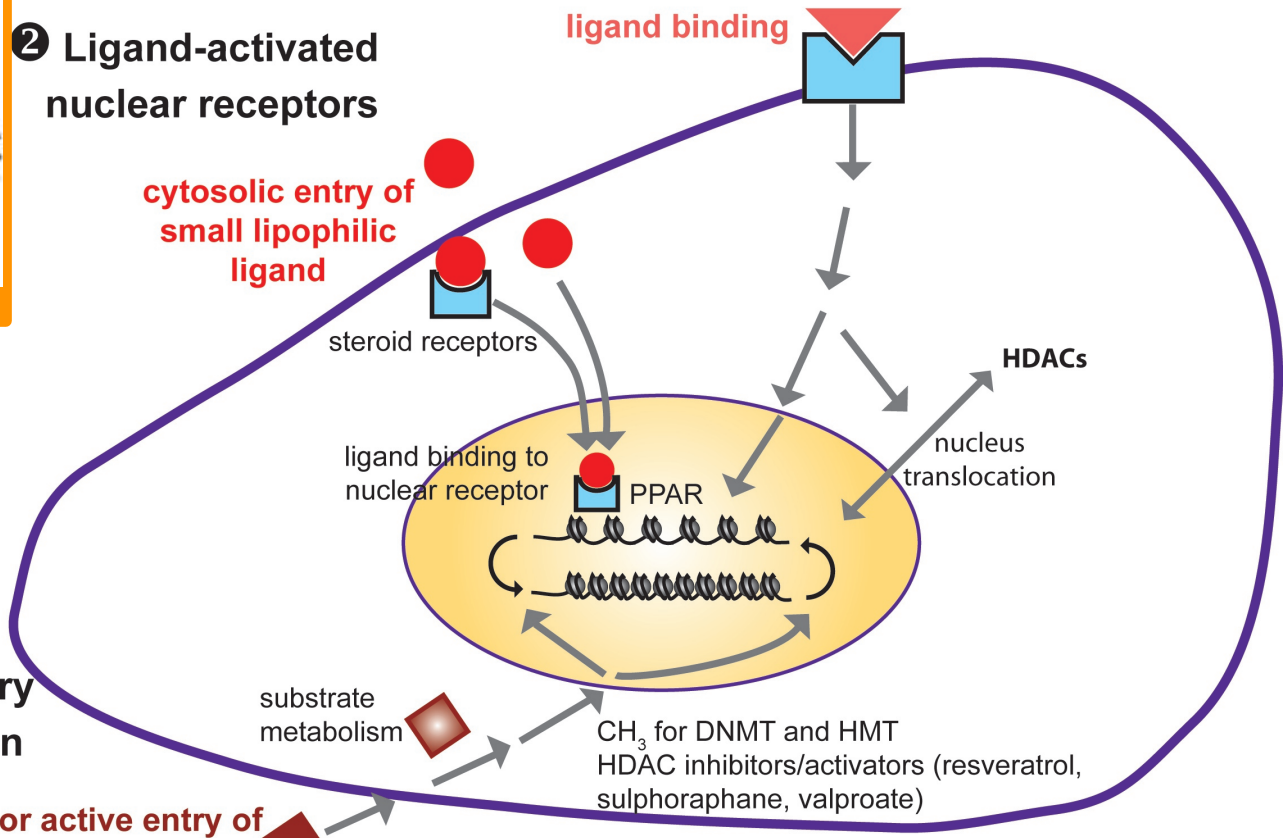
The first revolution : DOHaD
Developmental Origin of Health and Diseases



The second revolution : the environment and epigenetics

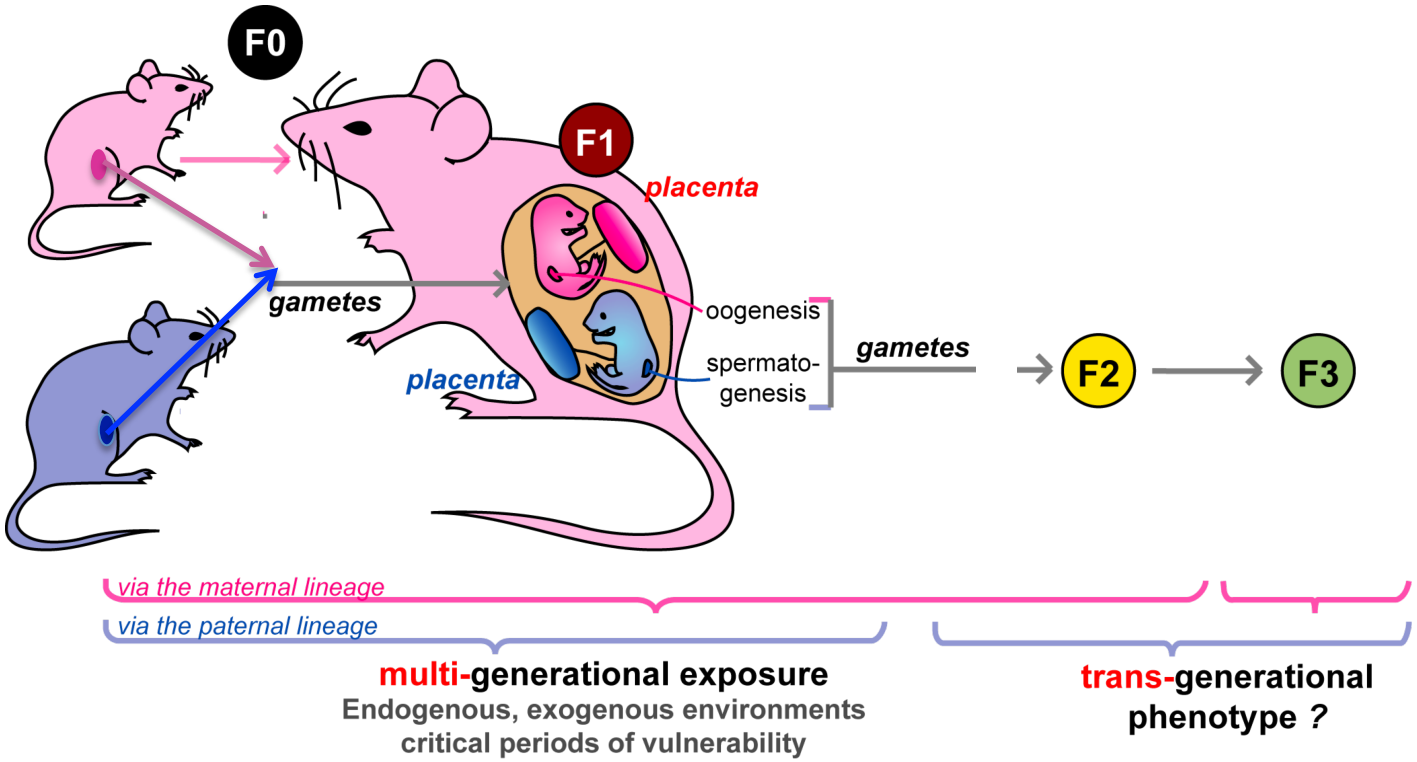
❷ Ligand-activated nuclear receptors

❸ Traditional membrane receptor signalling cascade



❶ Epigenetic machinery activation/inhibition

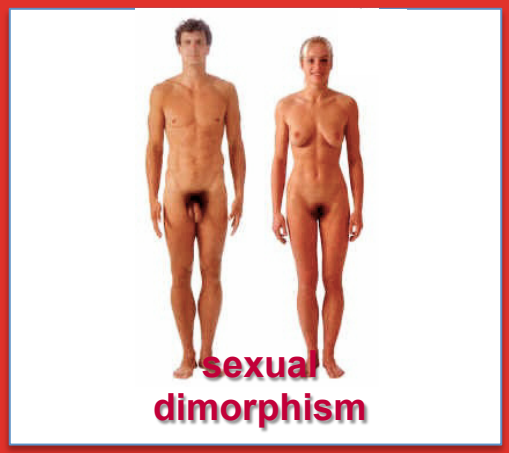
...the third revolution : sexual dimorphism omnipresent



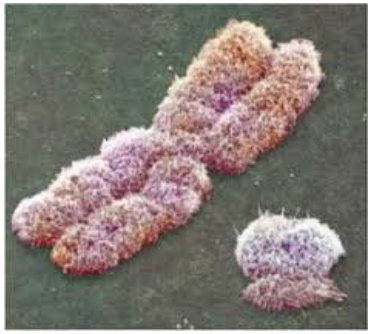
according to the sex of

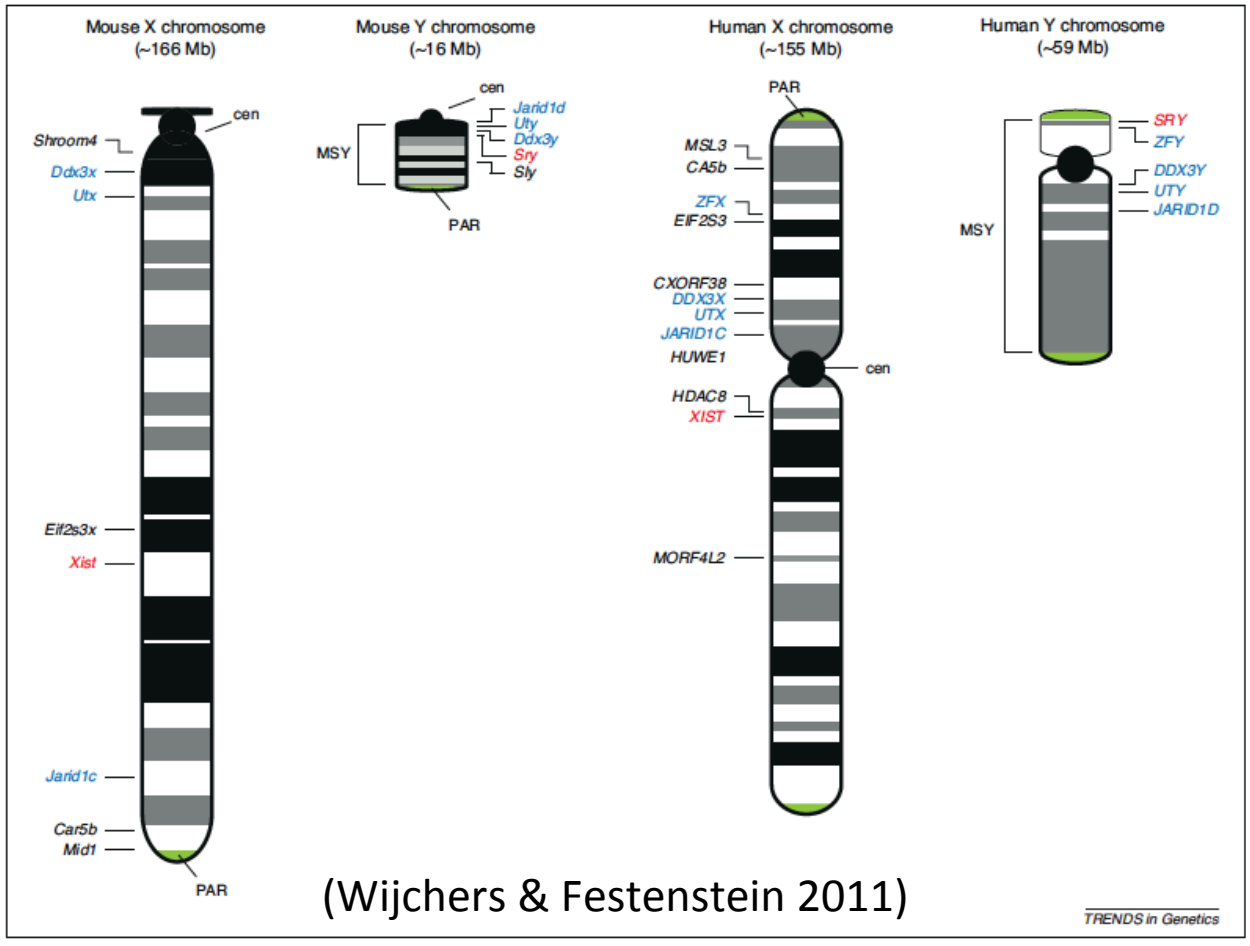
(Gabory et al BSD 2013)

Epigenetic mechanisms of sexual dimorphism

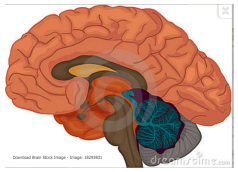


Y and X linked genes : Not just hormones!

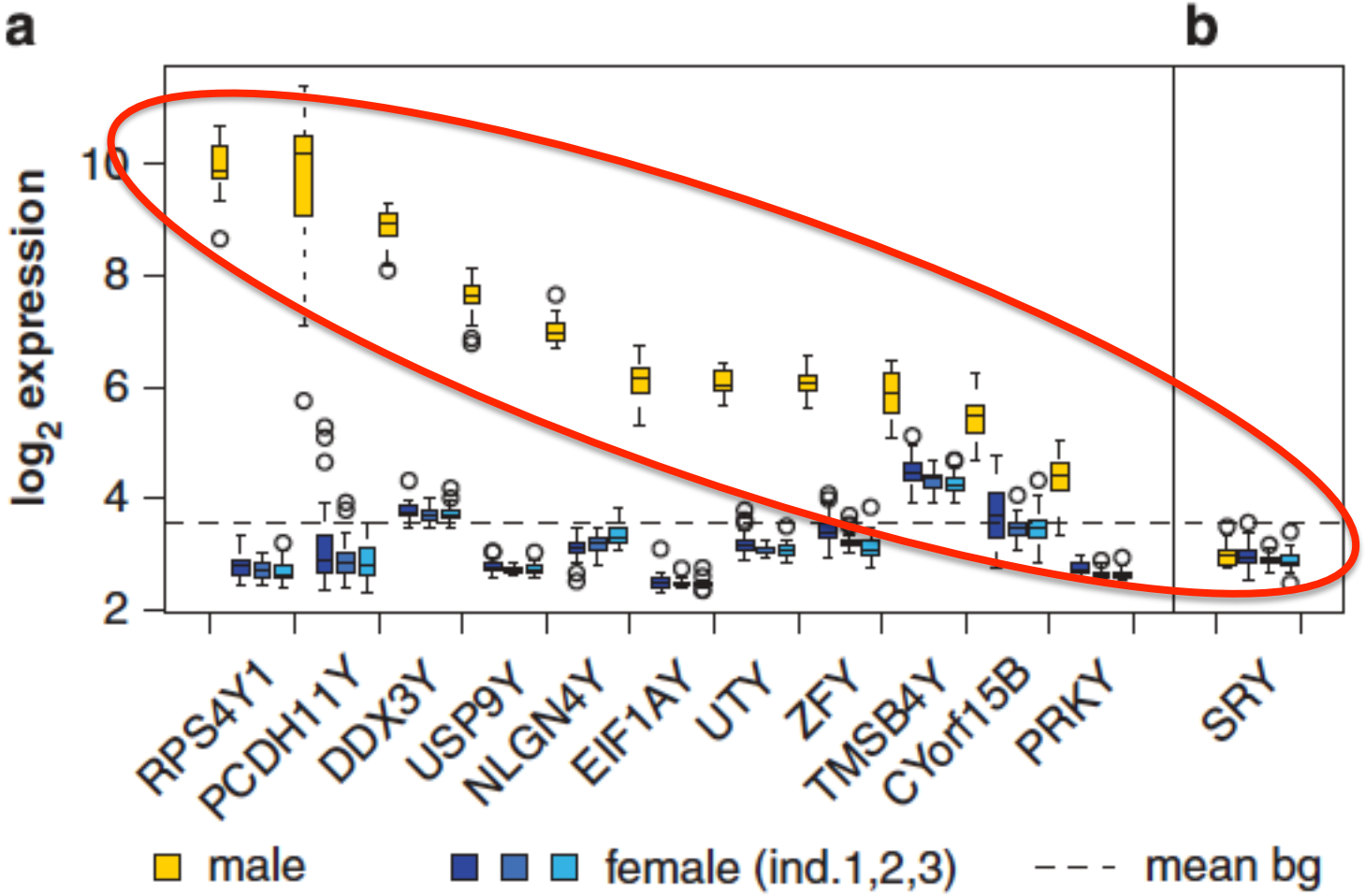




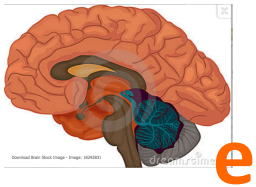
(Wijchers & Festenstein 2011)



Expression of Y-linked genes in male prenatal brain



(Reinius and Jazin 2009)



A novel mCH signature identifies genes escaping X-chromosome inactivation in neurons

www.rndsystems.com

Science
AAAS

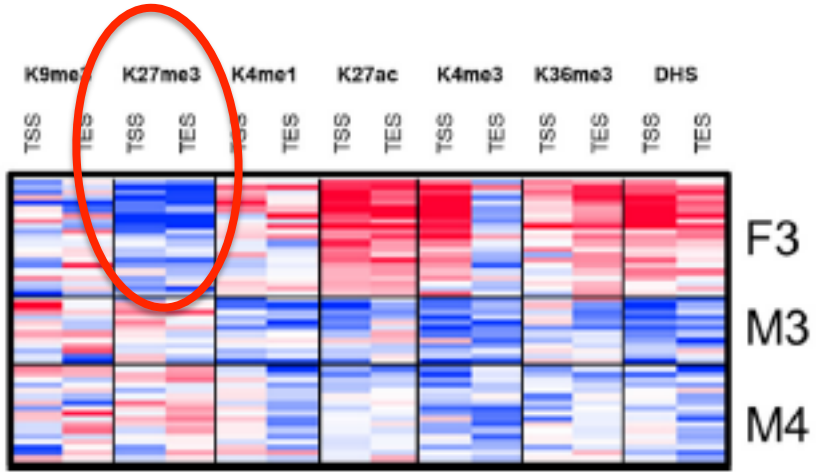
Global Epigenomic Reconfiguration During Mammalian Brain Development

Ryan Lister *et al.*

Science **341**, (2013);

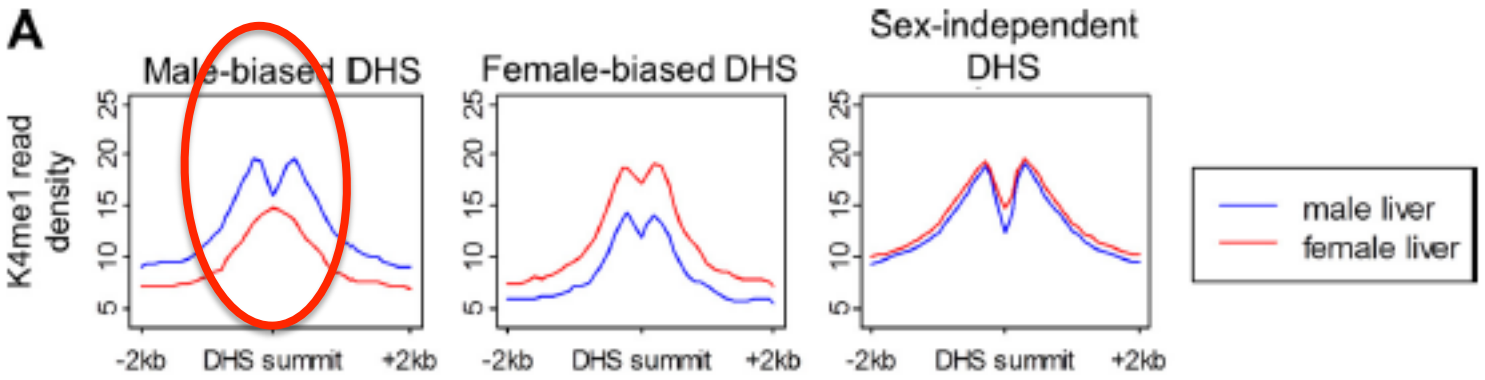
DOI: 10.1126/science.1237905

Type, distribution and location of marks and TF differenciate classes of sex-biased genes



male bias

female bias



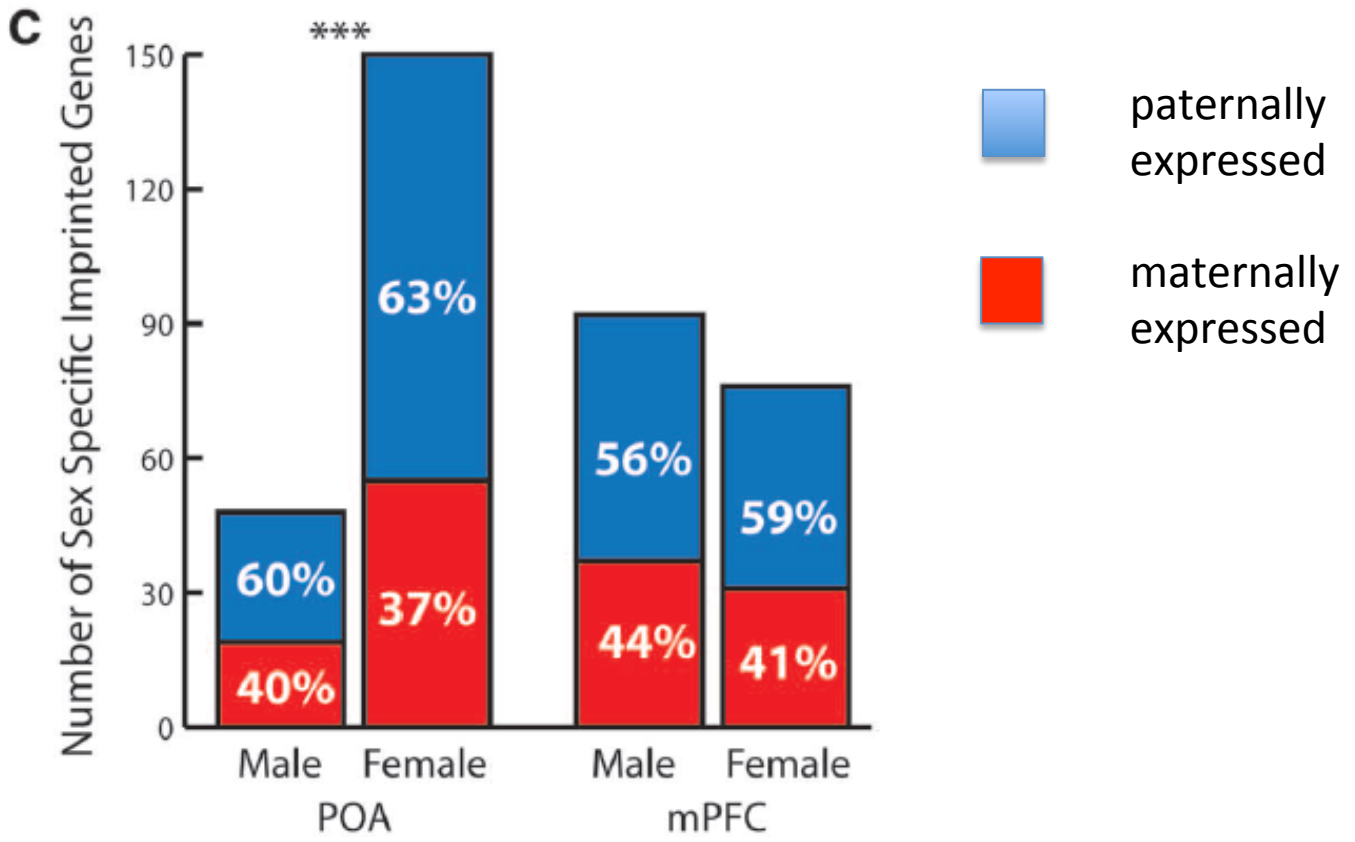
Molecular and Cellular Biology

Genome-Wide Analysis of Chromatin States Reveals Distinct Mechanisms of Sex-Dependent Gene Regulation In Male and Female Mouse Liver

Aarathi Sugathan and David J. Waxman
Mol. Cell. Biol. 2013, 33(18):3594. DOI:

Parents differentially influence imprinted gene expression in the brain of daughters versus sons

Imprinted genes expression

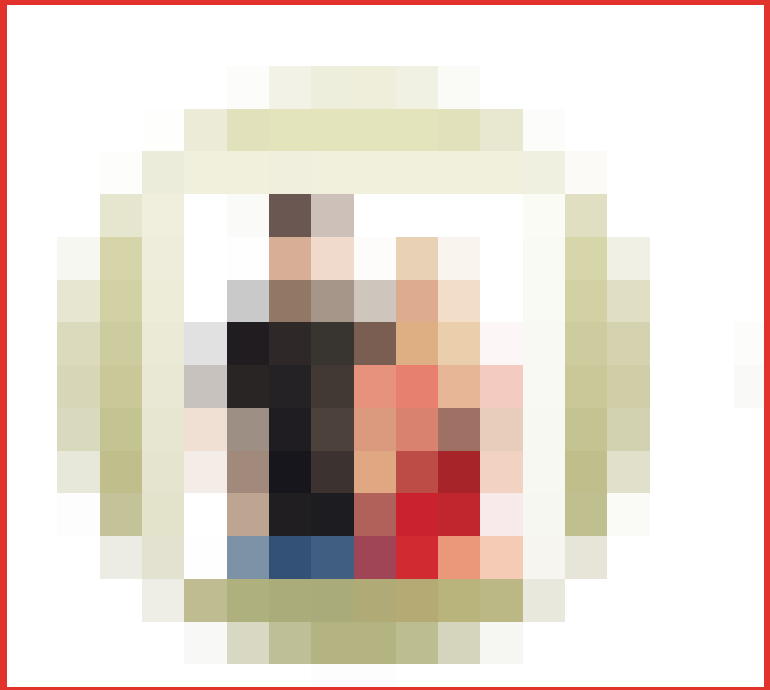


Science
AAAS

Sex-Specific Parent-of-Origin Allelic Expression in the Mouse Brain
Christopher Gregg, *et al.*
Science **329**, 682 (2010);
DOI: 10.1126/science.1190831

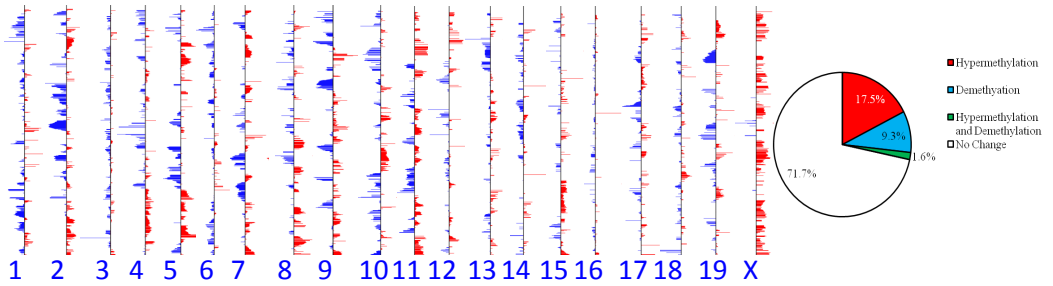
Effects of environmental exposure

according to the sex of

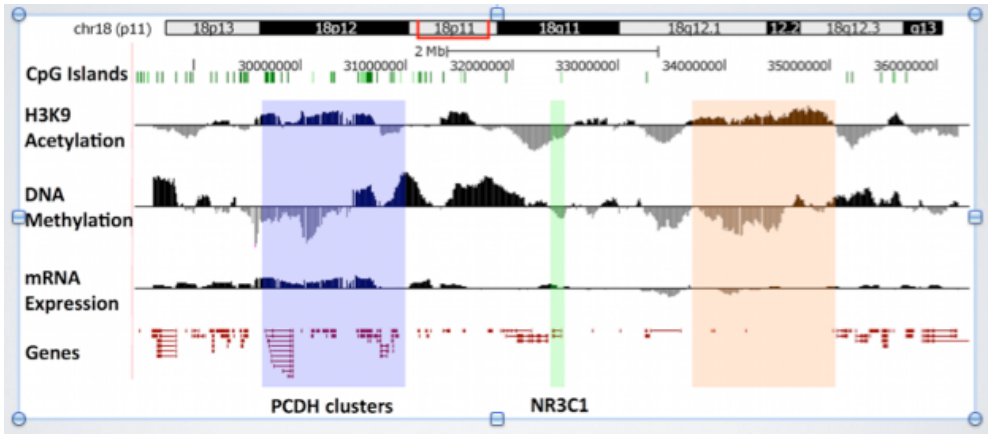


Environmental factors leave marks

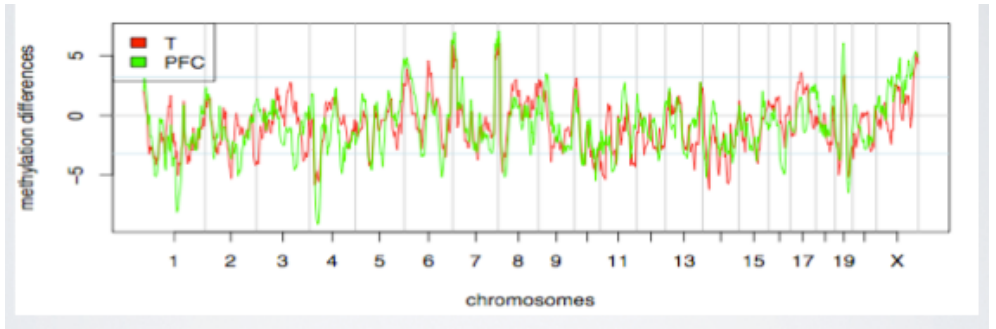
Throughout the genome –
memory -> allostatic charge
Kainate 2h -> Hippocampus



On regions (clusters) –
Different types of marks affected
maternal care



In different tissues (PFC, T) -
Common and different marks
maternal care



(Moshe Szyf et al2012, 2013)

the father also :
epigenetically transmitted to the next generations

Cell Metabolism
Previews

You Are What Your Dad Ate

Anne C. Ferguson-Smith[1,2,*] and Mary-Elizabeth Patti[3,*]

nature COMMUNICATIONS

Low paternal dietary folate alters the mouse sperm epigenome and is associated with negative pregnancy outcomes

R. Lambrot[1,*], C. Xu[1,*], S. Saint-Phar[1], G. Chountalos[1], T. Cohen[1], M. Paquet[2], M. Suderman[3], M. Hallett[3] & S Kimmins[1,4]

LETTER
doi:10.1038/nature09491

Chronic high-fat diet in fathers programs β-cell dysfunction in female rat offspring

Sheau-Fang Ng[1], Ruby C. Y. Lin[2], D. Ross Laybutt[3], Romain Barres[4], Julie A. Owens[5] & Margaret J. Morris[1]

Paternal Transmission of Stress-Induced Pathologies

David M. Dietz, Quincey LaPlant, Emily L. Watts, Georgia E. Hodes, Scott J. Russo, Jian Feng, Ronald S. Oosting, Vincent Vialou, and Eric J. Nestler

BIOL PSYCHIATRY 2011;70:408–414

Epigenetic Transmission of the Impact of Early Stress Across Generations

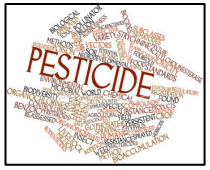
Tamara B. Franklin, Holger Russig, Isabelle C. Weiss, Johannes Gräff, Natacha Linder, Aubin Michalon, Sandor Vizi, and Isabelle M. Mansuy

BIOL PSYCHIATRY 2010;68:408–415

Cell

Paternally Induced Transgenerational Environmental Reprogramming of Metabolic Gene Expression in Mammals

Benjamin R. Carone,[1,10] Lucas Fauquier,[1,10] Naomi Habib,[4,5,10] Jeremy M. Shea,[1,10] Caroline E. Hart,[1] Ruowang Li,[2] Christoph Bock,[6,7] Chengjian Li,[1] Hongcang Gu,[6] Phillip D. Zamore,[1,3] Alexander Meissner,[6,7] Zhiping Weng,[2] Hans A. Hofmann,[8] Nir Friedman,[4,9] and Oliver J. Rando[1,*]



The Journal of Neuroscience, May 22, 2013 • 33(21):9003–9012

Paternal Stress Exposure Alters Sperm MicroRNA Content and Reprograms Offspring HPA Stress Axis Regulation

Ali B. Rodgers, Christopher P. Morgan, Stefanie L. Bronson, Sonia Revello, and Tracy L. Bale
Department of Animal Biology, School of Veterinary Medicine, University of Pennsylvania Philadelphia, Pennsylvania 19104

0013-7227/06/$15.00/0
Printed in U.S.A.
Endocrinology 147(12):5515–5523
Copyright © 2006 by The Endocrine Society
doi: 10.1210/en.2006-0640

Endocrine Disruptor Vinclozolin Induced Epigenetic Transgenerational Adult-Onset Disease

Matthew D. Anway, Charles Leathers, and Michael K. Skinner

ARTICLES
nature neuroscience

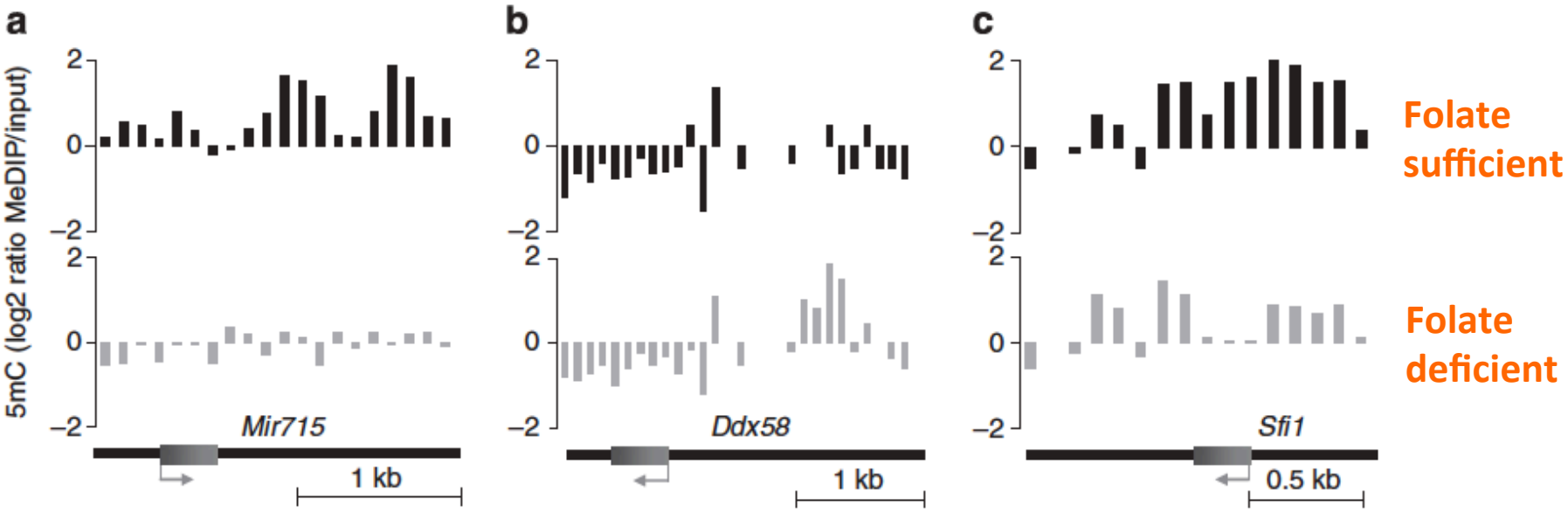
Epigenetic inheritance of a cocaine-resistance phenotype

Fair M Vassoler[1], Samantha L White[1], Heath D Schmidt[1], Ghazaleh Sadri-Vakili[2,3] & R Christopher Pierce[1,3]

nature COMMUNICATIONS

Low paternal dietary folate alters the mouse sperm epigenome and is associated with negative pregnancy outcomes

R. Lambrot[1,*], C. Xu[1,*], S. Saint-Phar[1], G. Chountalos[1], T. Cohen[1], M. Paquet[2], M. Suderman[3], M. Hallett[3] & S Kimmins[1,4]



...programmed resilience

Cocaine self-administration

Only sons resist!

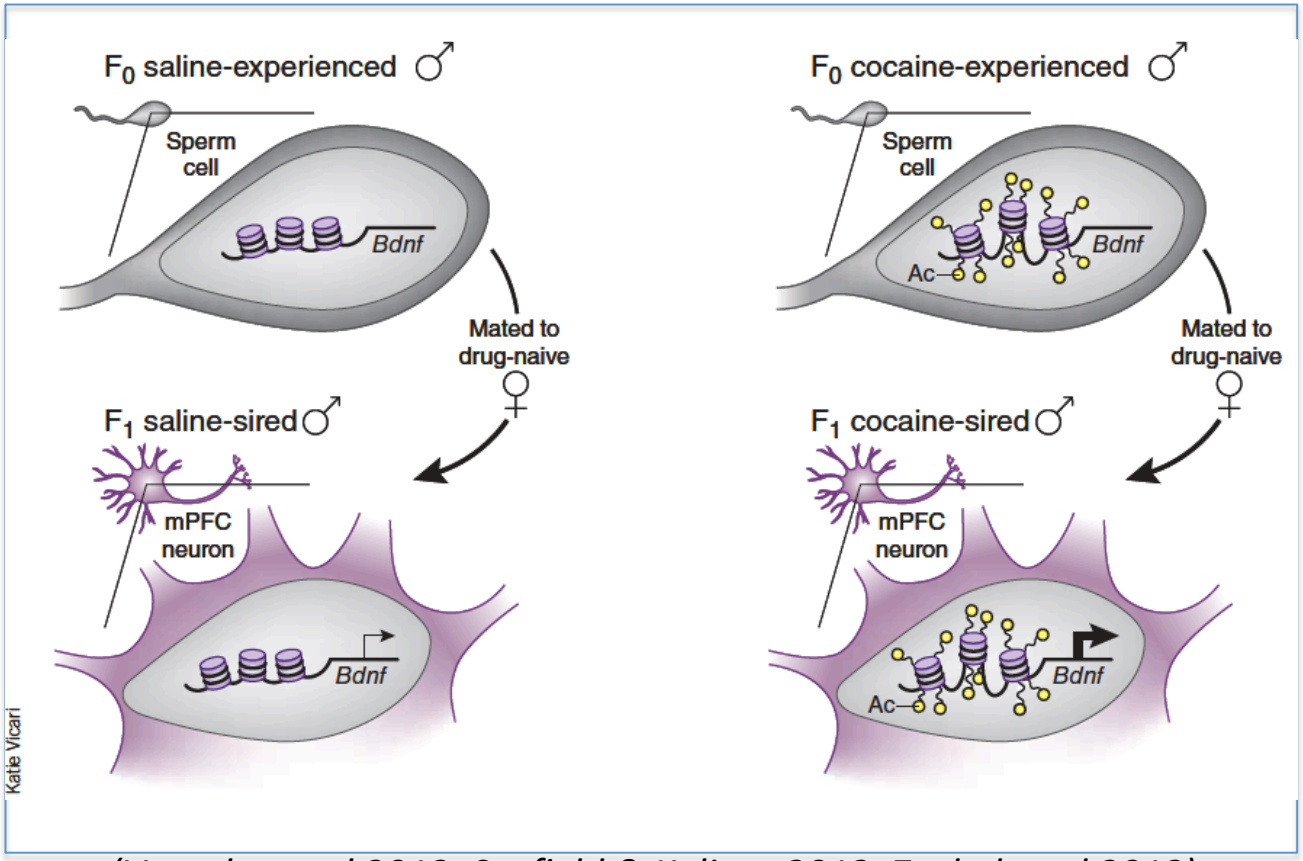
-> Sexual dimorphism

Control

Cocaine

Father's Sperm

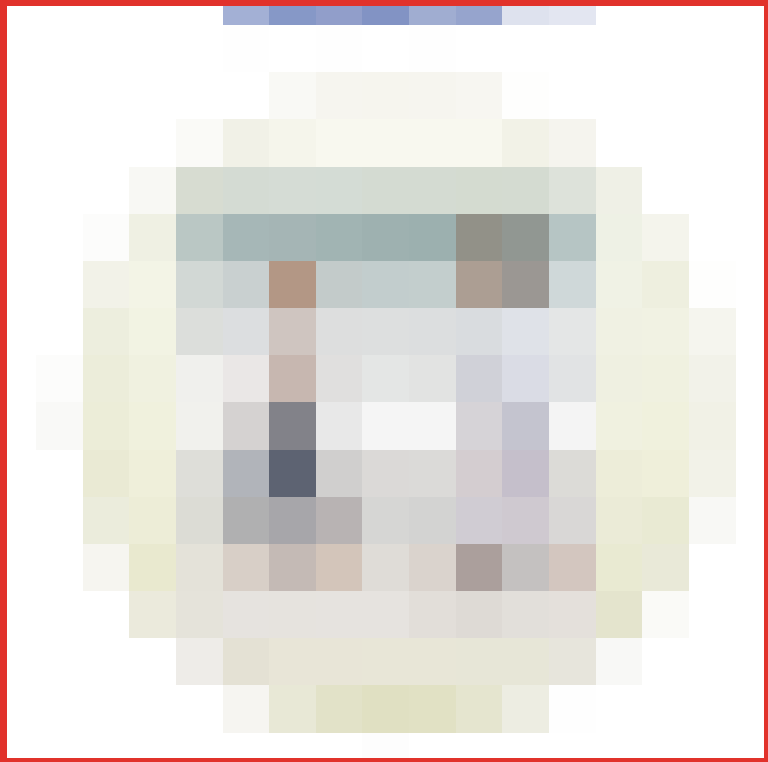
Son's mPFC



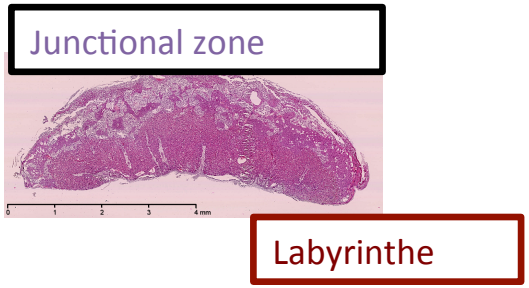
(Vassoler et al 2013; Scofield & Kalivas 2013, Zeybel et al 2012)

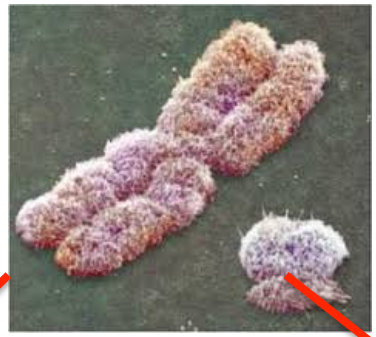
Effects of environmental exposure

according to the sex of

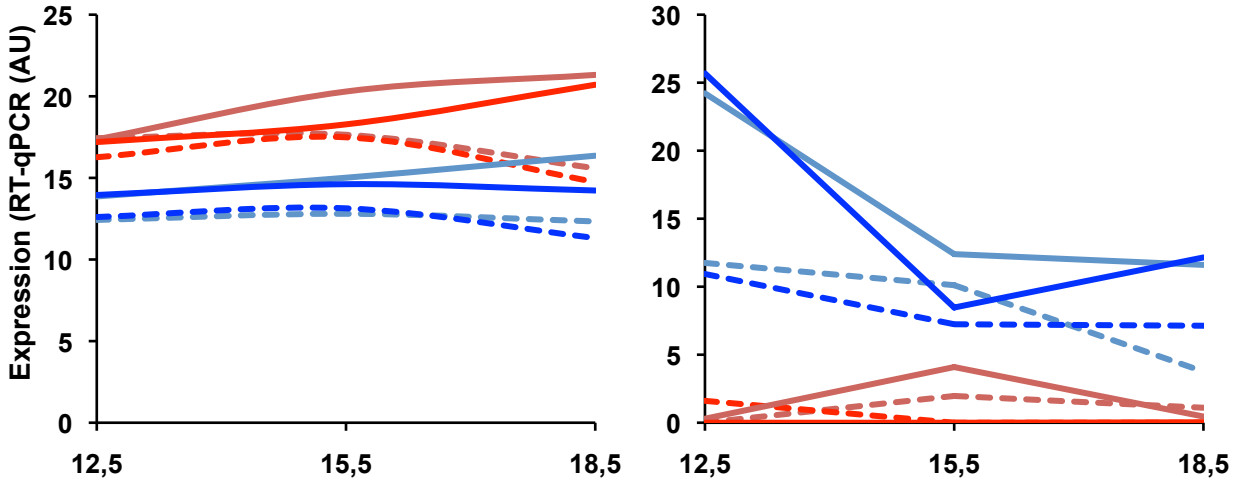


Kdm5c and *5d (histone demethylases)* : Ontogenic expression and tissue distribution





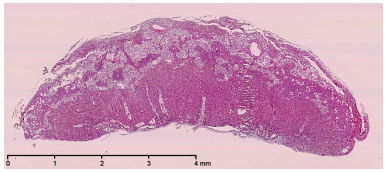
Kdm5c ***(Jarid1c)*** ***Kdm5d*** ***(Jarid1d)***



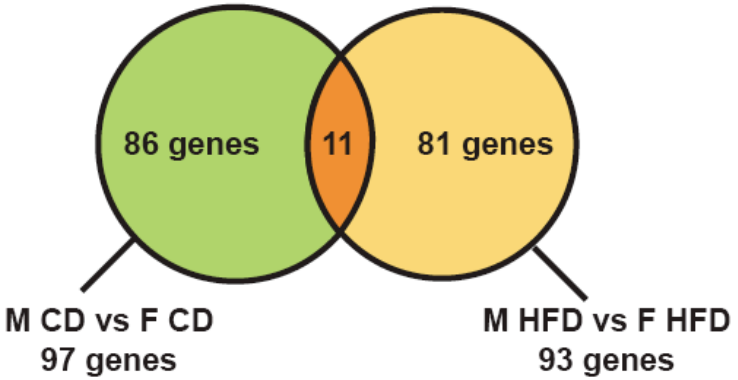
(Gabory et al unpublished)

Kruskall-Wallis test $p<0.05$

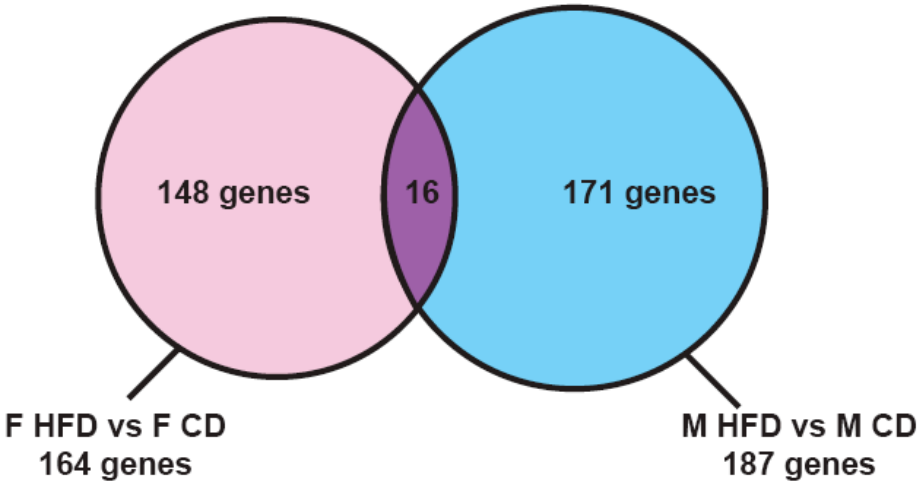
Striking sexual dimorphism at the basal level and in response to maternal high-fat diet



A. Sexual dimorphism in placental gene expression, under control or high fat diet



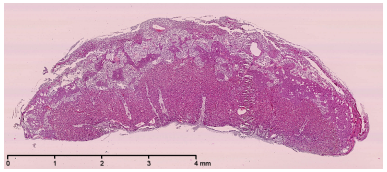
B. Effect of maternal high fat diet on gene expression, in female or in male placentae



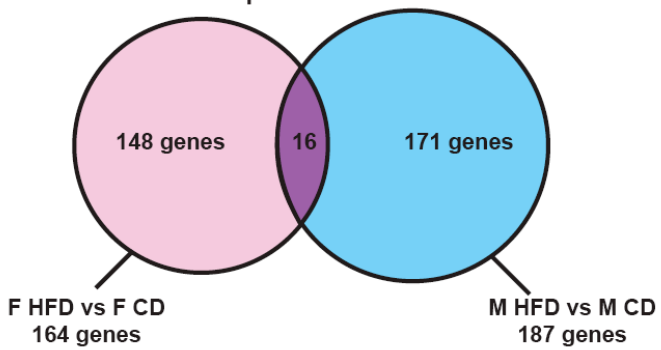
Not the same gene sets affected by maternal diet in male and female placenta

(Gabory et al Plos One 2012)

Sexual dimorphism in response to diet



B. Effect of maternal high fat diet on gene expression, in female or in male placentae



Not the same gene sets :
NOT THE SAME BIOLOGICAL FUNCTIONS !

(Gabory et al Plos One 2012)

Category / Functions Annotation	*p-value*	nb gene	Regulation z-score	Molecules
Diet effect in female (F HFD vs F CD)				
Cell Death	1,09E-04-1,59E-02	18		
cell death of neuroblastoma cell lines	0,00483	5	1,48	ATXN1, MAOA, SNCA, TP53 (includes EG:22059), TXN (includes EG:116484)
Cell Signaling	1,09E-04-1,43E-02	7		
stimulation of lymphocytes	0,00490	4	0,337	C3, ENPP3, TNFSF15, TXLNA
binding of phagocytes	0,00626	4	0,082	C3, CXCL2, FPR1, LIPG
quantity of monoamines	0,00786	4	1,978	C3, MAOA, SLC22A3, SNCA
stimulation of cells	0,00892	6	0,297	C3, CCK, ENPP3, EPX, TNFSF15, TXLNA
Cellular Development	2,92E-04-1,4E-02	11		
growth of tumor cells	0,00957	5	-0,119	COX17 (includes EG:10063), PDGFB, TFG, TP53 (includes EG:22059), TXLNA
Digestive System Development and Function	2,92E-04-7,02E-03	5		
Organ Development	2,92E-04-1,4E-02	3		
Organ Morphology	2,92E-04-1,4E-02	6		
Small Molecule Biochemistry	2,92E-04-1,43E-02	23		
uptake of amino acids	0,00042	4	-0,873	SLC1A1, SLC36A1, SLC7A2, TP53 (includes EG:22059)
quantity of glutathione	0,00084	4	1,789	SNCA, TP53 (includes EG:22059), TXN (includes EG:116484), VNN1
phosphorylation of L-tyrosine				1, PDGFB, TP53 (includes
quantity of monoamines				
Tissue Development				
mass of connective tissue	0,01490	4	-0,842	C3, GCGR, RXRG, TP53 (includes EG:22059)
Amino Acid Metabolism	4,2E-04-1,4E-02	9		
uptake of amino acids	0,00042	4	-0,873	same genes
phosphorylation of L-tyrosine	0,00154	5	0,410	CCK, FGF10, GATA1, PDGFB, TP53 (includes EG:22059)
Molecular Transport	4,2E-04-1,4E-02	16		
uptake of amino acids	0,00042	4	-0,873	same genes
quantity of glutathione	0,00084	4	1,789	same genes
quantity of monoamines	0,00786	4	1,978	same genes
Diet effect in male (M HFD vs M CD)				
Cardiovascular System Development and Function	1,88E-06-1,1E-02	24		
blood pressure	0,00000	11	-1,989	ACTG2, ADRA2A, AOC3, CACNA1B, COL1A2, CYP4A11, GCGR, HSD11B1, IGF1, SGK1, SNTB2
development of blood vessel	0,00087	14	0,104	ADRA2A, AOC3, COL1A1, COL1A2, COL3A1, CXCL2, GJA1, IGF1, IRS1, LTB4R, PDGFB, PITX2, SFRP2, TBX3
systolic pressure	0,00129	4	-1,971	ADRA2A, CYP4A11, IGF1, SNTB2
Embryonic Development	1,43E-05-1,1E-02	30		
development of organ	0,00125	26	0,041	ADRA2A, CD14, CEBPA, CELSR1, COL1A1, COL1A2, COL3A1, CRABP2, GJA1, HAND2, HSD11B1, IGF1, IRS1, MAB21L2, MAS1, PDGFB, PITX2, PLAG1, RAB3A, C2, ZFP37
Organismal Development				
development of blood vessel				
development of organ				
Lipid Metabolism				
oxidation of fatty acid				RS1
quantity of triacylglycerol				
Small Molecule Biochemistry				
uptake of 2-deoxyglucose				
oxidation of fatty acid				
quantity of D-glucose	0,00562	5	0,217	ADRA2A, GCGR, HADH, IGF1, IRS1
quantity of triacylglycerol	0,01100	5	-1,845	same genes
Cell Morphology	2,6E-05-9,22E-03	9		
extension of cellular protrusions	0,00922	5	-0,202	ARHGAP4, IGF1, LTB4R, ROR2, S100B
Nervous System Development and Function	2,6E-05-1,1E-02	34		
memory	0,00023	7	0,563	GABRB3, GJA1, HSD11B1, IGF1, KLK8, S100B, SGK1
spatial memory	0,00050	4	0,217	GJA1, HSD11B1, IGF1, S100B
proliferation of neuroglia	0,00064	5	-0,06	CXCL2, IGF1, PDGFB, PLAG1, S100B

Aminoacid metabolism

Vascularization

Glucose and lipid metabolism

Take home messages

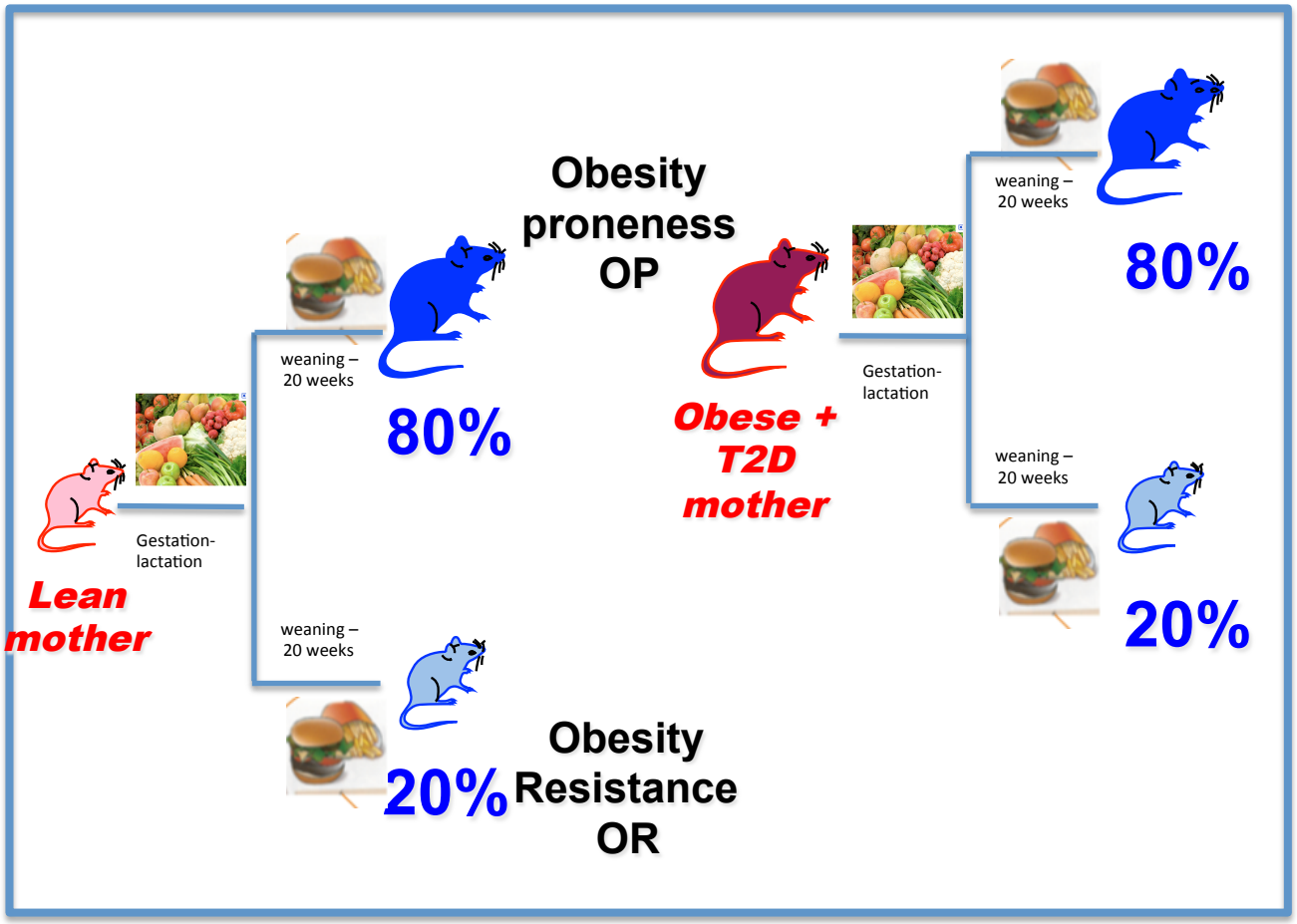
- Not just hormones : Y and X linked genes after fertilisation (before gonads)
- Expression of Y-linked genes in male prenatal brain
- A novel mCH signature identifies genes escaping X-chromosome inactivation in neurons
- Type, distribution and location of epigenetic marks and TF differenciates classes of sex-biased genes and sex-specific mechanisms in the liver
- Parents differentially influence imprinted genes expression in the brain of daughters versus sons
- Paternal germ cells memories of environmental exposure (food, folate, stress, drugs, toxics...) epigenetically transmitted
- Species- Tissue- Timing- and Diet – specific sexual dimorphism in placenta

Effects of environmental exposure

according to the sex of

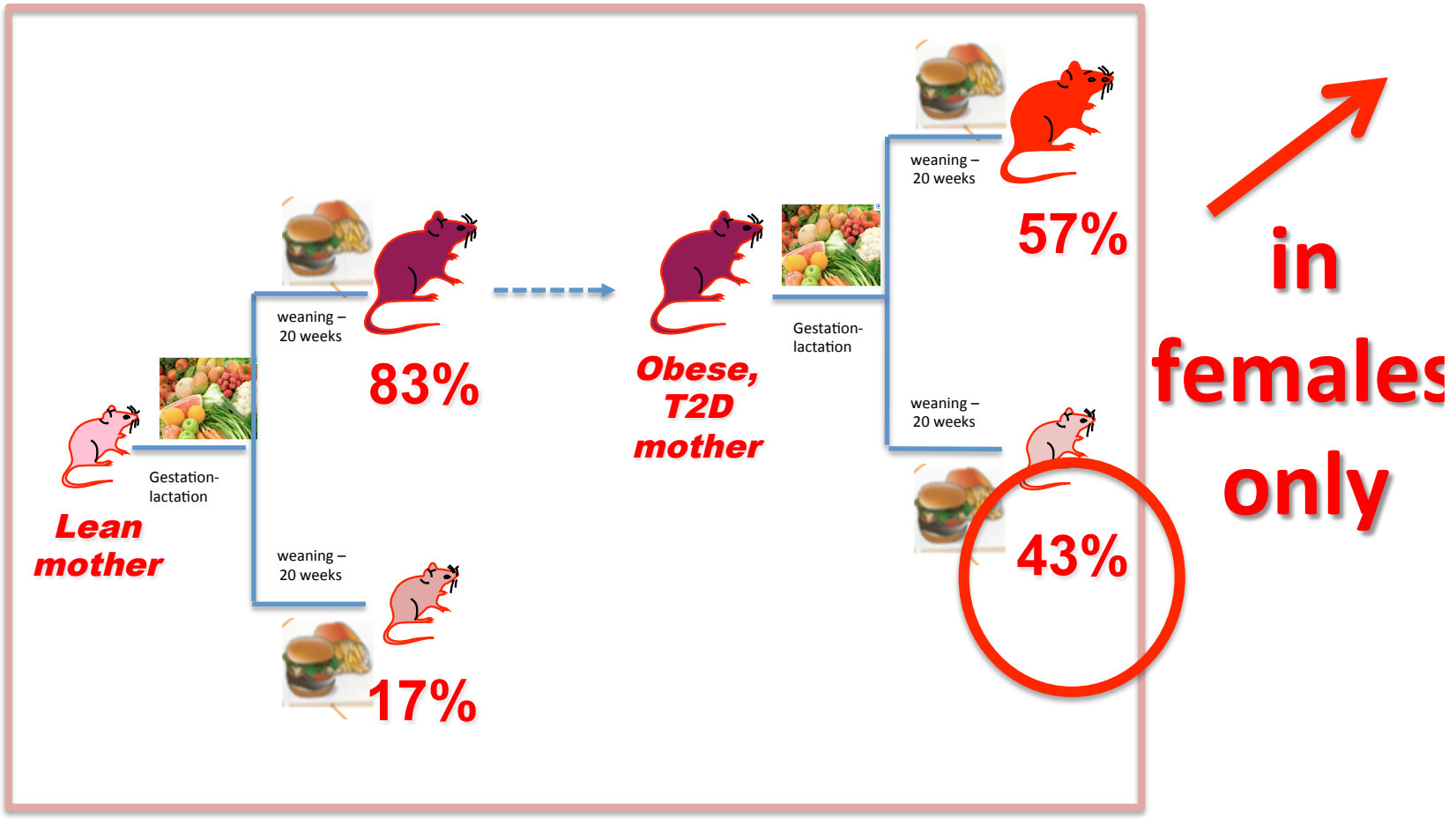
Stochastic
High fat diet-**resistance**
males

C57BL/6J mice



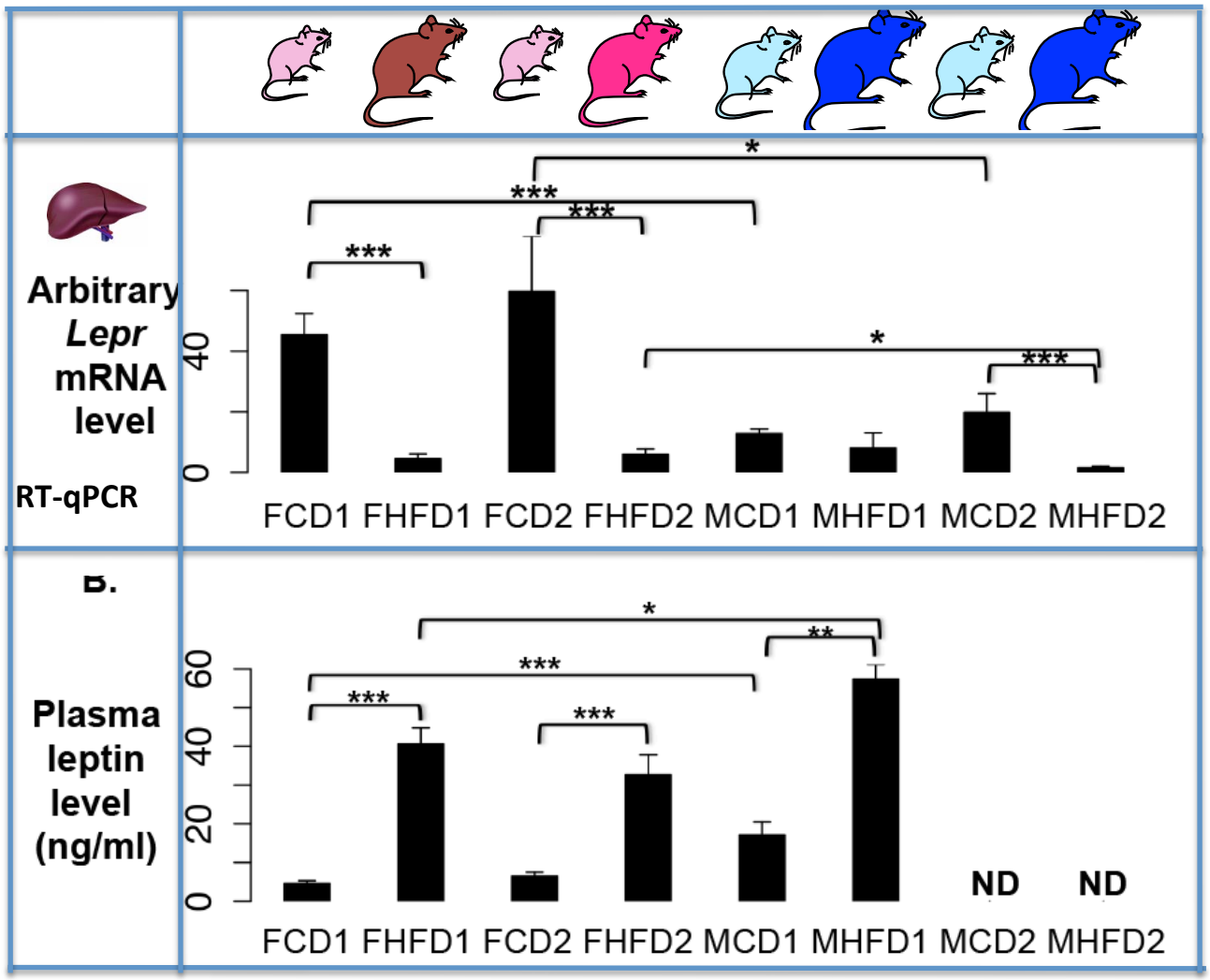
(Gallou-Kabani et al 2007, Attig et al PlosOne 2013, Attig et al, Wu et al, J DOHaD 2013 and unpublished)

Stochastic + **Programmed**
High fat diet-**resistance**



(Gallou-Kabani et al 2007, Attig et al PlosOne 2013, Attig et al, Wu et al, J DOHaD 2013 and unpublished)

Sexual dimorphism : *Lepr* and Leptin



Leptin receptor

M<F

30%

Leptin

F<M

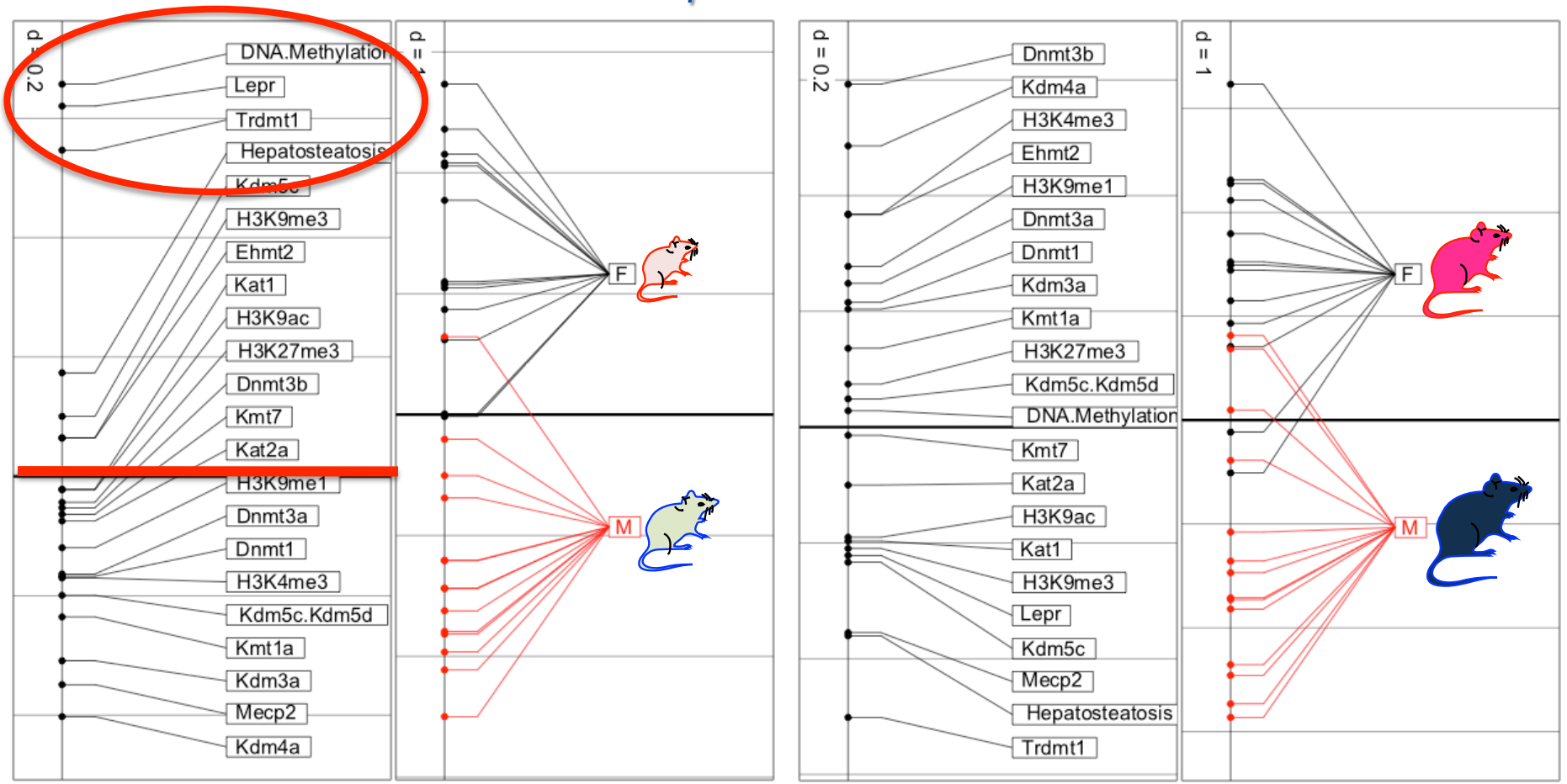
22%

(Attig et al unpublished, Wu et al J DOHaD 2013)

Sexual dimorphism

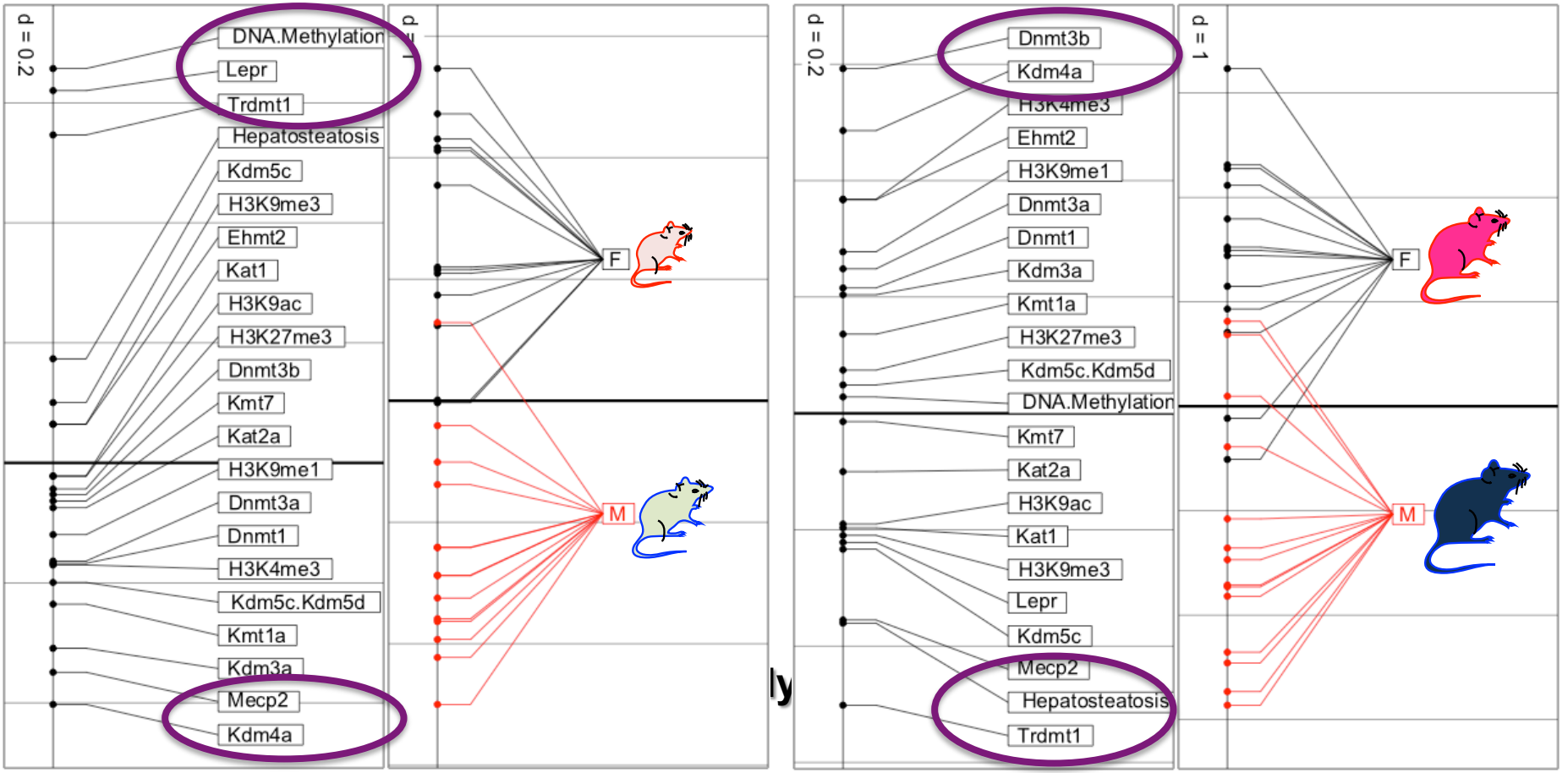
Principal Component A. : Discrimination Plots

Lepr
global DNA methylation
14 genes epigenetic modifiers
5 histone marks,
hepatosteatosis



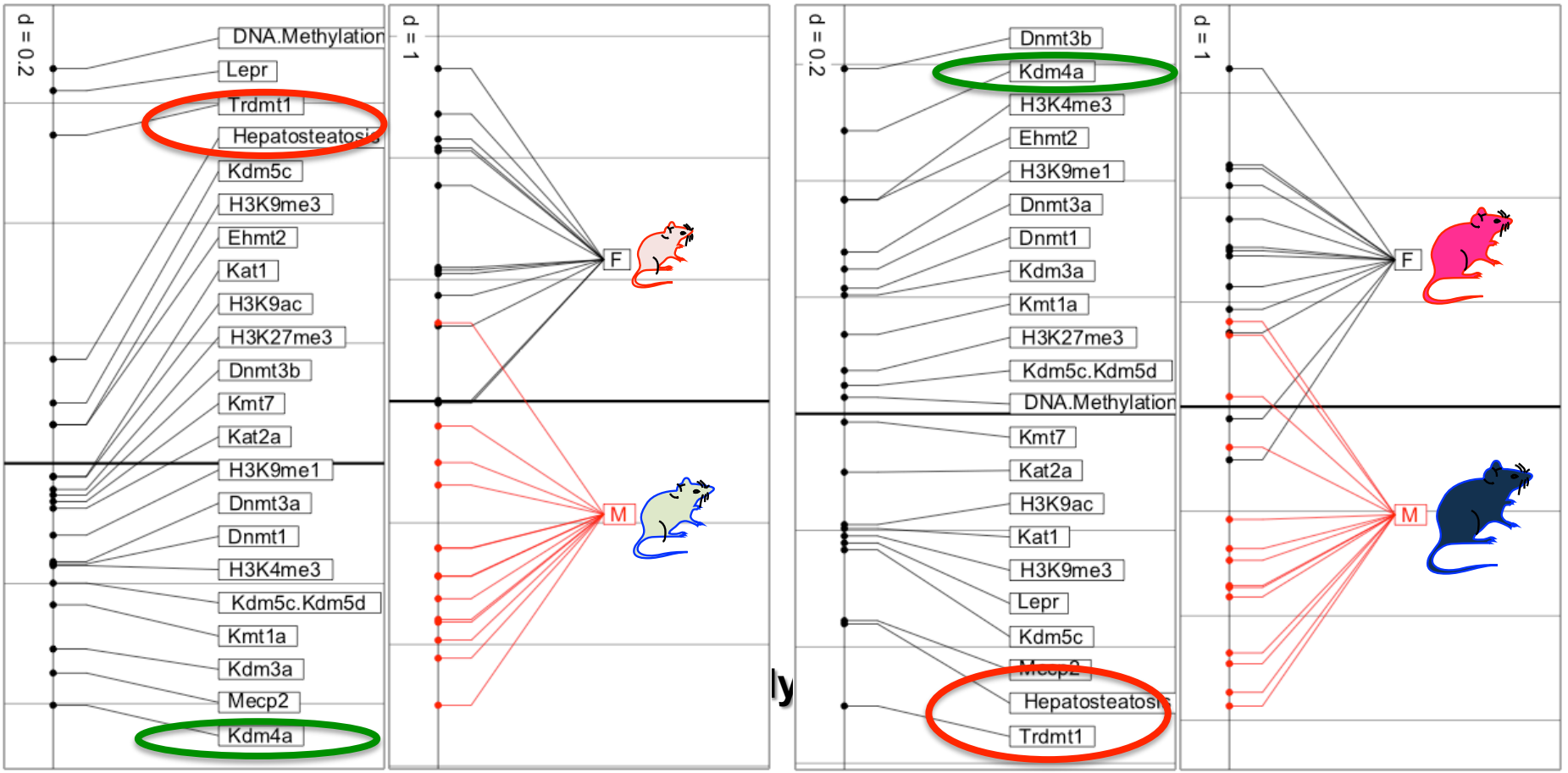
(Wu et al J DOHaD 2013 & unpublished)

Epigenetic modifiers that best characterize the separation between the sexes



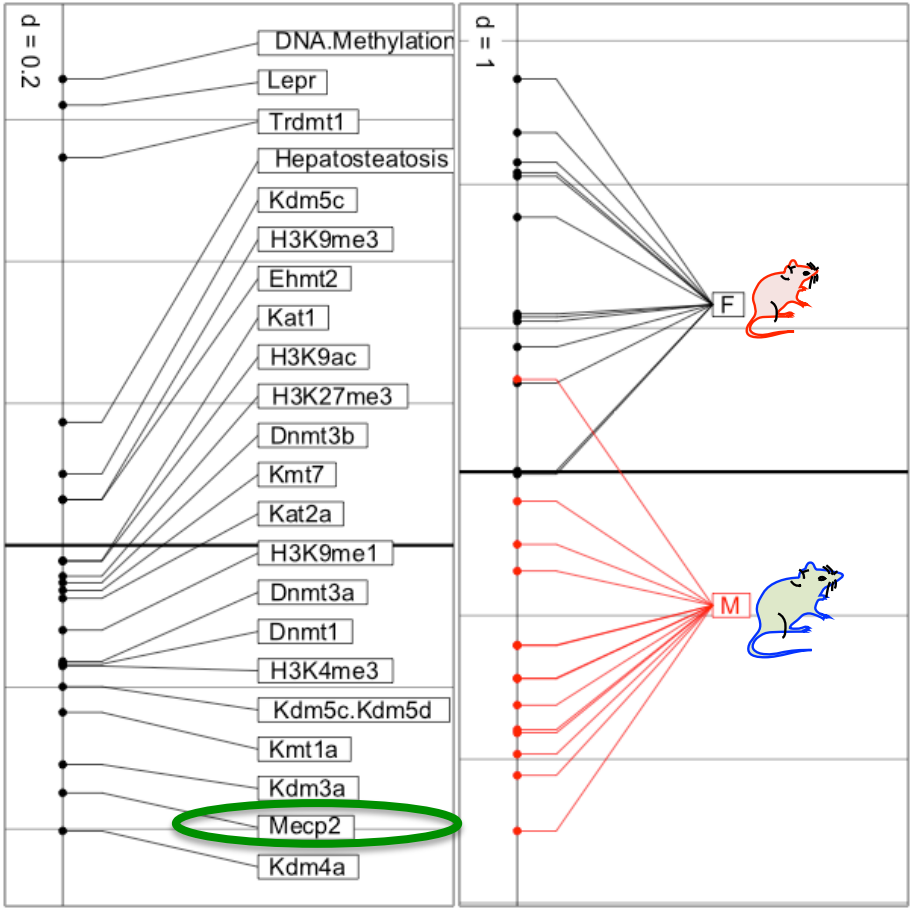
(Wu et al J DOHaD 2013 & unpublished)

..but vary according to the diet



(Wu et al J DOHaD 2013 & unpublished)

or do not change with diet



(Wu et al J DOHaD 2013 & unpublished)

Take home messages

- Not just hormones : Y and X linked genes after fertilisation (before gonads)
- Expression of Y-linked genes in male prenatal brain
- A novel mCH signature identifies genes escaping X-chromosome inactivation in neurons
- Type, distribution and location of epigenetic marks and TF differenciates classes of sex-biased genes and sex-specific mechanisms in the liver
- Parents differentially influence imprinted genes expression in the brain of daughters versus sons
- Paternal germ cells memories of environmental exposure (food, folate, stress, drugs, toxics...) epigenetically transmitted
- Species- Tissue- Timing- and Diet – specific sexual dimorphism in placenta and liver