Sex chromosome genes as proximate factors causing sex differences in disease

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Sexual differentiation theory provides conceptual framework

If you want to find the causes of sex-specific susceptibility / protection from disease, you have to start a list of factors that could cause sex differences.

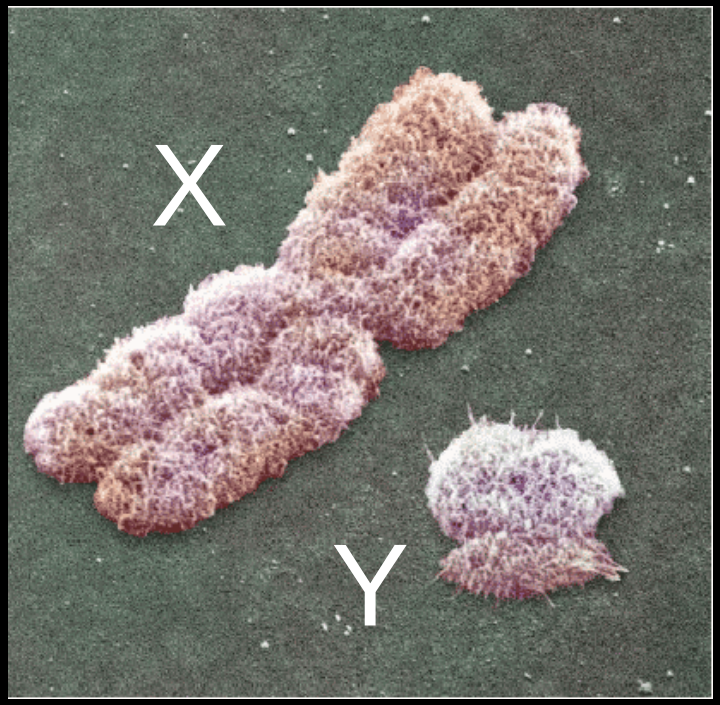
Where do sex differences come from?

What biological factors cause sex differences?

XY vs. XX

At the genetic level, all sex differences result from X and Y imbalance*

Aren't autosomal genes involved in sex differences?



*in species with heteromorphic sex chromosomes

20th Century Model

XY

Sry (Y-linked)

testes

testicular hormones

Masculine
body & brain

XX

absence of *Sry*

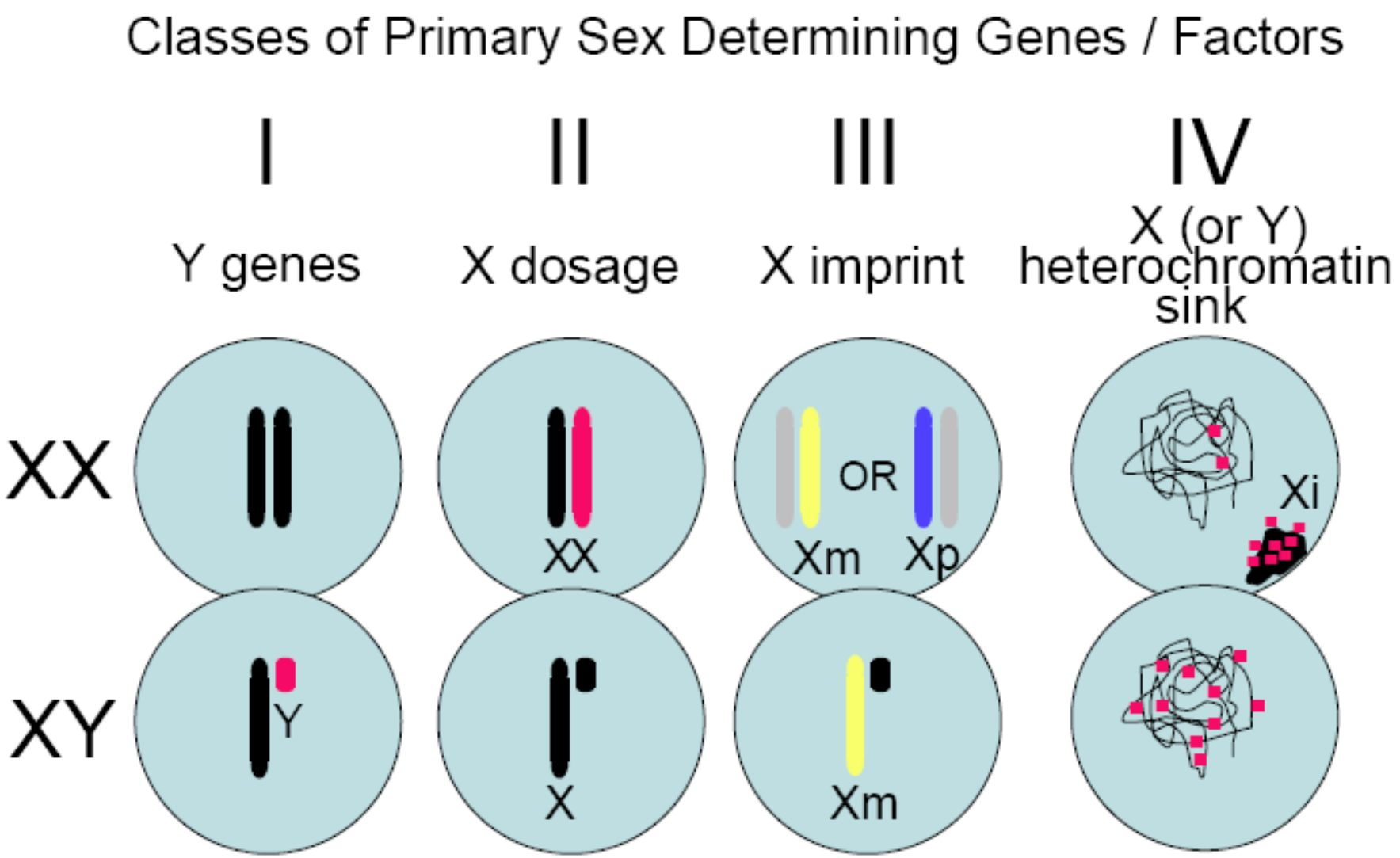
ovaries

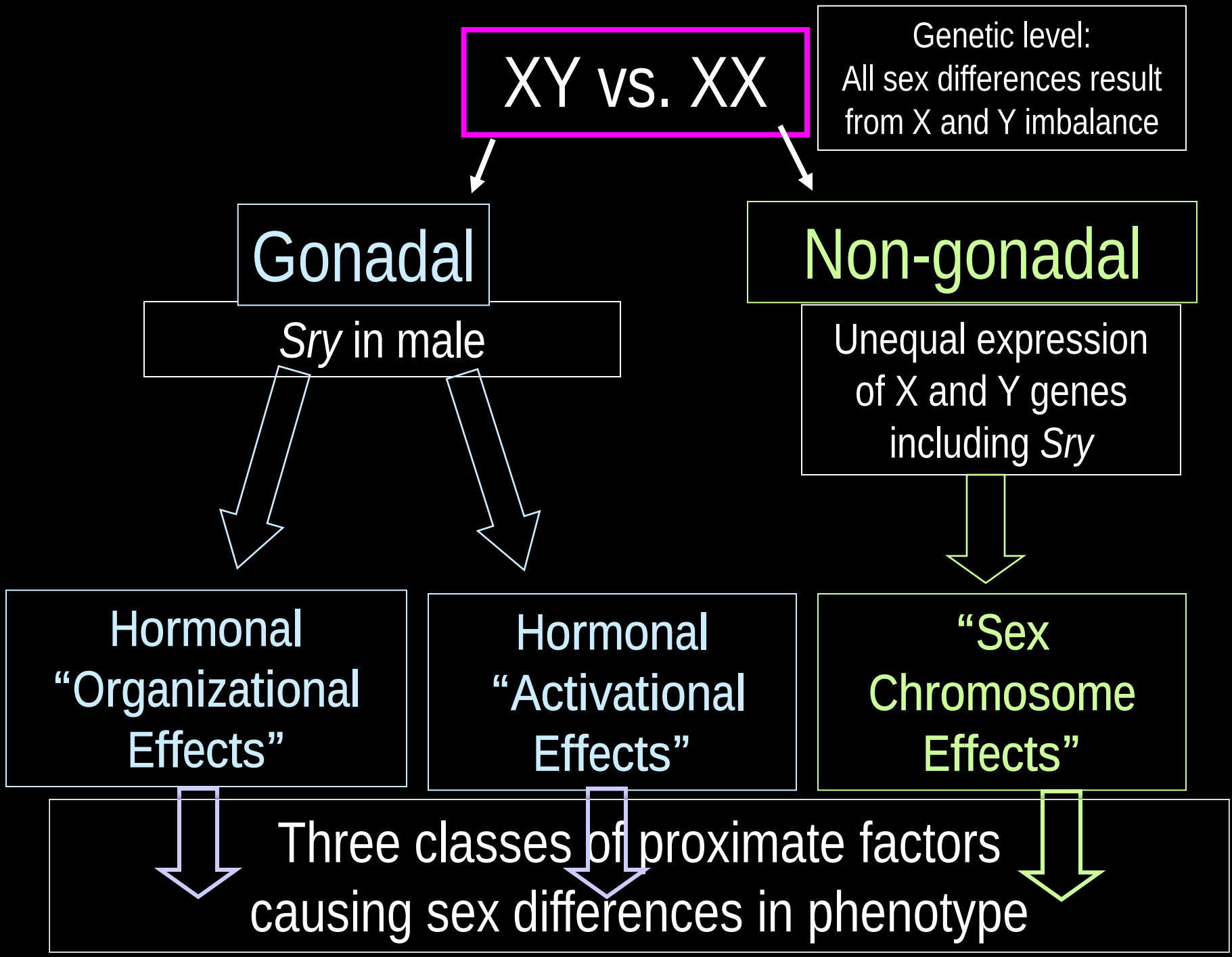
female hormones
lack of male hormones

Feminine
body &
brain

More than just Sry

Primary sex determining genes are those that are differentially represented in male and female zygotes




XY vs. XX
Genetic level:
All sex differences result from X and Y imbalance
Gonadal
Sry in male
Non-gonadal
Unequal expression of X and Y genes including Sry
Hormonal "Organizational Effects"
Hormonal "Activational Effects"
"Sex Chromosome Effects"
Three classes of proximate factors causing sex differences in phenotype

How to vary sex chromosome complement (XX vs. XY) to observe differential effects without confounding hormonal differences?

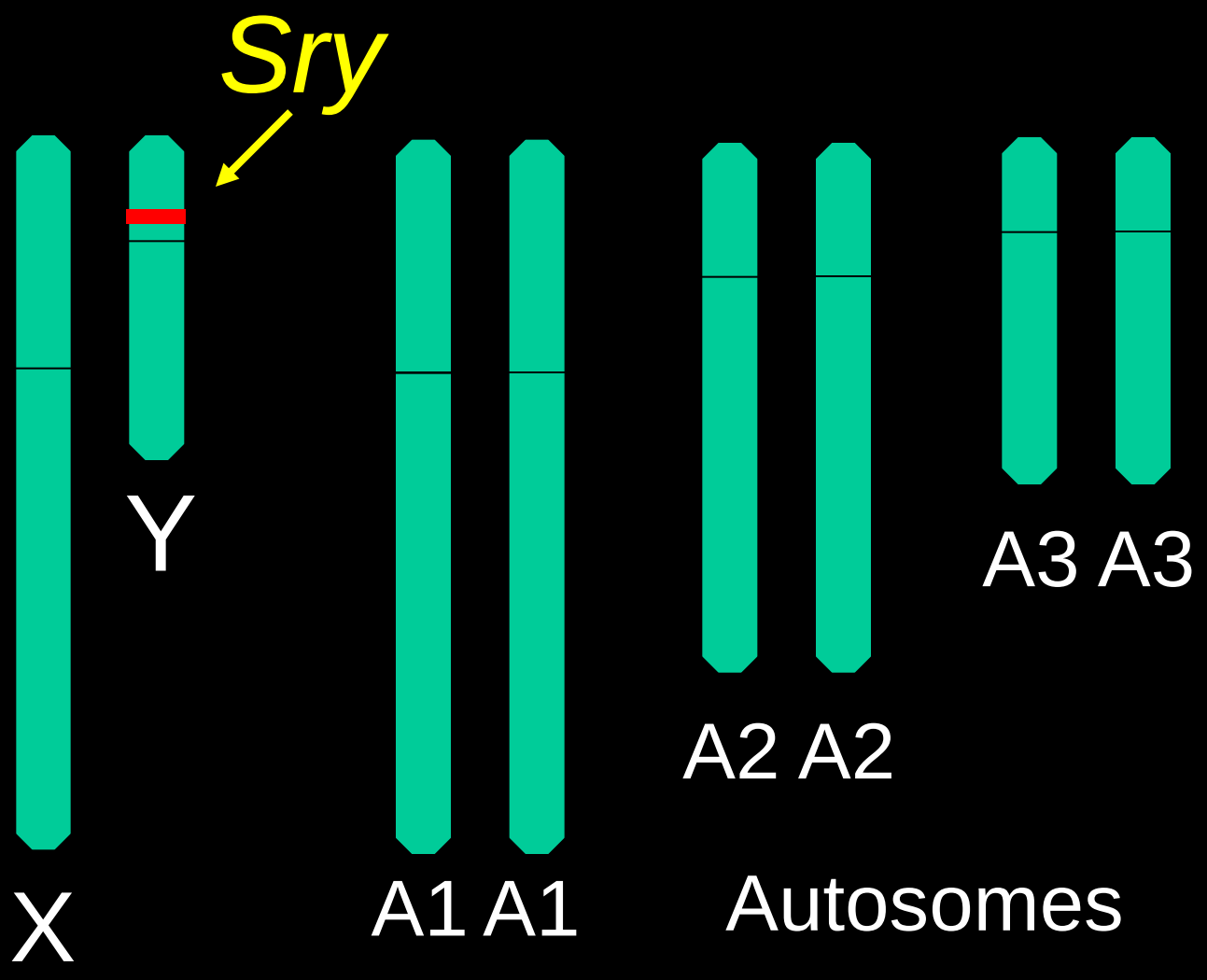
Two mouse models: FCG and XY*

“Four Core Genotypes” (FCG) Mice

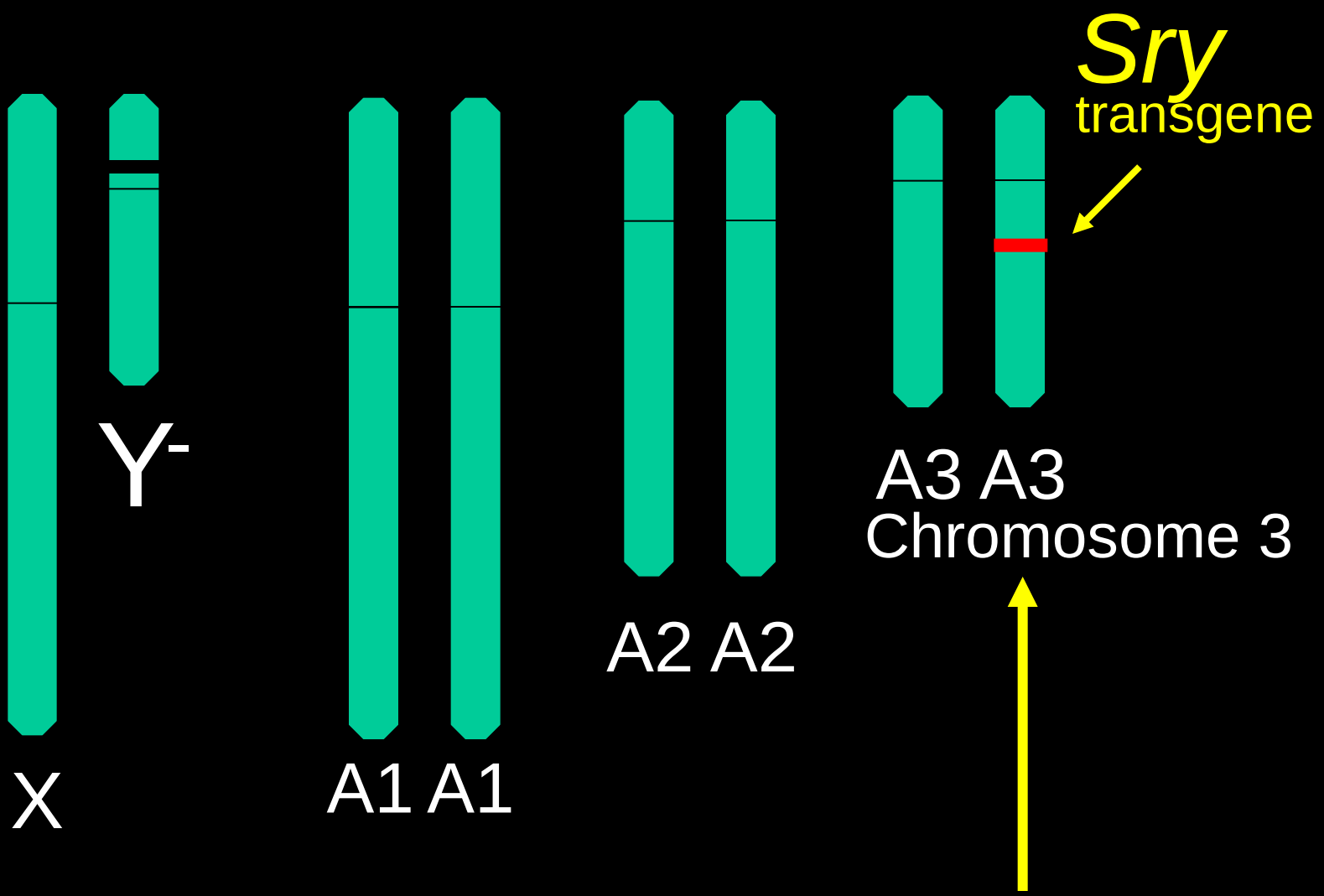
Paul Burgoyne and Robin Lovell-Badge

Make gonadal determination independent of sex chromosome complement

Y-linked *Sry* is testis-determining



Sry "moved" to Chromosome 3

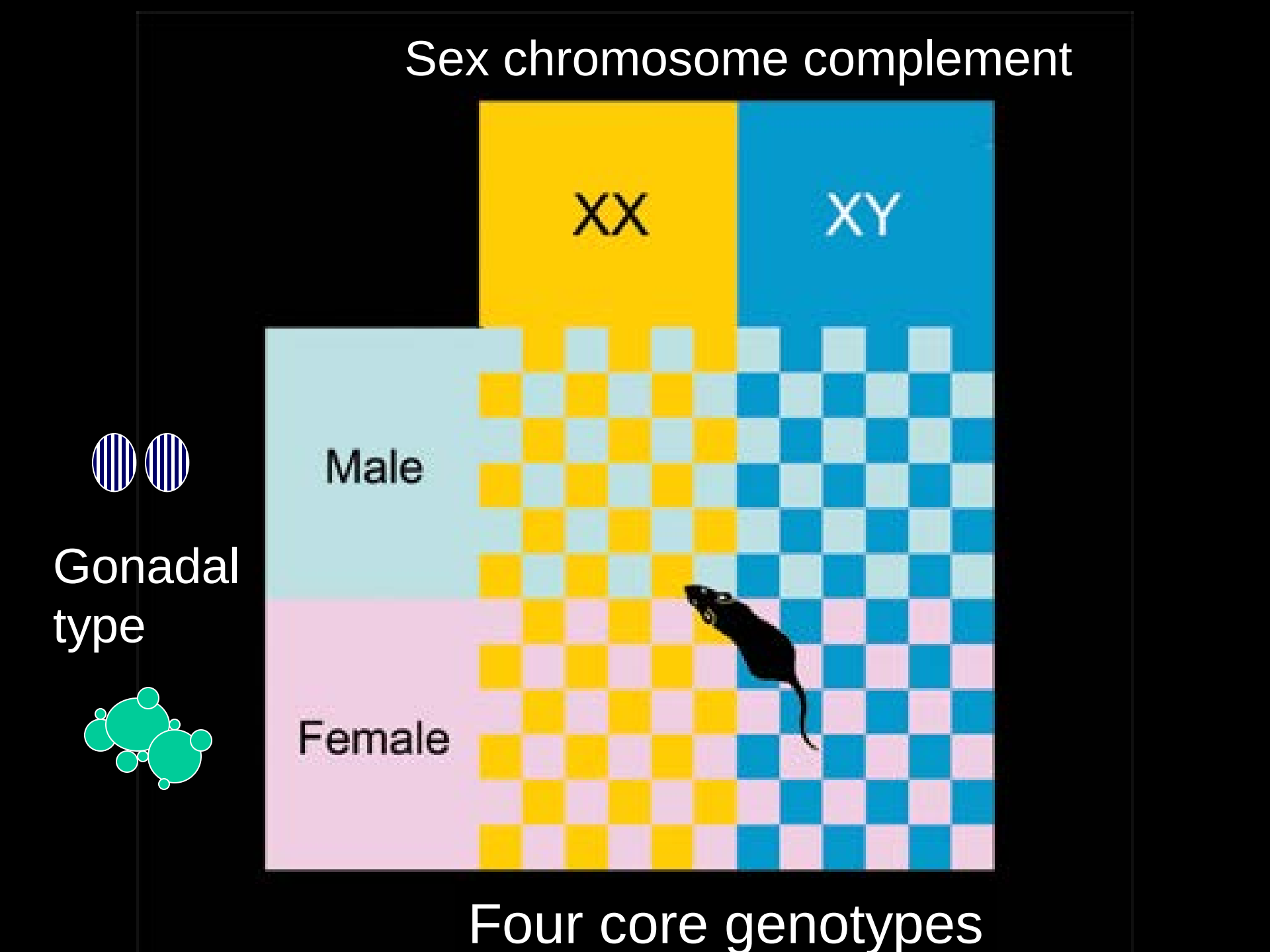


"Four Core Genotypes Model"
XY^{-}*Sry* father x XX mother

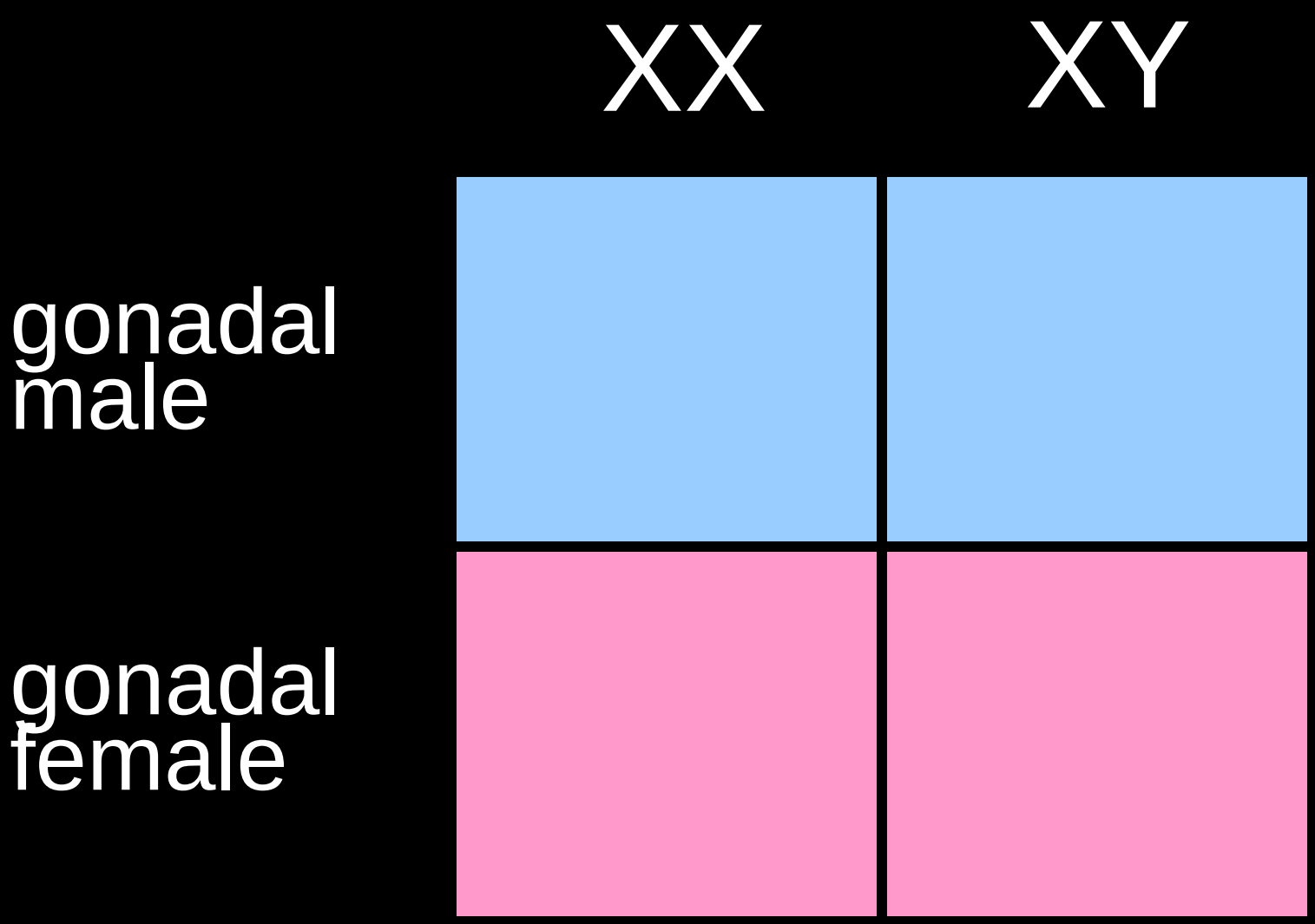
MICE

offspring:

genome	gonads	
XX	♀	XXF
XY^{-}	♀	XYF
XX*Sry*	♂	XXM
XY^{-}*Sry*	♂	XYM


Sex chromosome complement
XX
XY
Male
Female
Gonadal type
Four core genotypes

Test phenotype in GDX mice (no activational effects)
This is an organizational effect of gonadal hormones



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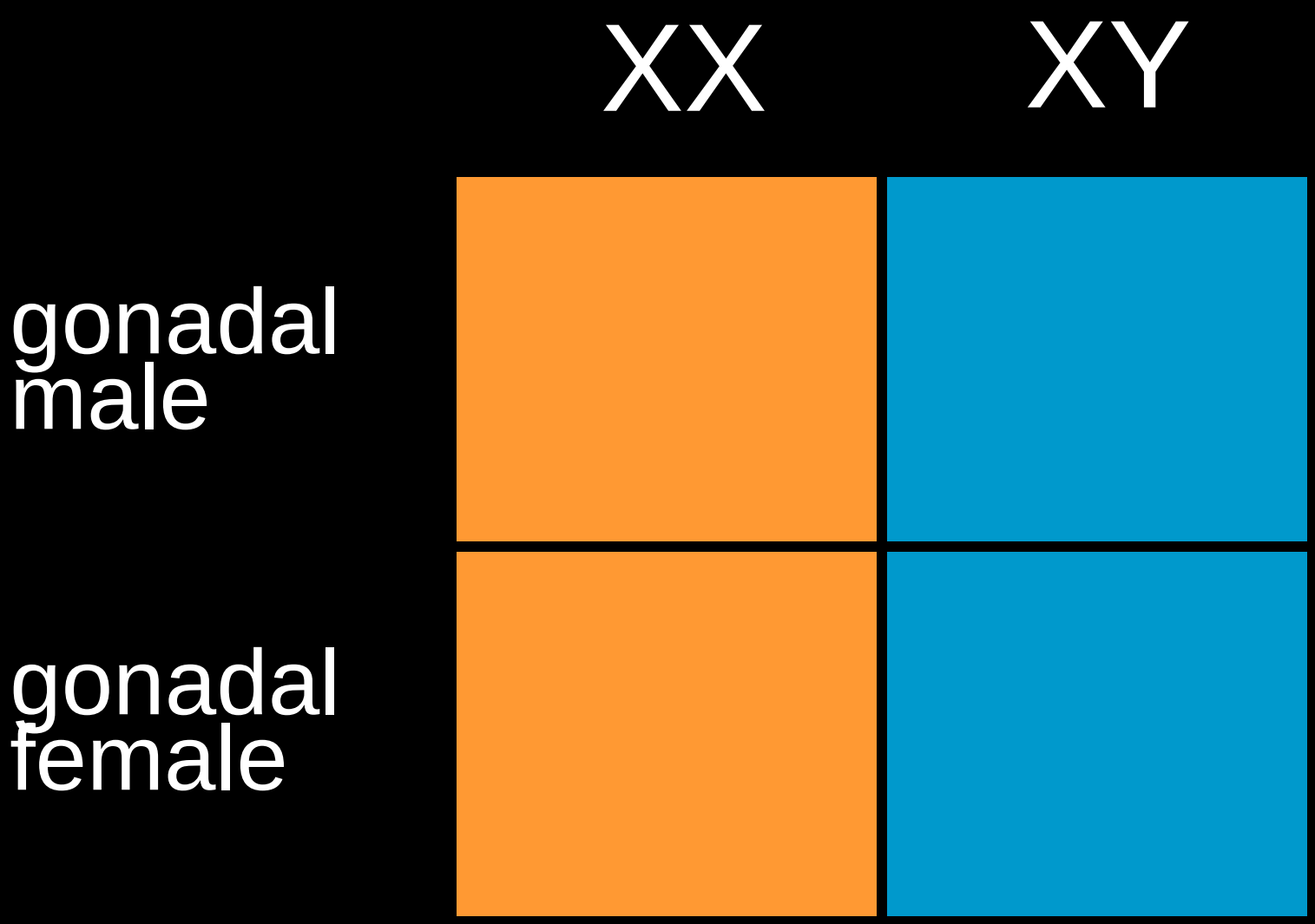


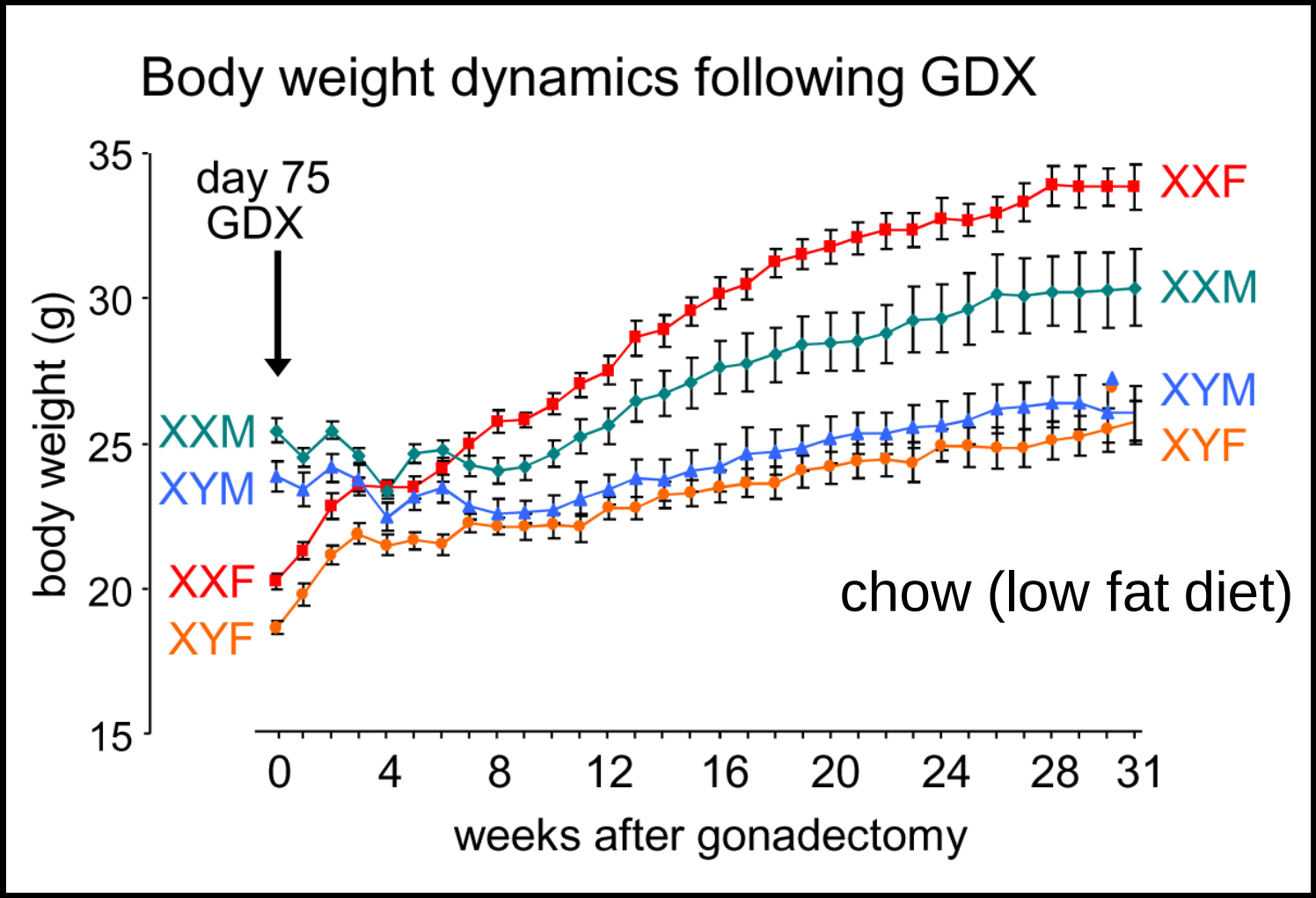
Sex chromosome and hormonal effects on adiposity and metabolism

Xuqi Chen

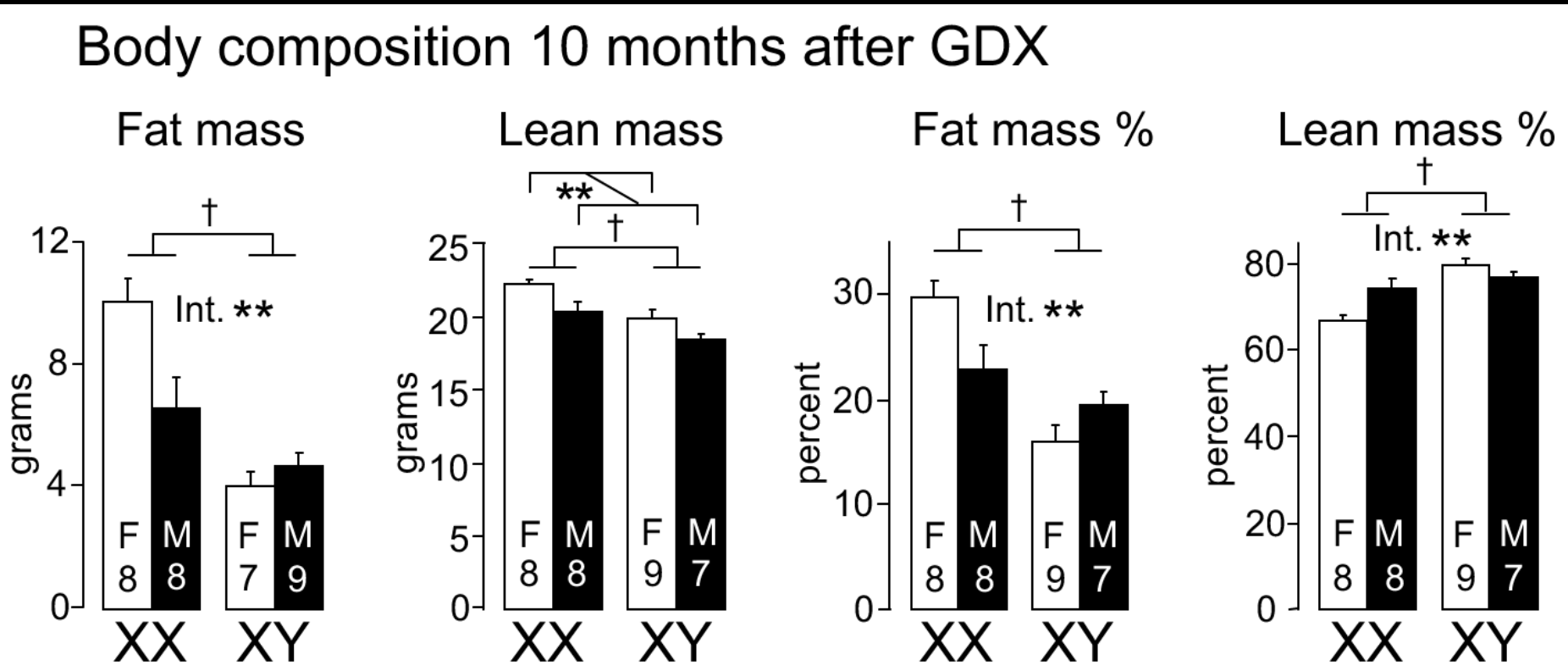
Karen Reue
UCLA
Human Genetics

Jenny Link

Interaction of sex hormones and sex chromosomes

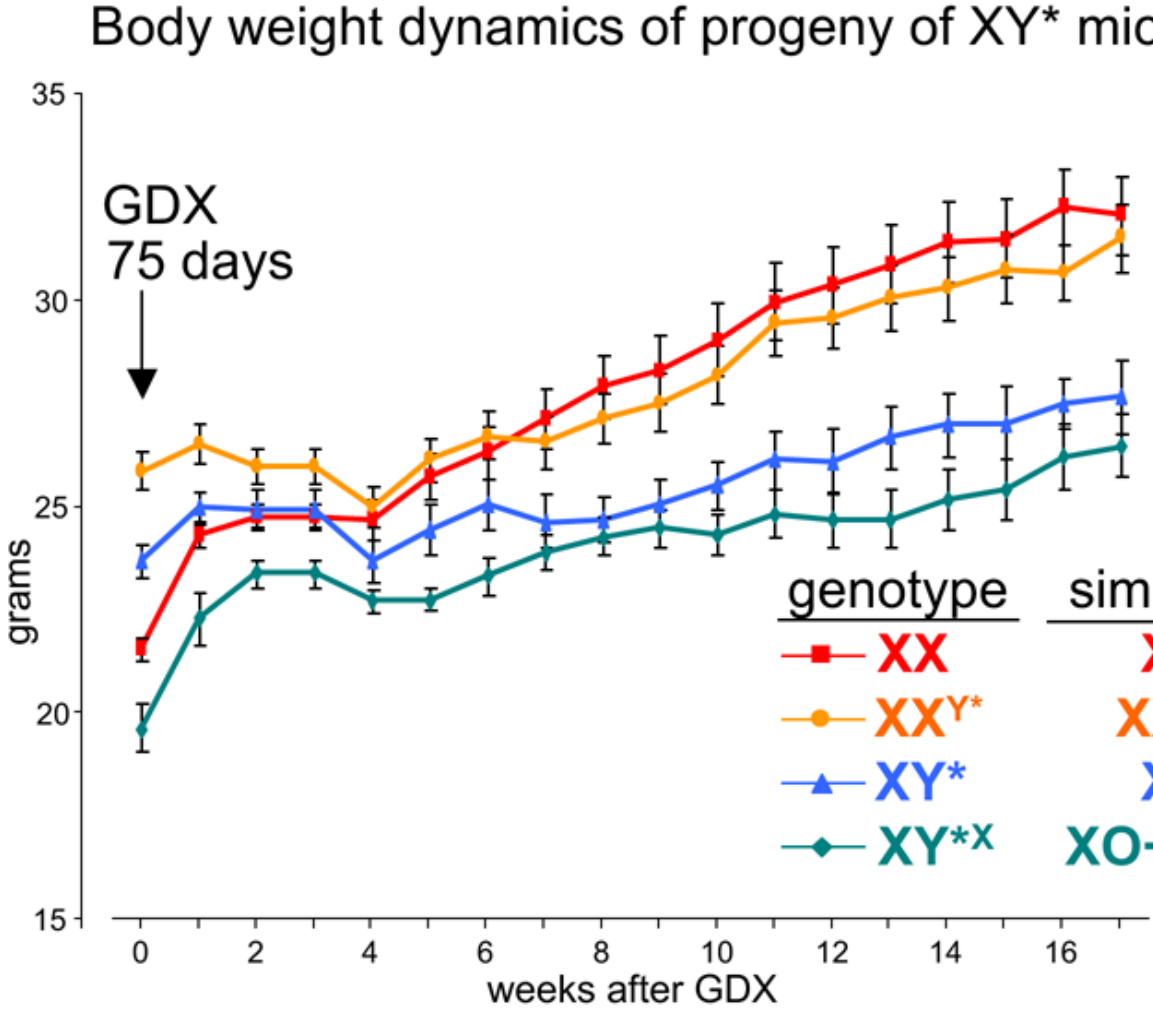


Large sex chromosome effect on fat mass
XX >> XY



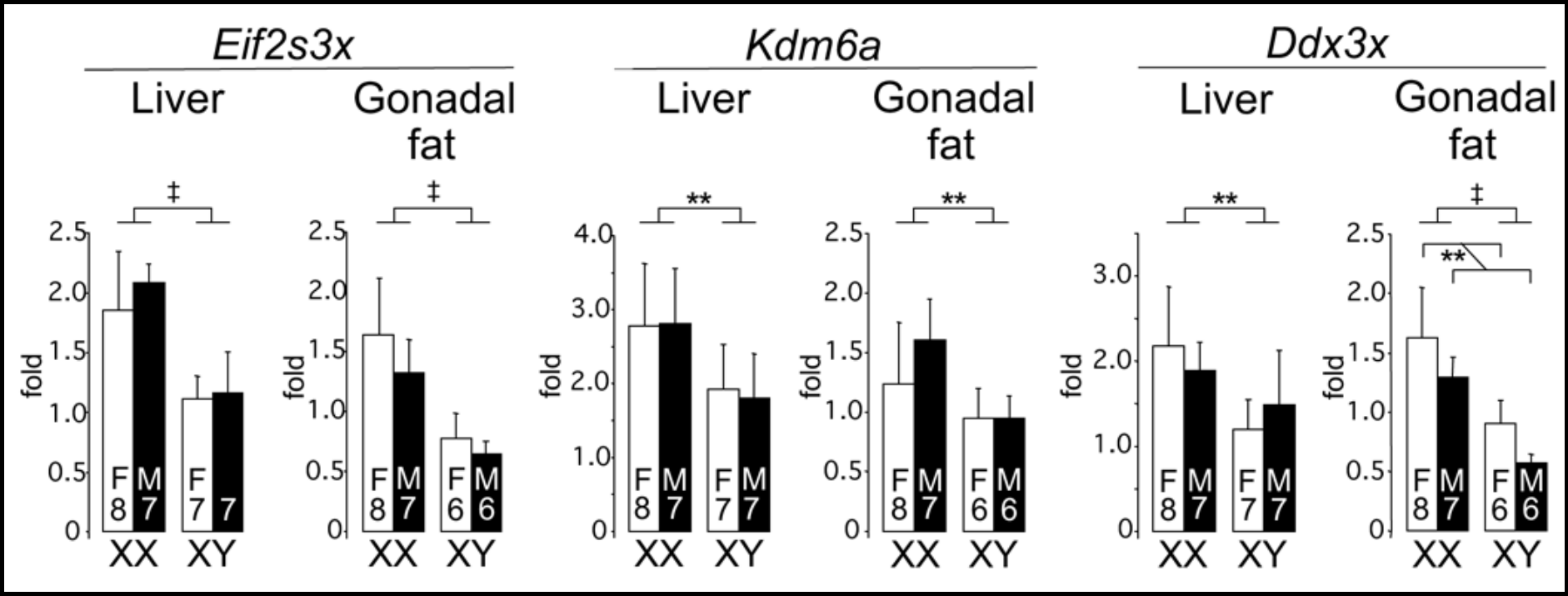
Second Model: XY*

Mice with two X chromosomes are heavier and fatter than mice with one X chromosome



genotype	similar to	gonadal sex	#X	#Y
XX	XX	F	2	0
XX^{Y*}	XXY	M	2	1
XY*	XY	M	1	1
XY^{*X}	XO+PAR	F	1	0

Genes escaping X-inactivation are expressed higher in XX than XY mice and have Y partners. Candidates for sex-biasing genes

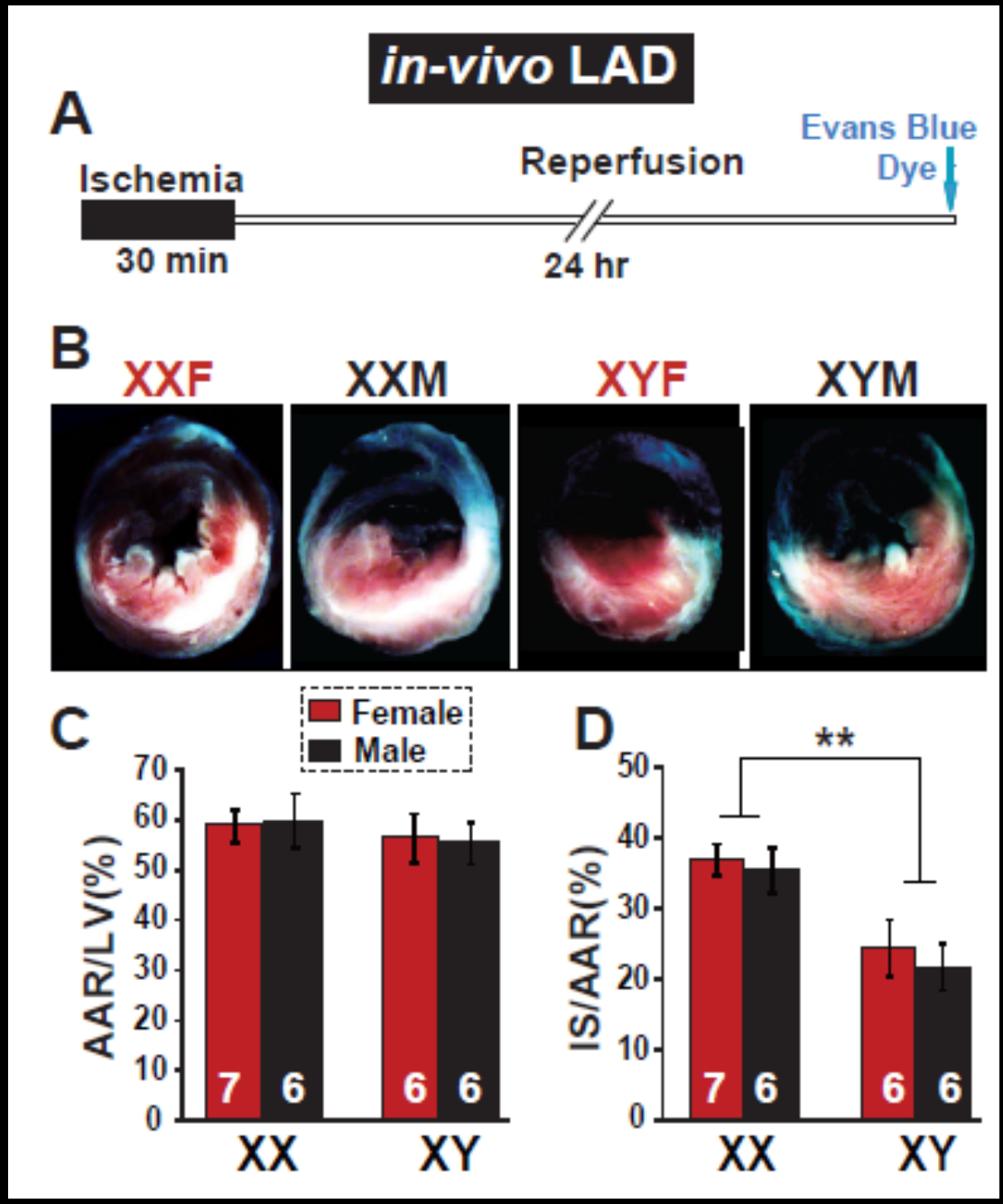


Jenny Link

XX Mice are more susceptible to cardiac ischemia/reperfusion injury than XY mice

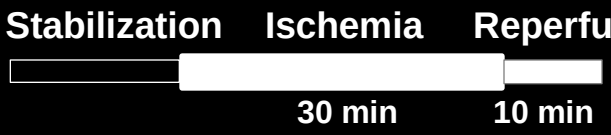
Jingyuan Li,
Maureen Ruiz-Sundstrom,
Yuichiro Itoh, Xuqi Chen,
Arthur P. Arnold
Mansoureh Eghbali
UCLA

Mansoureh Eghbali, PhD
UCLA Dept Anesthesiology

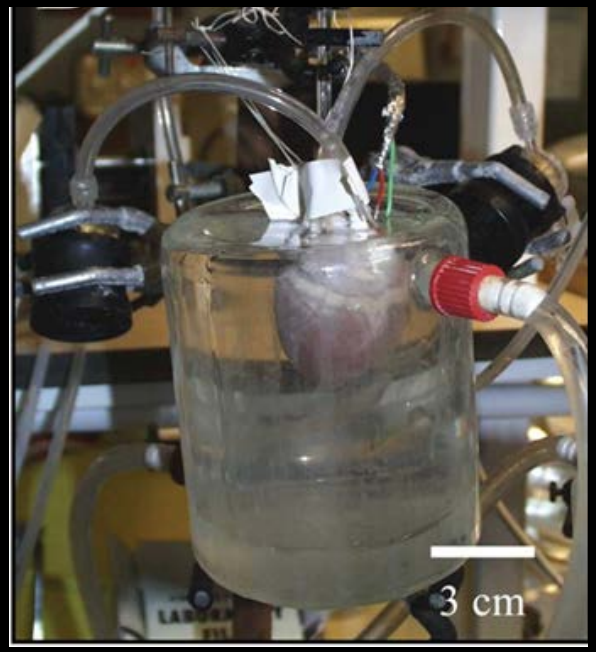

in-vivo LAD
A
Ischemia
30 min
Reperfusion
24 hr
Evans Blue Dye
B
XXF
XXM
XYF
XYM
C
Female
Male
AAR/LV(%)
70
60
50
40
30
20
10
0
7
6
6
6
XX
XY
D
**
IS/AAR(%)
50
40
30
20
10
0
7
6
6
6
XX
XY

Langendorff Perfused hearts

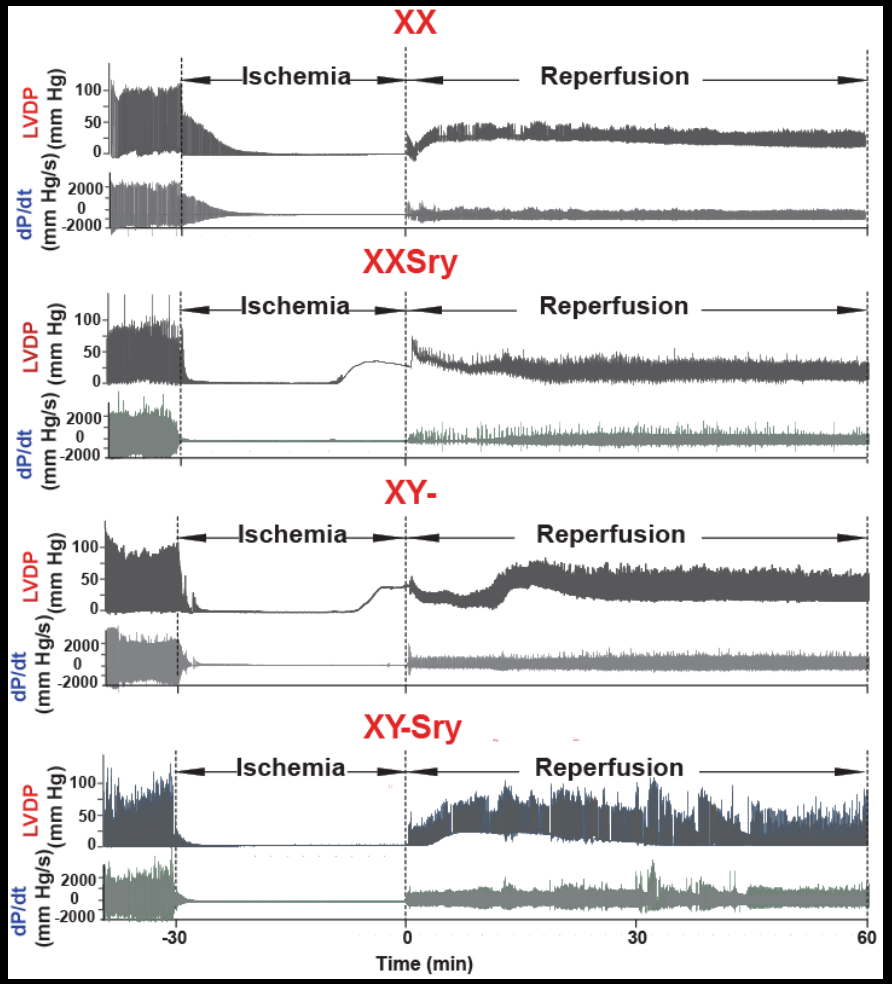
Infarct size
Hemodynamic



Calcium retention capacity



Gonadectomized XX mice have lower cardiac functional recovery after ischemia reperfusion injury compared to XY mice



XXF

XXM

XYF

XYM

Representative recordings:

left ventricular developed pressure (LVDP),

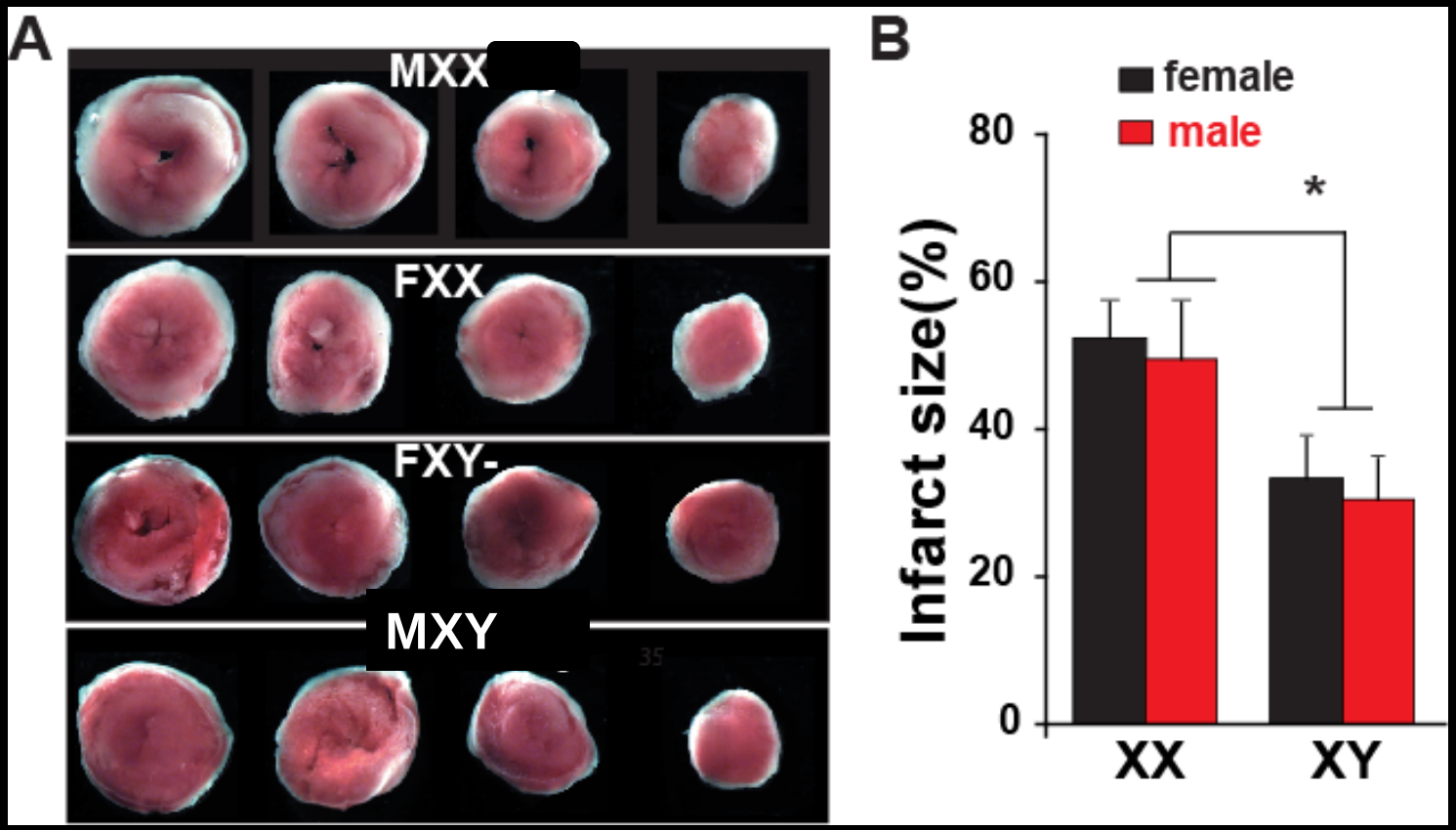
dP/dt_{Max} (the maximum rate of LV pressure rise)

dP/dt_{Min} (the maximum rate of LV pressure decline)

Infarct size XX > XY

A. Four slices of the same heart after TTC staining.
White area represents the infarct zone, red shows the viable area.

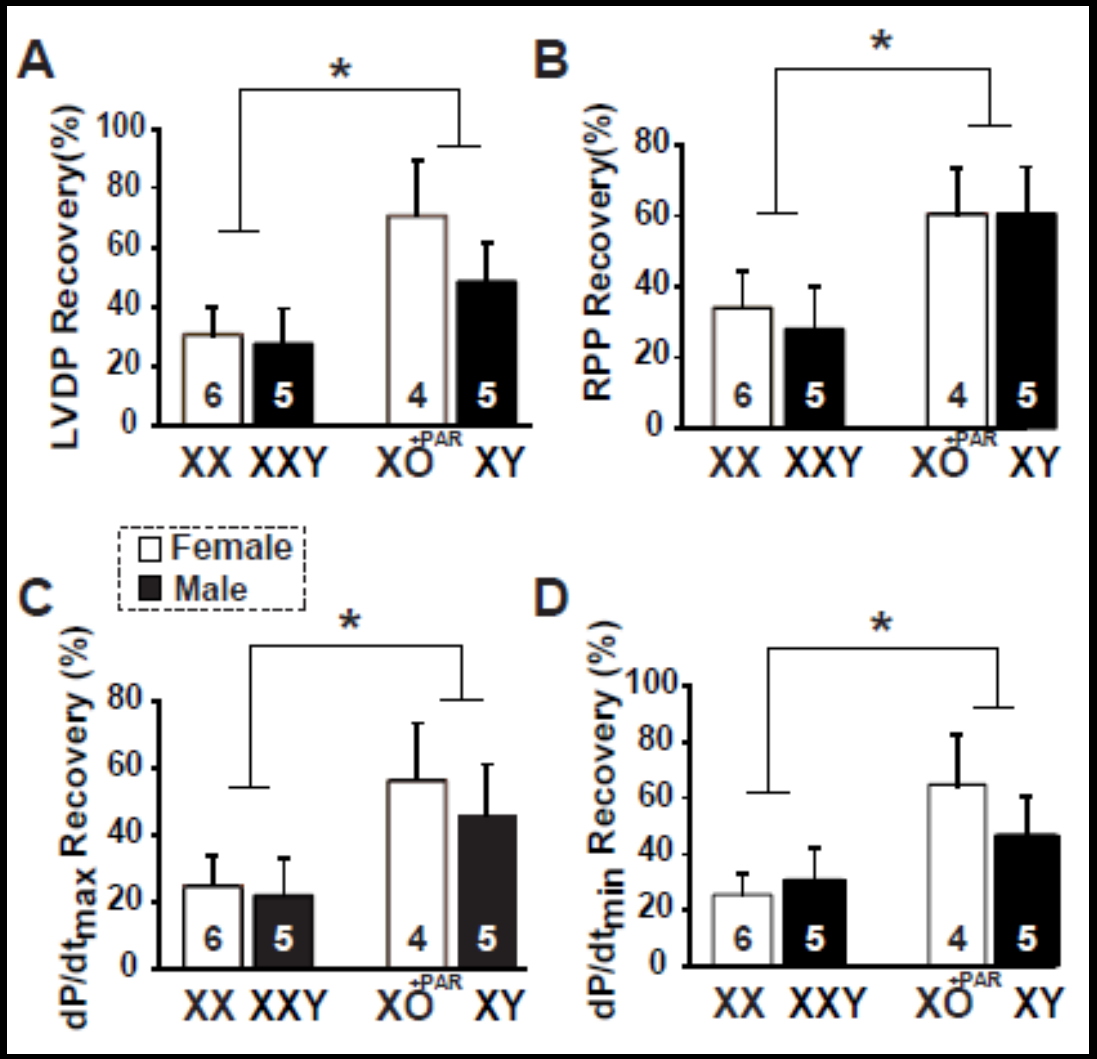
B. The area of necrosis as the percentage of total ventricular area, *P<0. 05(n=6-7).



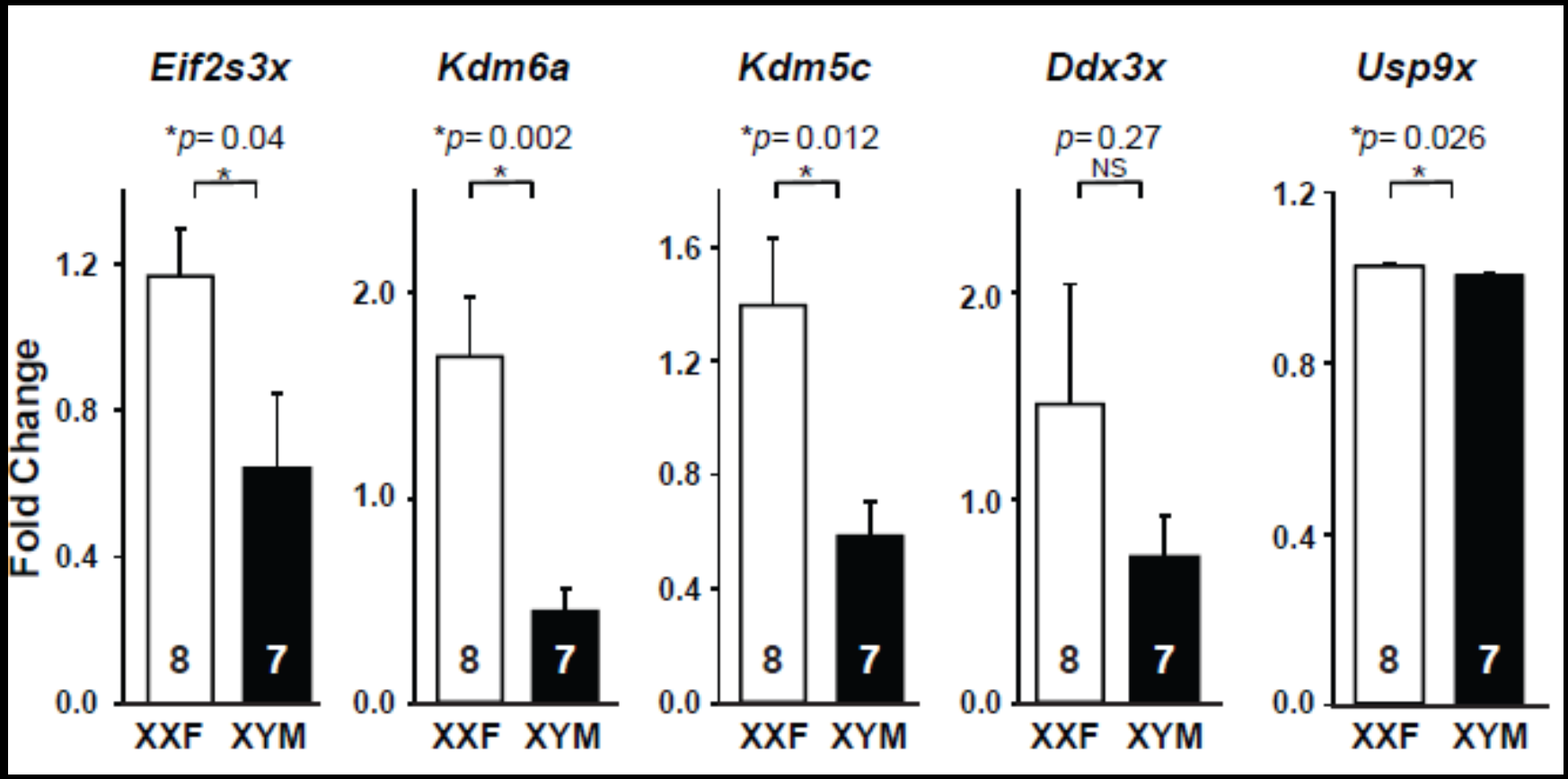
XY* Model

The sex chrom effect on IR injury is an X chrom effect

One X is better than two.



Heart: Genes escaping X inactivation are expressed higher in XX than XY



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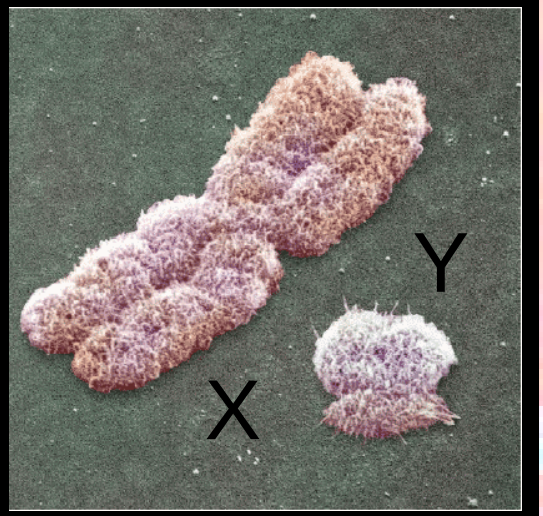
Y
X


sex chromosome research 5 ¢
THE DOCTOR IS IN