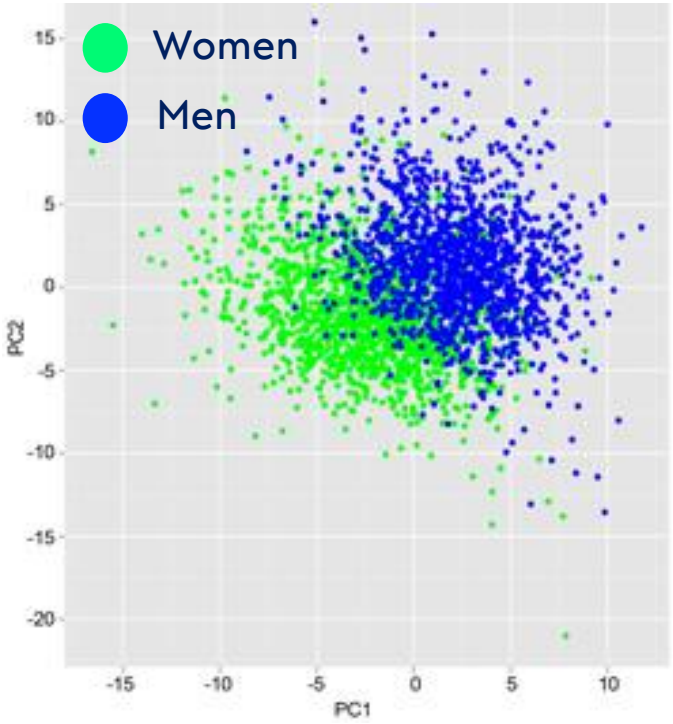
Mechanisms underlying sex differences in cardiometabolic disease

Karen Reue
Dept. of Human Genetics
David Geffen School of Medicine at UCLA

Men and women differ in serum metabolite levels

Serum metabolite concentrations in healthy young men and women



Mittelstrass et al. (2011) *PLoS Genet*

Women ≠ Men

for 80% of blood metabolites

Sex differences in cardiometabolism

XY

Testes

≠

fat:lean mass ratio
adipose distribution
plasma lipid profile
insulin resistance
hypertension
fatty liver
myocardial infarct risk
ischemic stroke risk

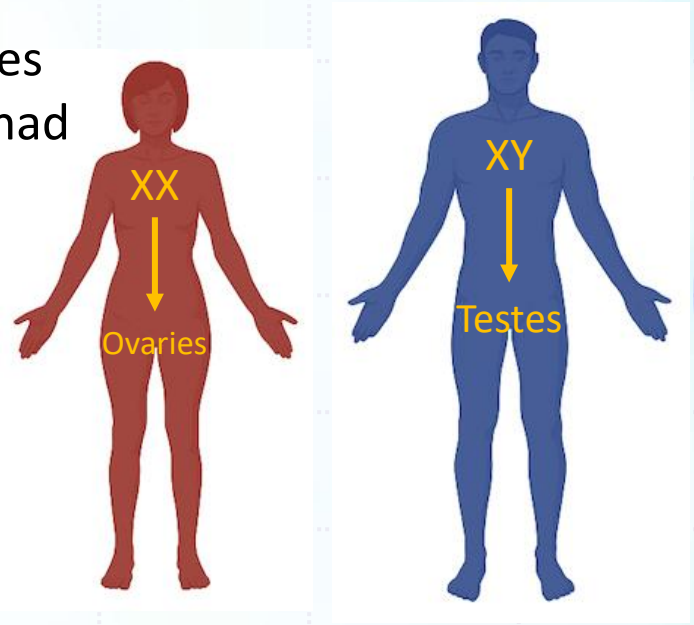
XX

Ovaries

Sex chromosomes function in all cells

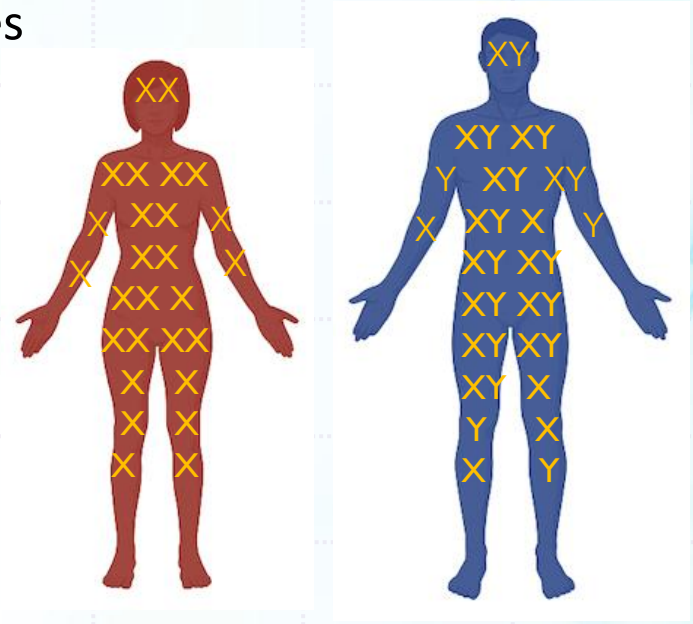
Traditional view

Sex chromosomes are critical for gonad development



Revised view

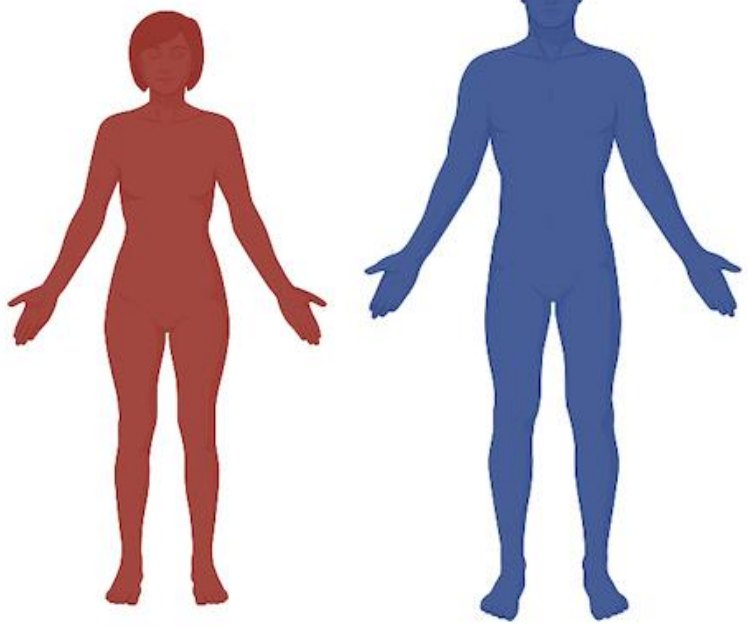
Sex chromosomes act in every cell throughout lifetime



Identify contributions of chromosomal and gonadal sex: Four Core Genotypes mouse model

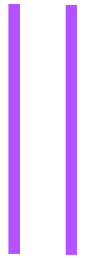
XX
Ovaries

XY
Testes



XX
Ovaries

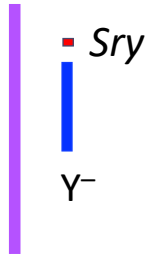
XX ovaries



X X

XY
Ovaries

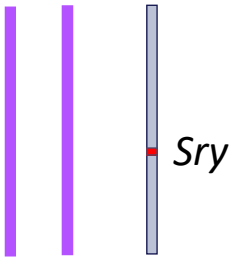
XY⁻ ovaries



X

XX
Testes

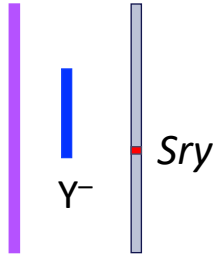
XX testes



X X 3

XY
Testes

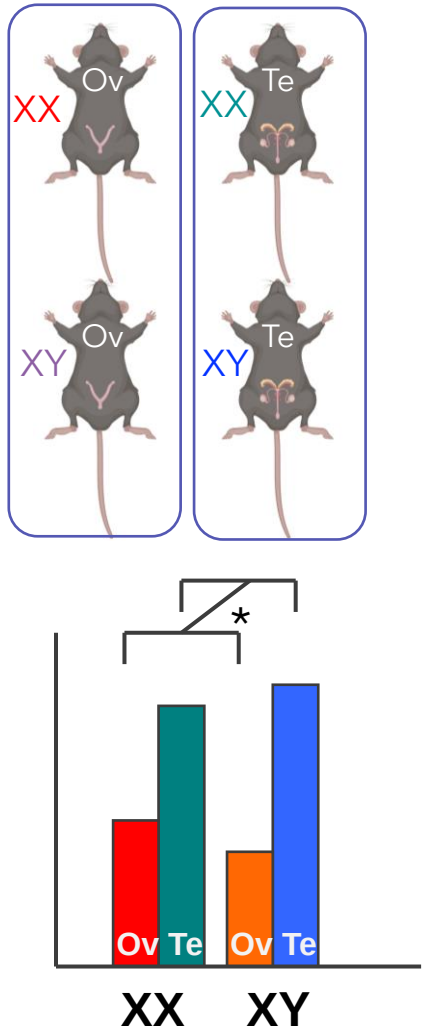
XY⁻ ovaries

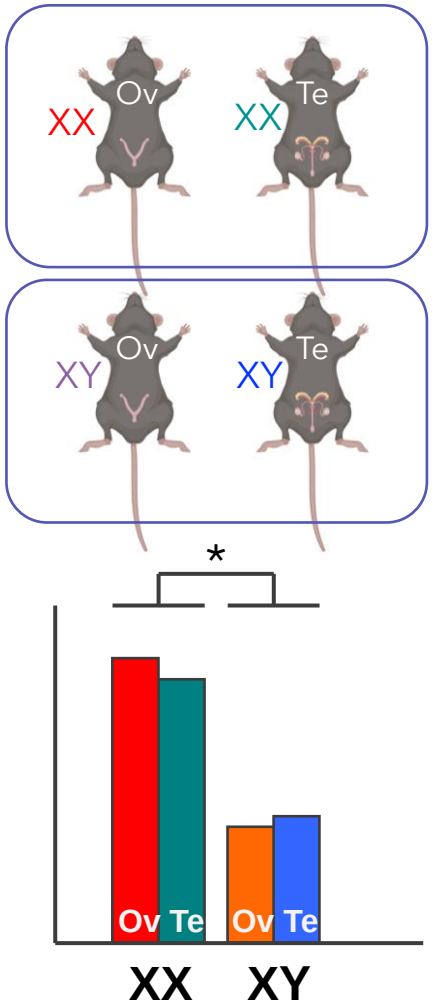


X 3

Detection of gonadal and sex chromosome effects

“Gonadal effect”



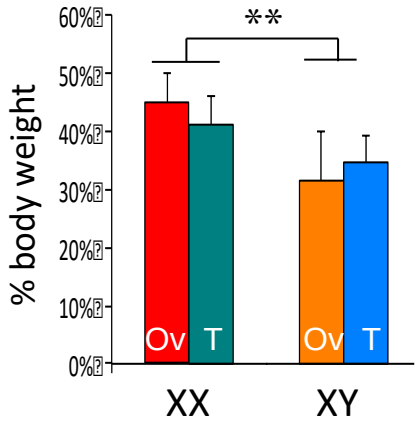


“Sex chromosome effect”

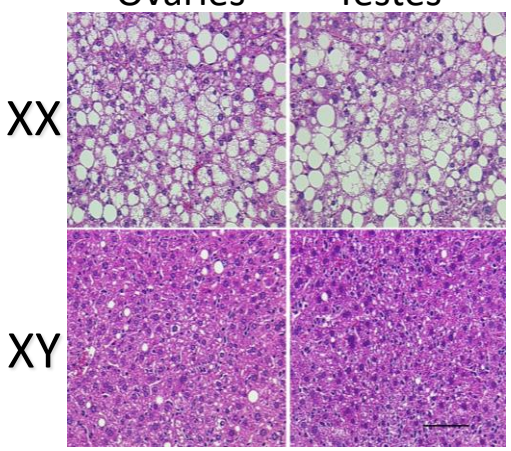
Sex chromosomes influence numerous cardiometabolic traits

XX > XY

Body fat

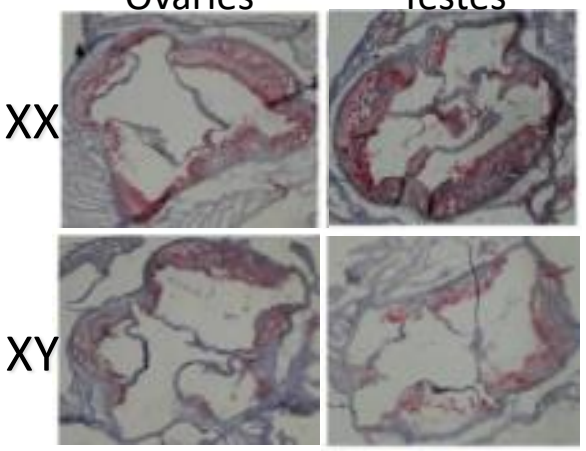


Fatty liver

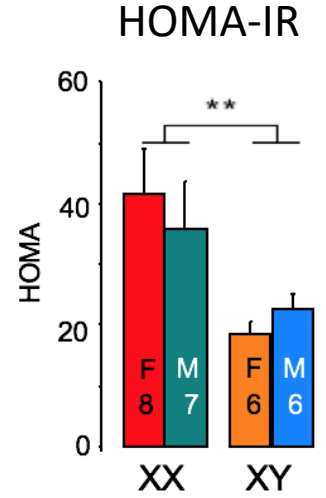


(GDX)

Atherosclerosis



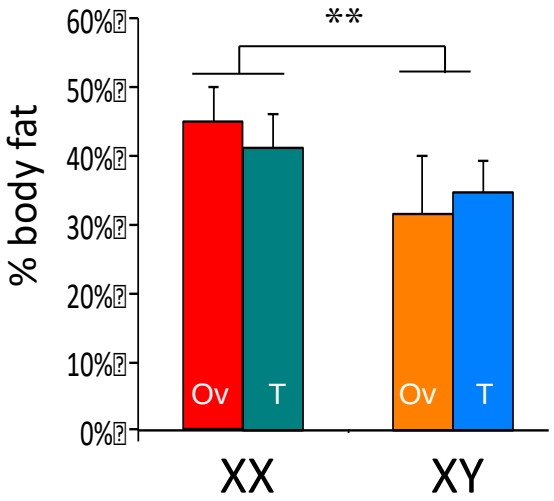
Insulin resistance



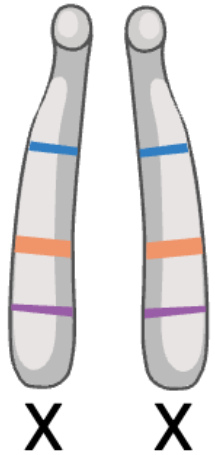
Chen et al. (2012) *PLoS Genetics*
Link et al. (2015) *ATVB*
AlSiraj (2019) *Nature Comm*
Link et al. (2020) *J Clin Invest*
Wiese et al. (2022) *Biol Sex Differ*

Genes that escape X chromosome inactivation may confer sex differences

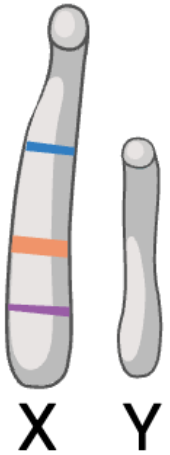
XX > XY body fat



XX

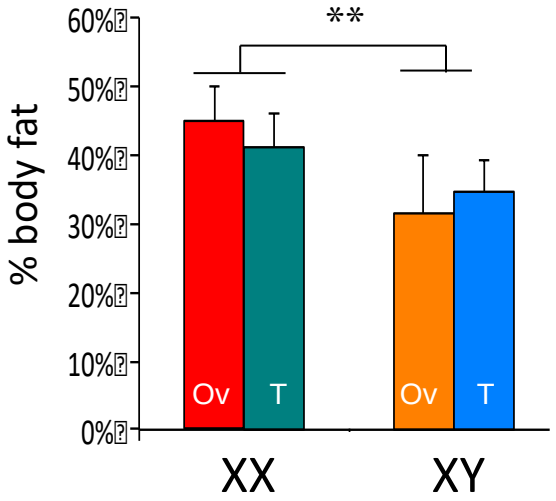


XY

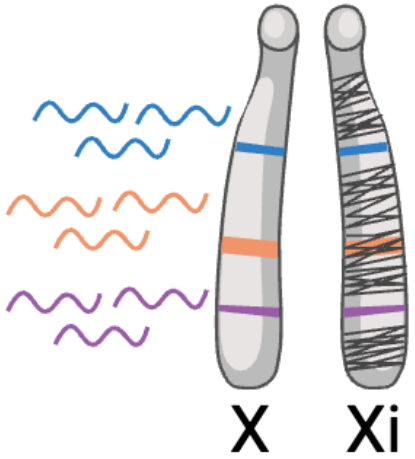


Genes that escape X chromosome inactivation may confer sex differences

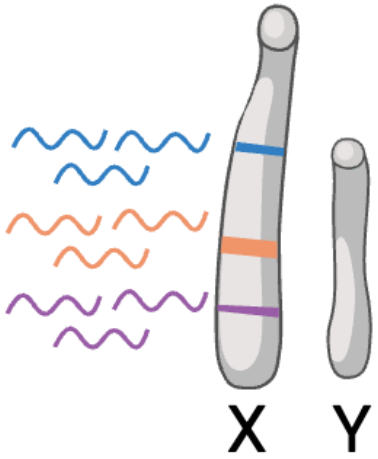
XX > XY body fat



XX

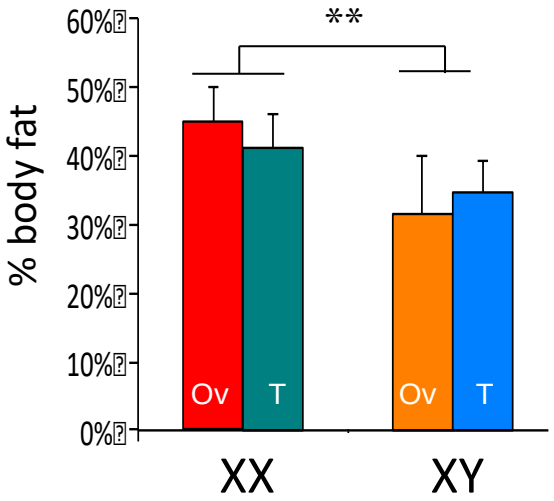


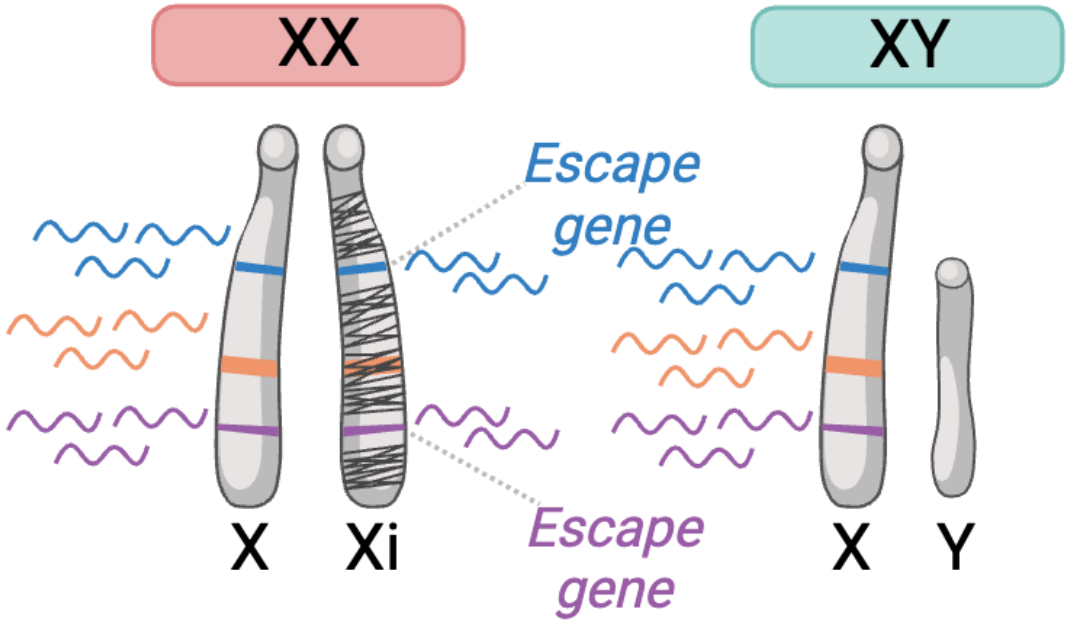
XY



Genes that escape X chromosome inactivation may confer sex differences

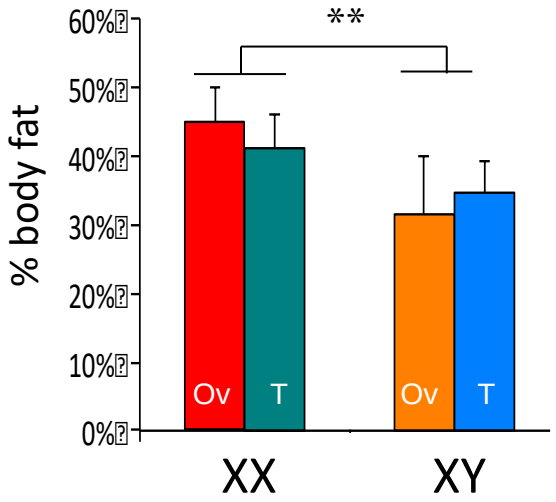
XX > XY body fat

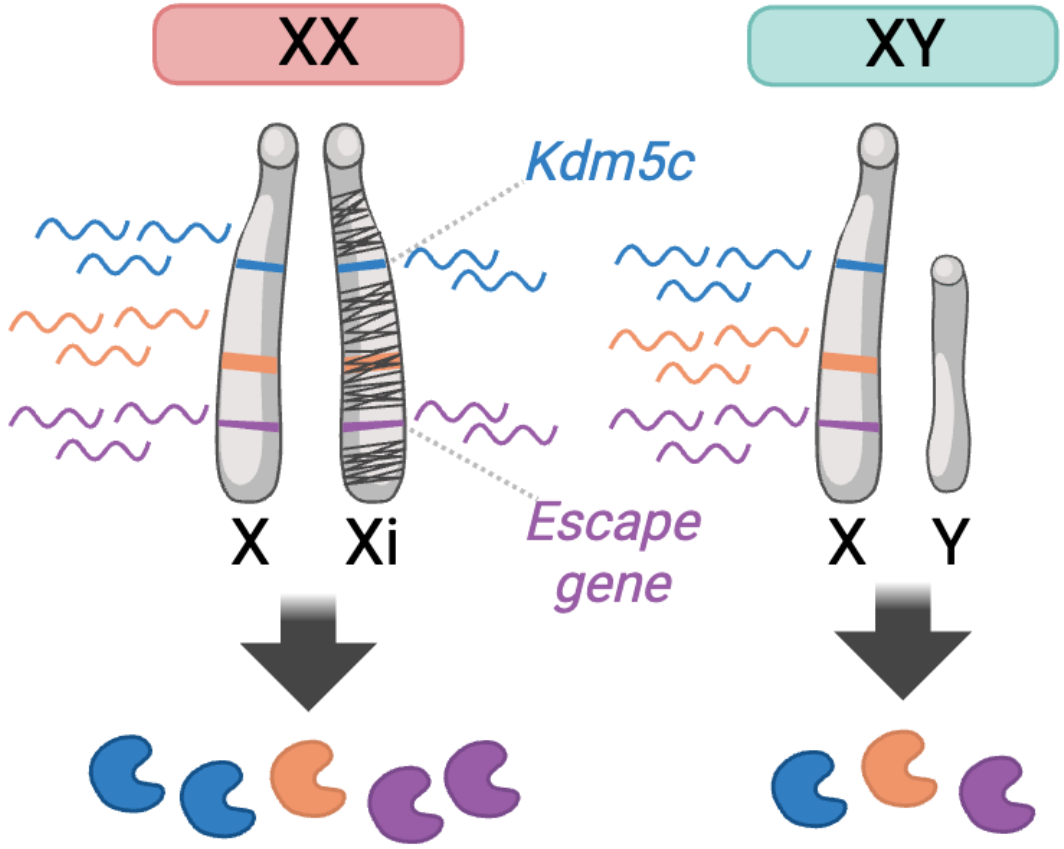




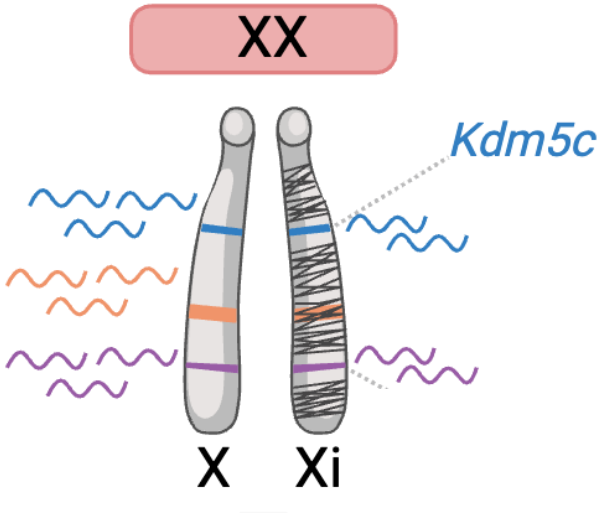
Genes that escape X chromosome inactivation may confer sex differences

XX > XY body fat

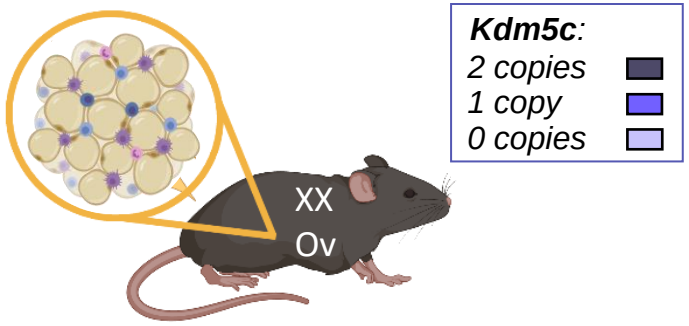




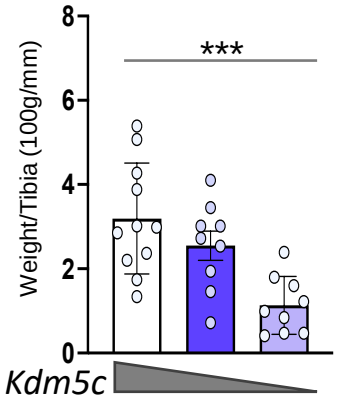
X escape gene *Kdm5c* modulates fat mass and energy expenditure

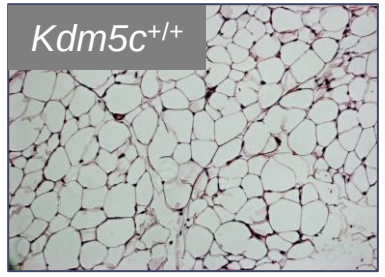


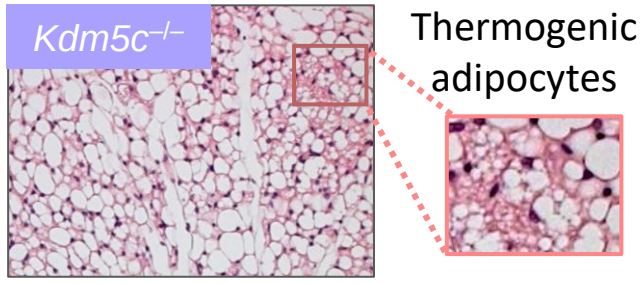
Change *Kdm5c* gene dosage in fat tissue



Fat mass

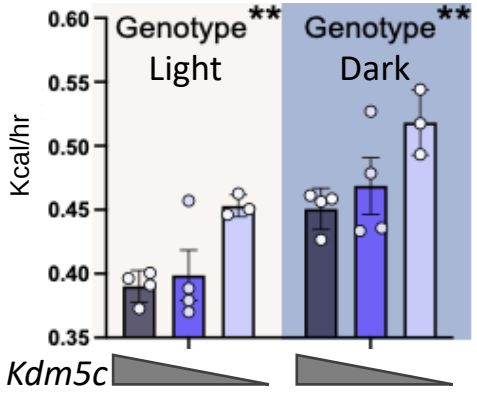






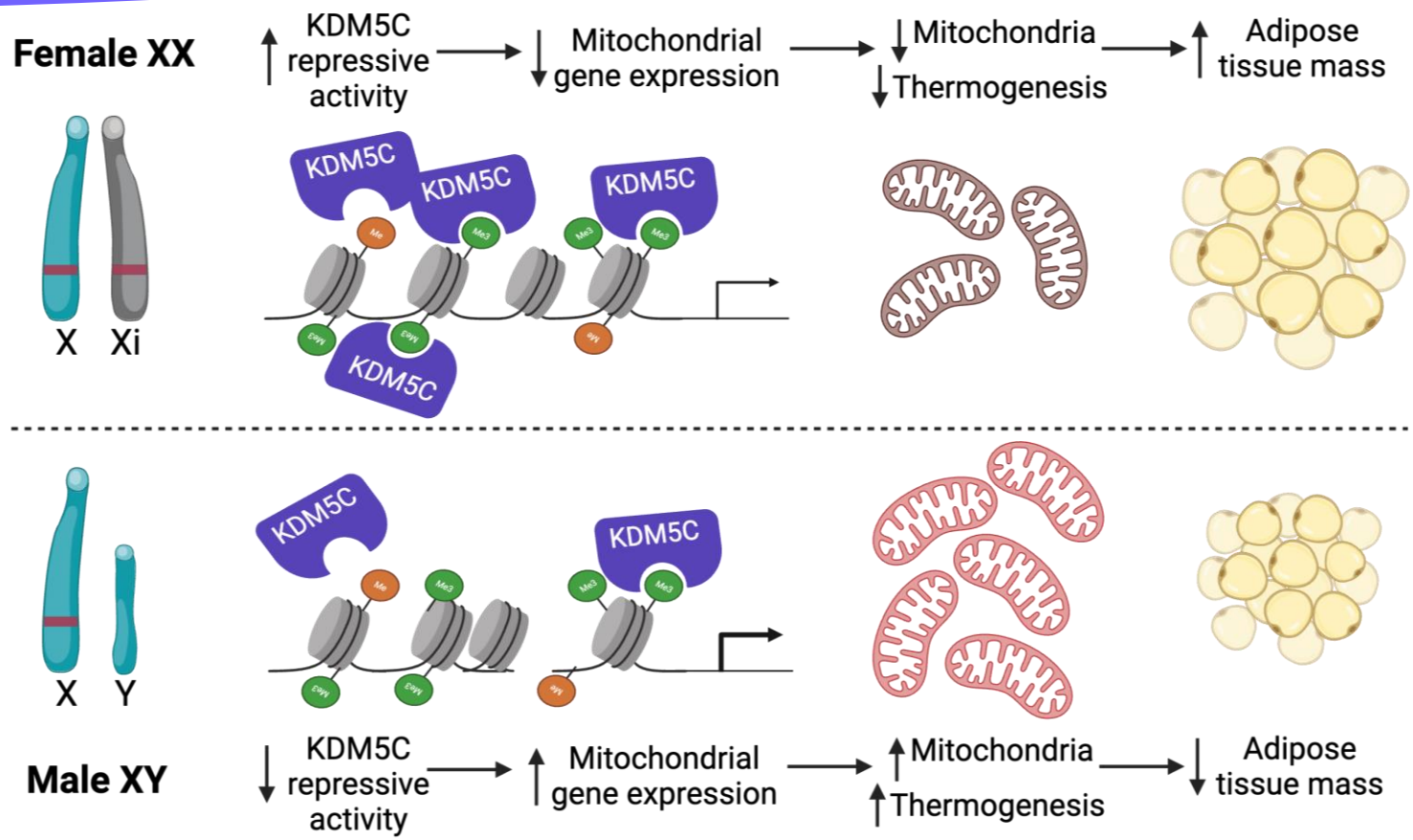
Thermogenic adipocytes

Energy expenditure

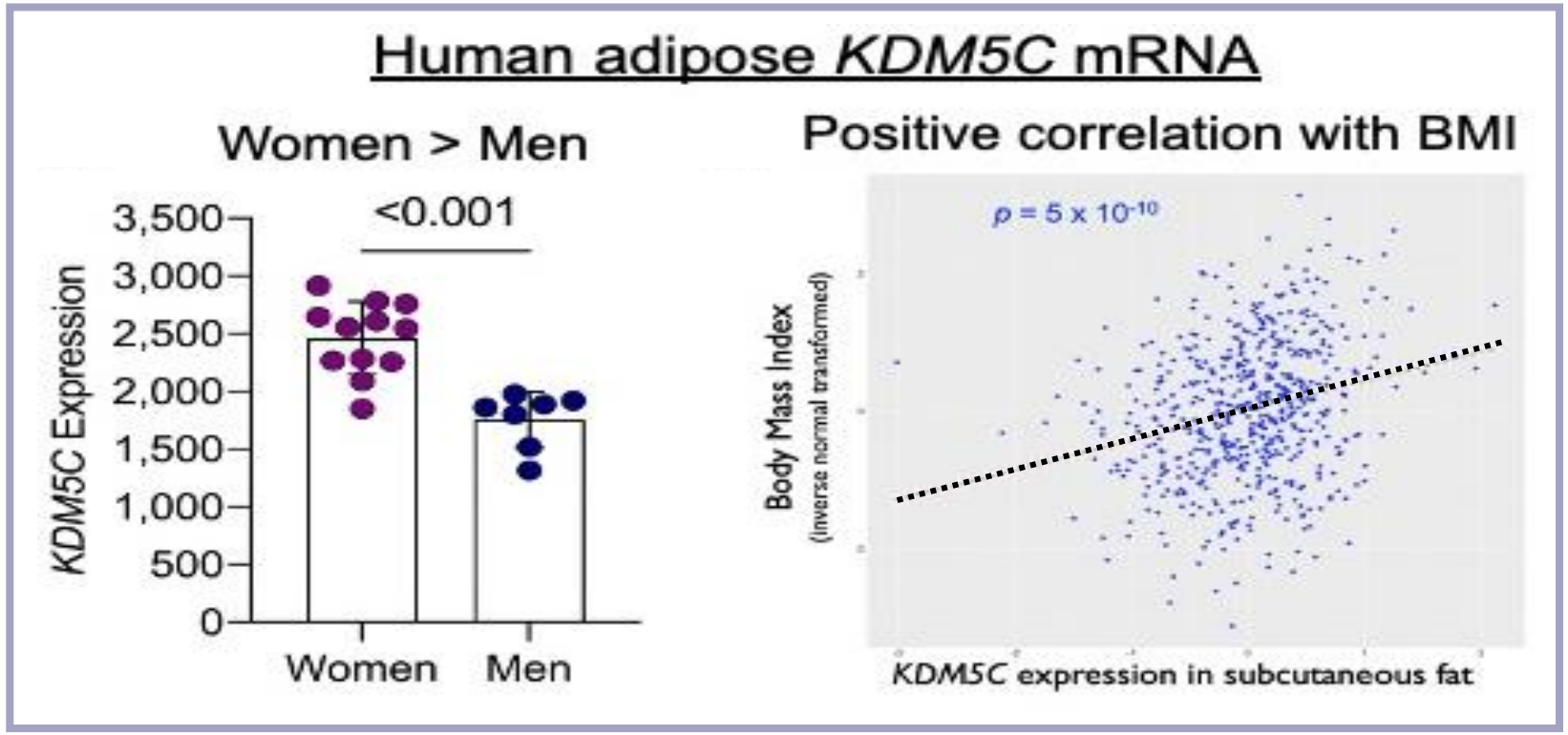


Avetisyan et al. *submitted*

Summary: XX > XY dosage of KDM5C histone demethylase affects gene expression and adiposity

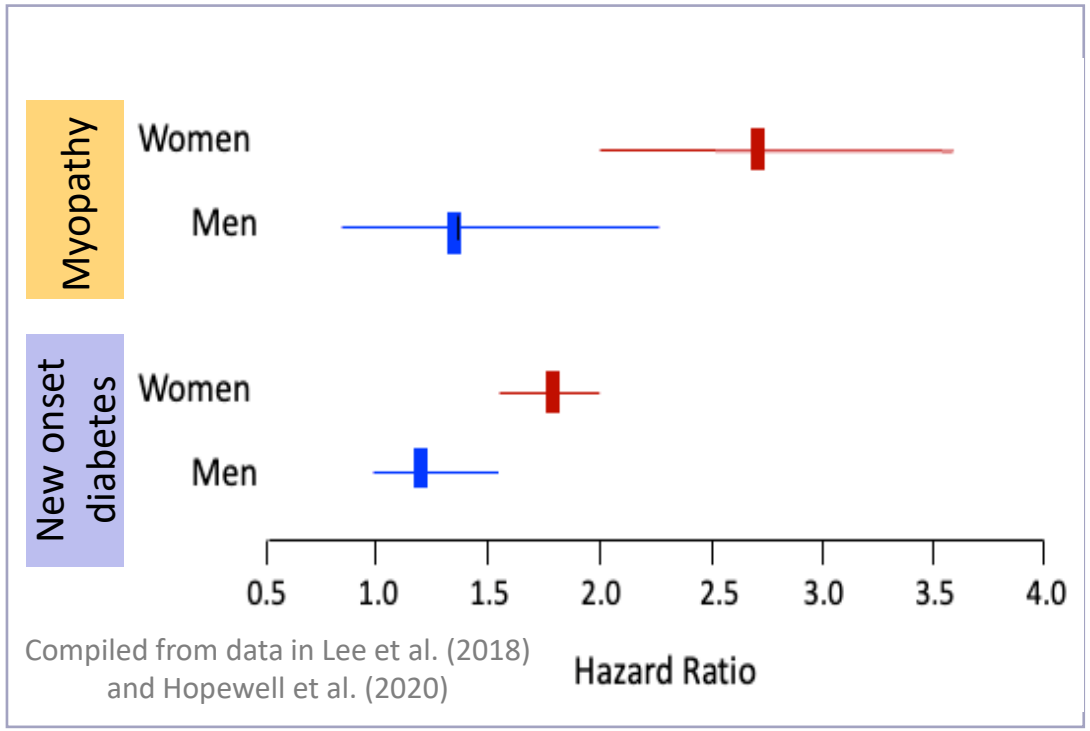


Human *KDM5C* expression correlates with fat mass



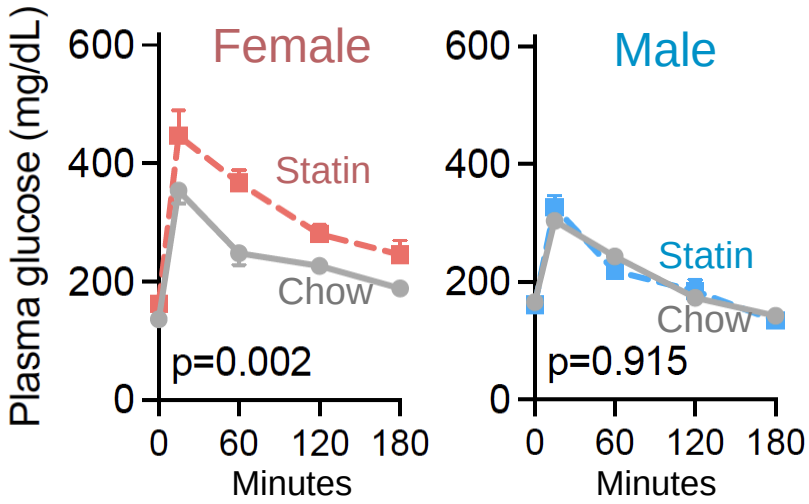
Female sex promotes statin drug adverse effects

Statin adverse risk score: Women > Men

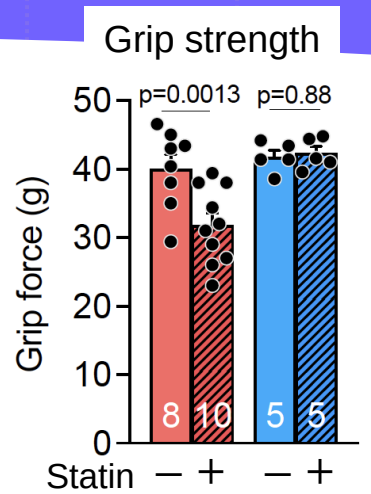


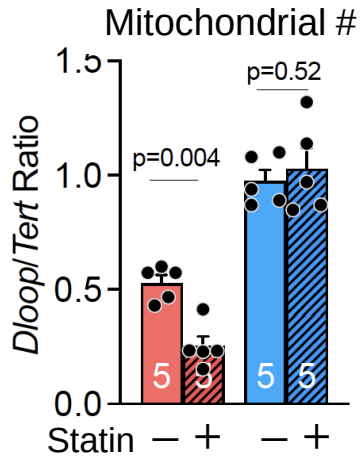
Compiled from data in Lee et al. (2018) and Hopewell et al. (2020)

Statin-induced glucose intolerance in female mice



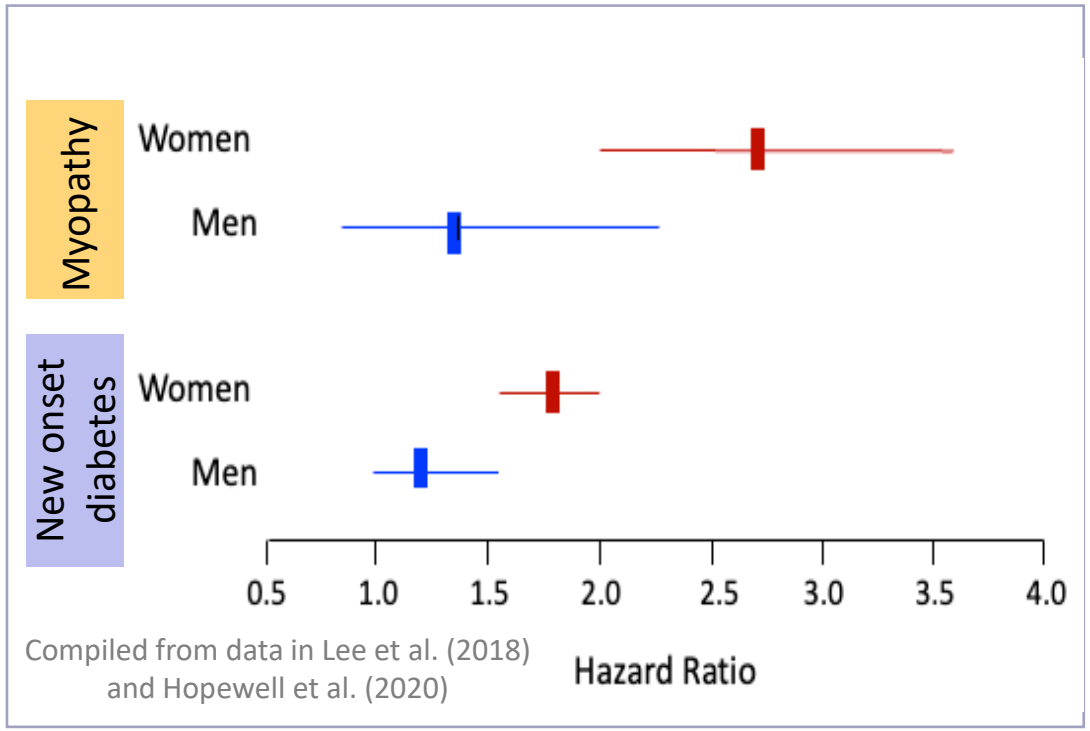
Zhang et al. *Nat Commun,* in press



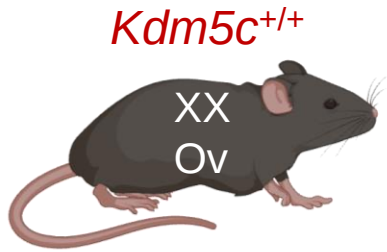


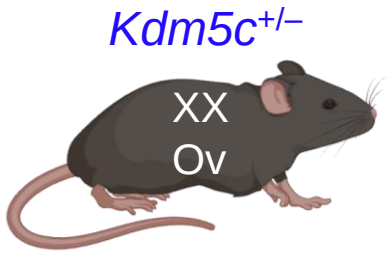
Female XX chromosome and *Kdm5c* gene dosage promotes statin drug adverse effects

Statin adverse risk score: Women > Men

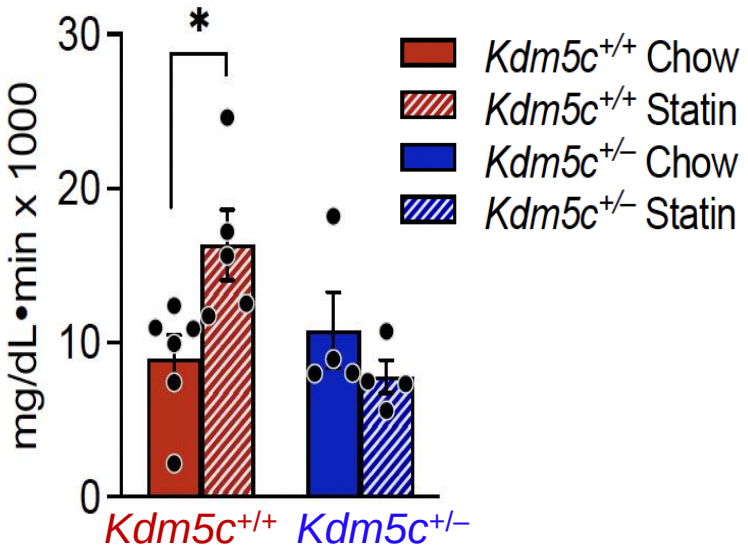


Compiled from data in Lee et al. (2018) and Hopewell et al. (2020)





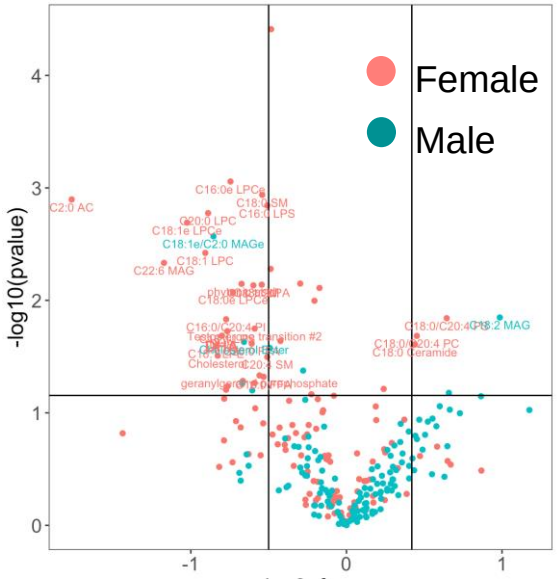
Statin-induced glucose Intolerance



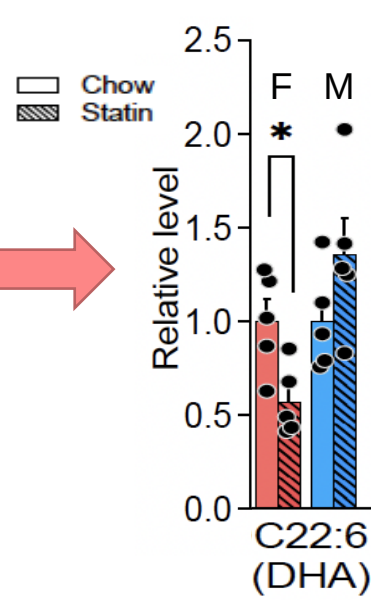
Zhang et al. *Nat Commun,* in press

Female-specific reduction of ω-3 fatty acids by statin drug; fish oil as preventive therapy

Metabolomics

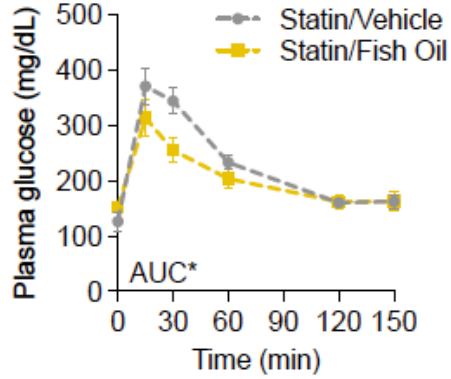


Statin reduces ω-3 FA in females

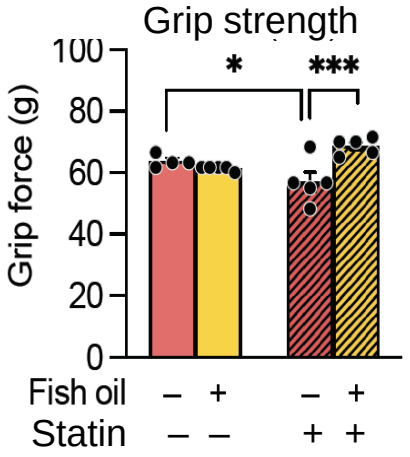


Dietary ω-3 FAs prevent adverse statin effects in female mice

Glucose intolerance

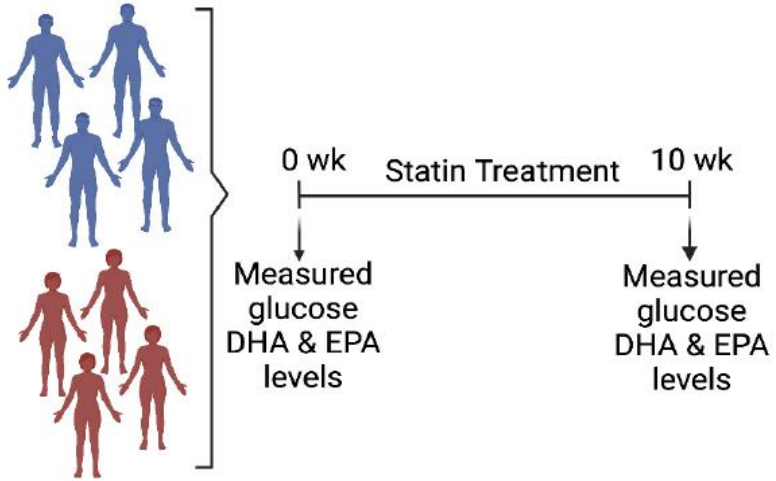


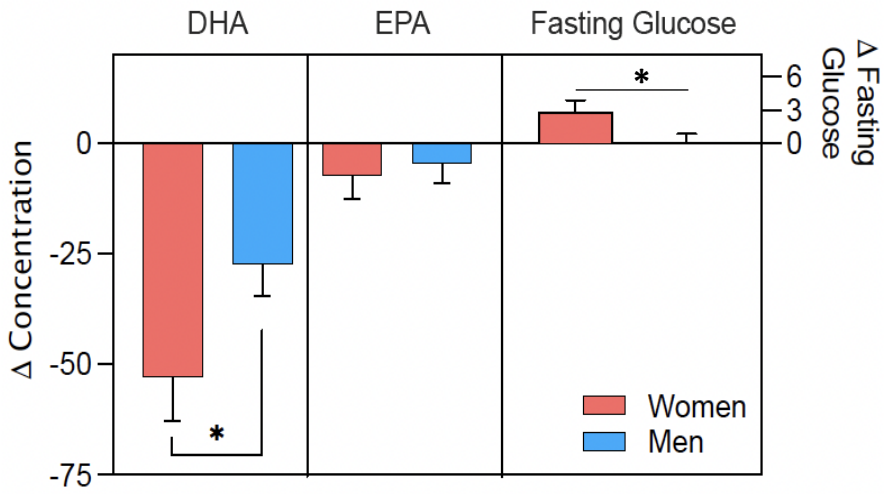
Grip strength

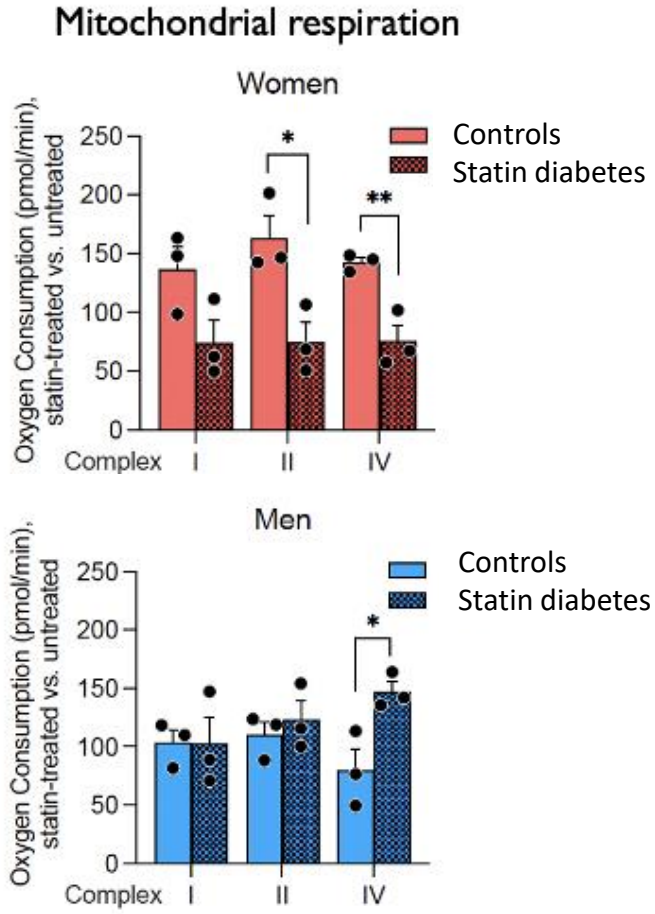


Zhang et al. *Nat Commun,* in press

Statin reduces w-3 fatty acid levels and mitochondrial activity in women more than men

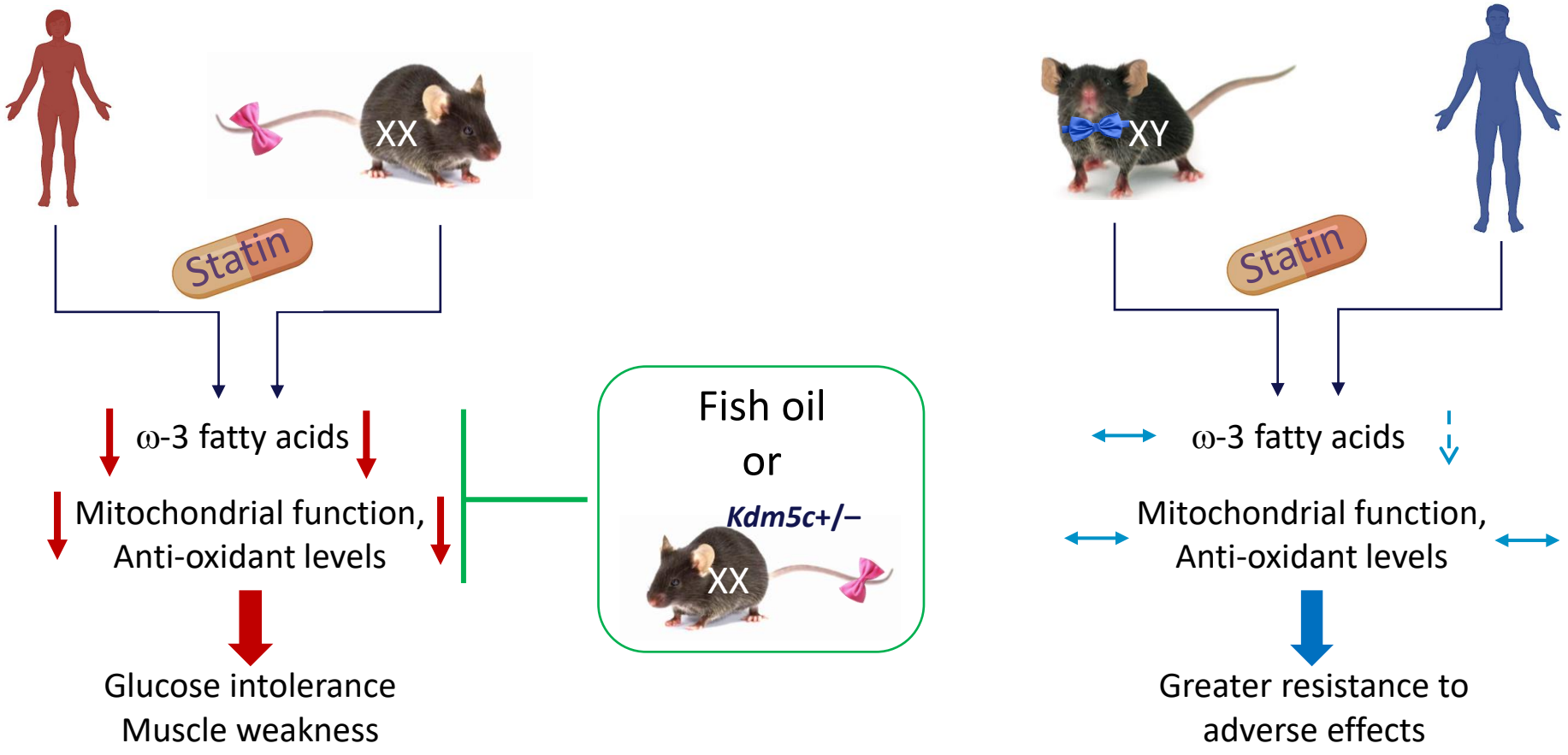






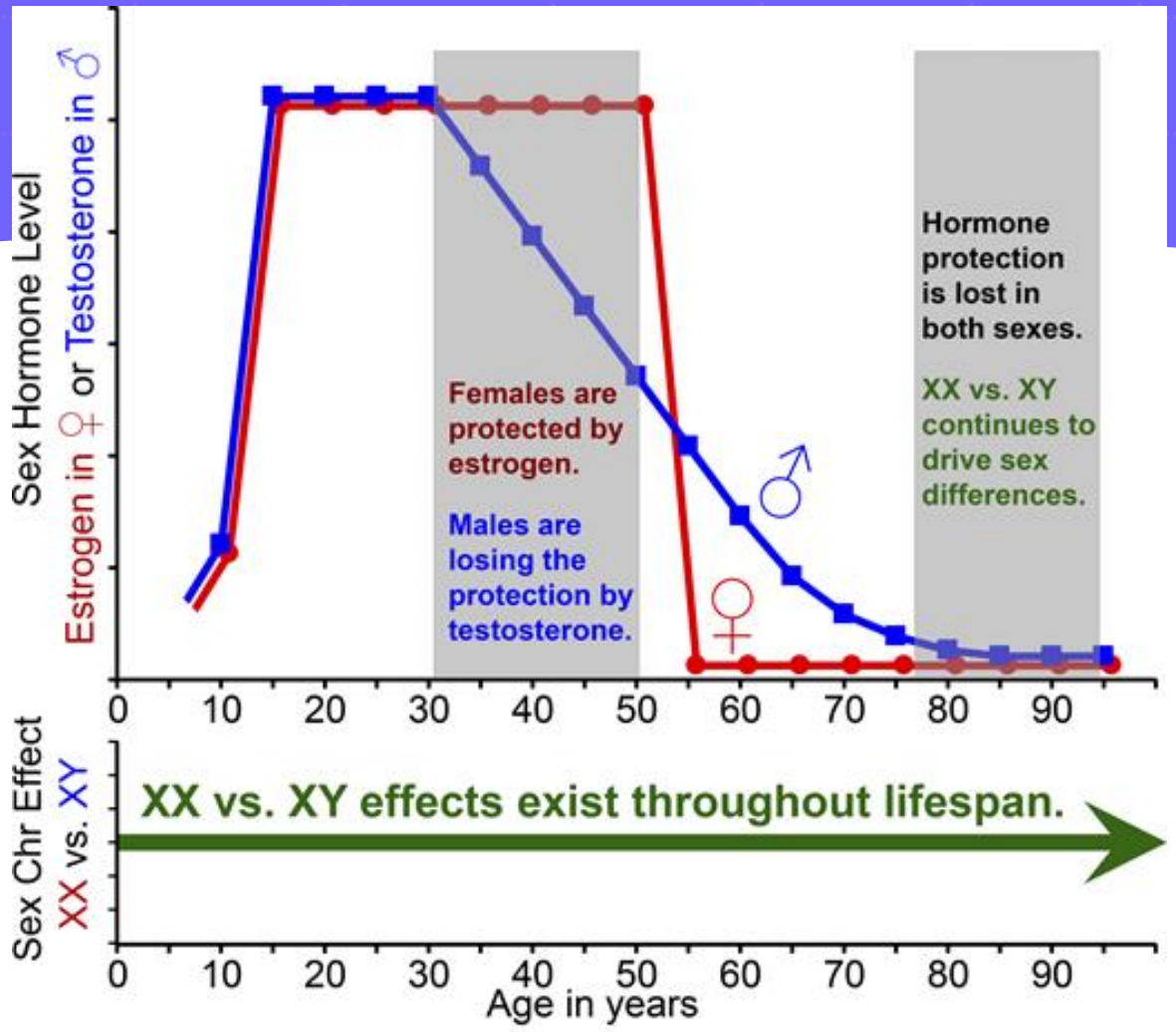
Zhang et al. *Nat Commun,* in press

XX chromosome dosage and sex differences in FA metabolism promote statin adverse effects



Implications

- Sex chromosome complement influences metabolic traits such as obesity, hyperlipidemia, atherosclerosis, and drug adverse effects.
- Partly mediated by X escape genes, which are conserved between humans and mice.
- Sex chromosome effects are likely important throughout the lifespan, even before puberty and after gonadal hormone levels wane with age.



Voskuhl and Itoh (2022) JEM

Impact of sex on cardiometabolic health and disease—knowledge gaps

- Define values for male vs. female cardiometabolic parameters in health and disease states
- Determine changes in cardiometabolic parameters throughout the lifespan (including effects of puberty, pregnancy, menopause)
- Identify mechanisms underlying sex differences in risk factors (obesity, hyperlipidemia, insulin resistance) and in disease prevalence, pathology, and progression (experimental models)
- Identify molecular differences between sexes in metabolic tissues at the level of chromatin organization, DNA methylation, and gene expression using state-of-the-art techniques (single cell-omics, multi-omics, spatial-omics in experimental models, human tissues)
- Assess effects on cardiometabolic traits of sex intersection with genetic background, environment, and gender
- Characterize drug action and adverse effects in both sexes and disaggregate data by sex. Use experimental models to identify mechanisms. Particular need for studies of widely used and newer drugs aimed at reducing cardiometabolic disease risk (statins, GLP-1 receptor agonists, SGLT-2 inhibitors, etc.).

Acknowledgements

Reue Lab

Laurent Vergnes

Carrie Wiese

Rozeta Avetisyan

Joe Munier

Zoey Agle

Jenny Link

Huan Wang

Emilio Ronquillo

Katherine Benitez

Peixiang Zhang

Collaborators

Art Arnold Lab—UCLA

Marisa Medina Lab—UCSF

Matteo Pellegrini Lab—UCLA

Kerrin Small Lab—London

Susan Fried Lab—Mount Sinai

Support

NIH National Institute of Diabetes and Digestive and Kidney Diseases

NIH National Heart, Lung, and Blood Institute

NIH National Institute of General Medical Sciences

NIH National Institutes of Health
Office of Research on Women's Health

Leducq Foundation