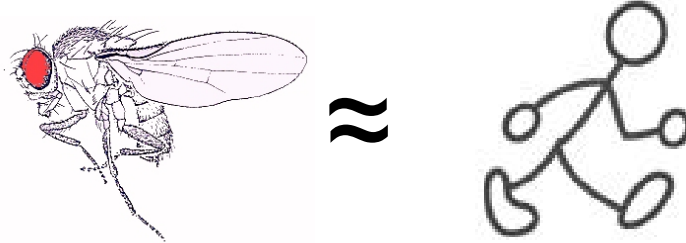


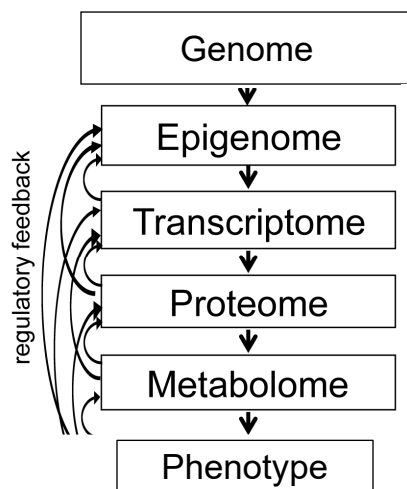
Disentangling the gene-by-environment interaction architecture of metabolic disease through the lens of evolutionary genetics and metabolomics



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1

Mechanisms of Phenotypic Variation



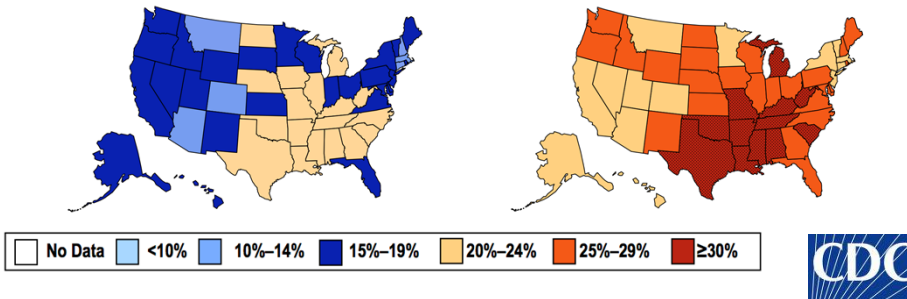
Reed et al, *Current Opinion in Chemical Biology* 2017

2

Obesity and its comorbidities (metabolic syndrome- MetS) have both genetic and environmental influences

Obesity Trends* Among U.S. Adults BRFSS, 1999 - 2010

(*BMI ≥ 30 , or ~ 30 lbs. overweight for 5' 4" person)



2960 Genetic Associations for Obesity in Humans*
Only a tiny proportion of the genetic variation is explained by a specific association.

Source: CDC Behavior Risk Factor Surveillance System

*Retrieved 3/29/2018, NHGRI-EBI GWAS Catalog

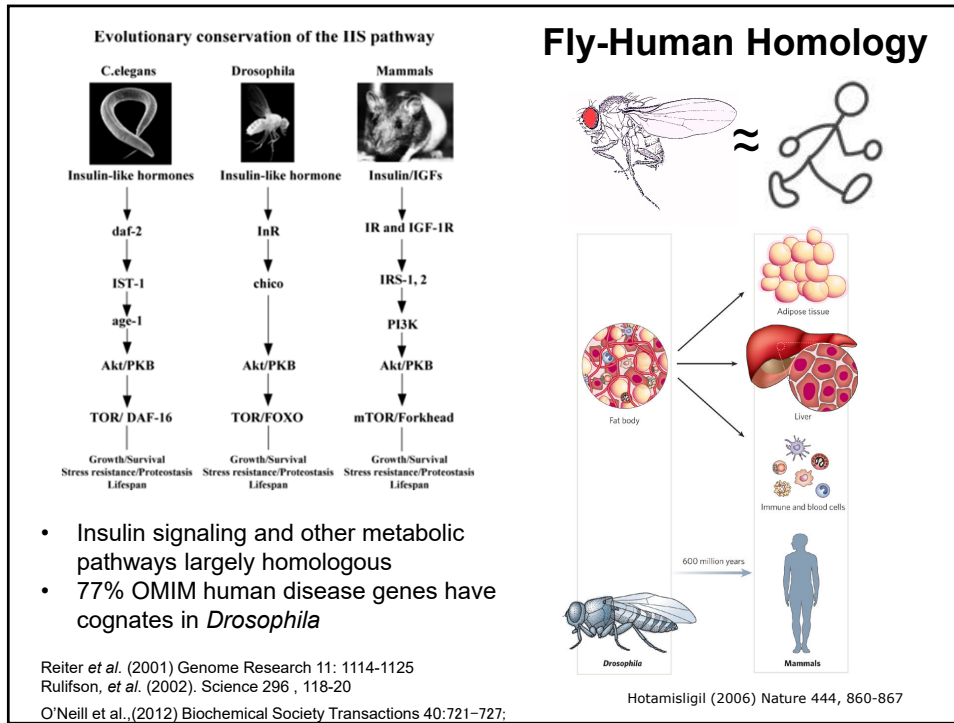
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Outline

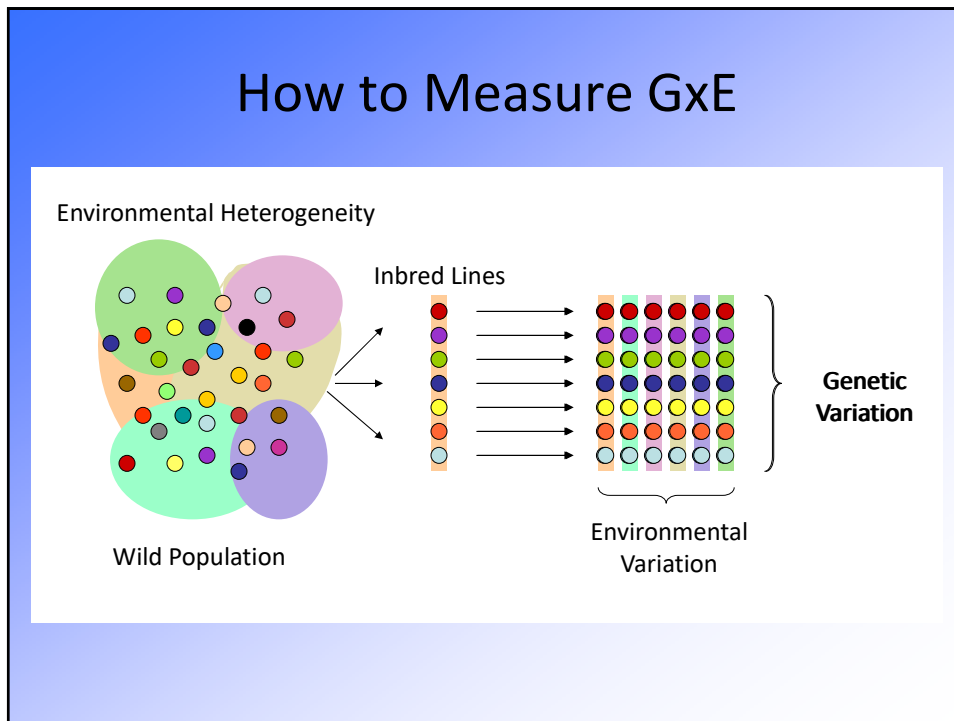
- The Fly as a MetS model
- Unlocking the black box of MetS using systems biology
- Determining genetic basis of Genotype x Diet Interactions
- Other environmental effects on MetS



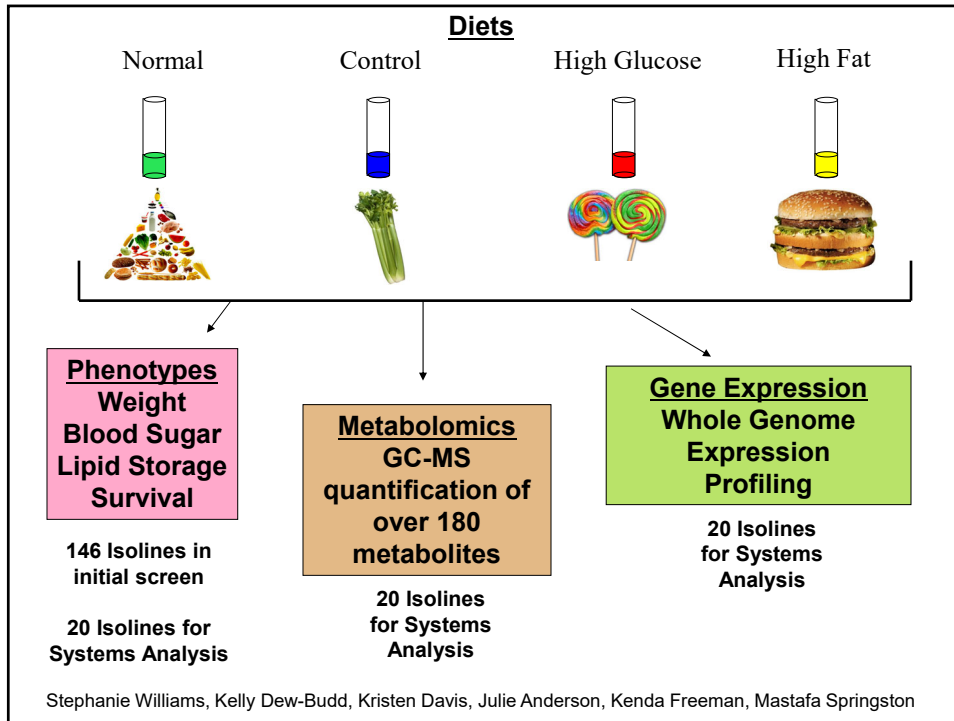
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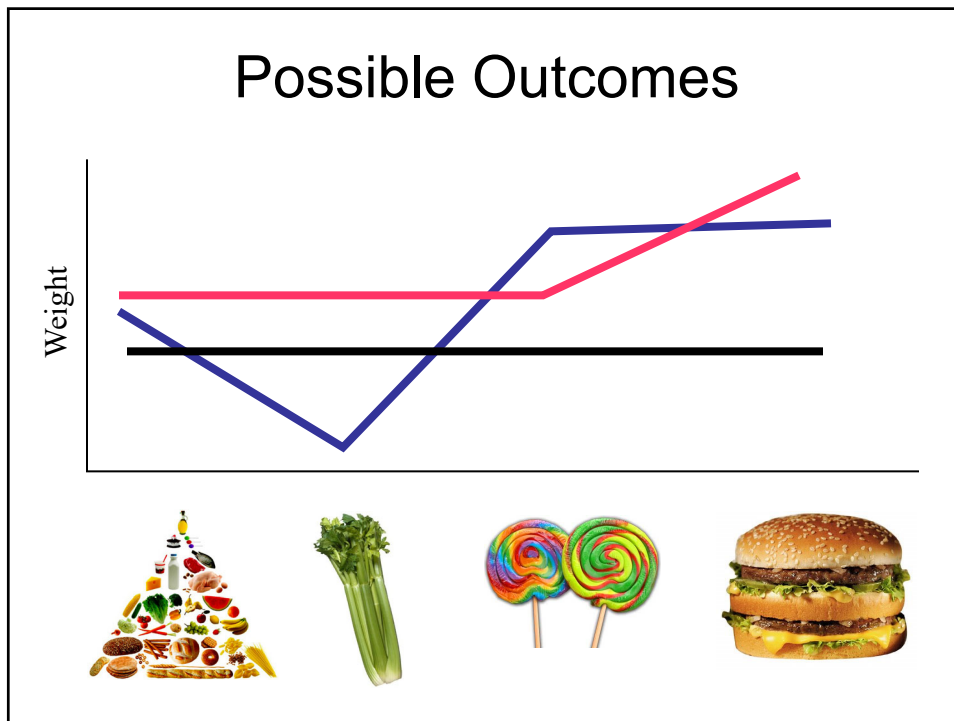
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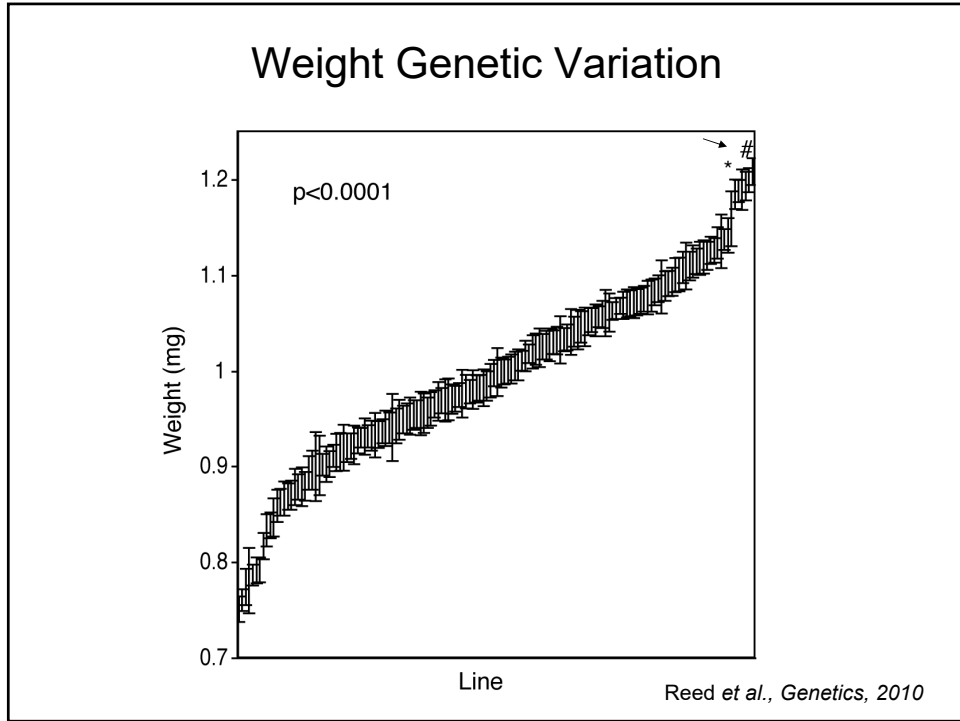
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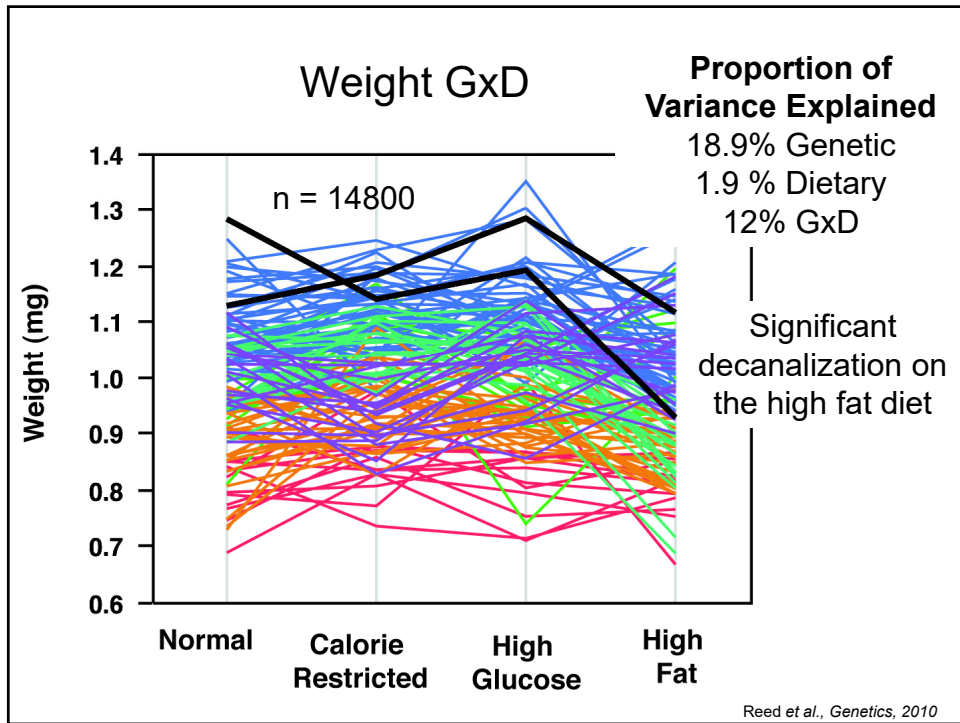
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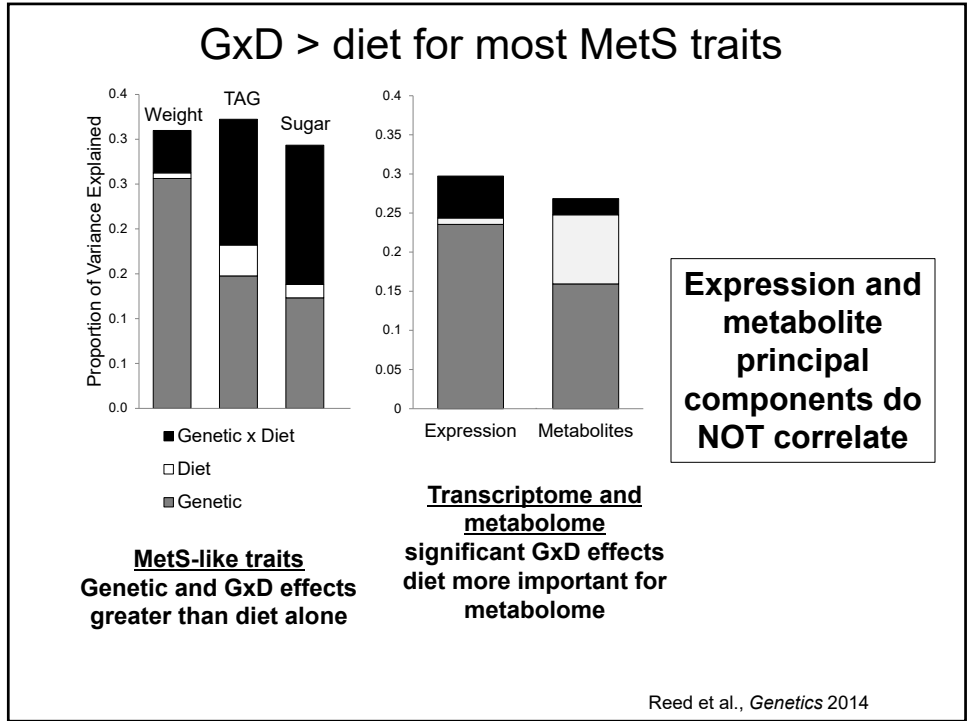
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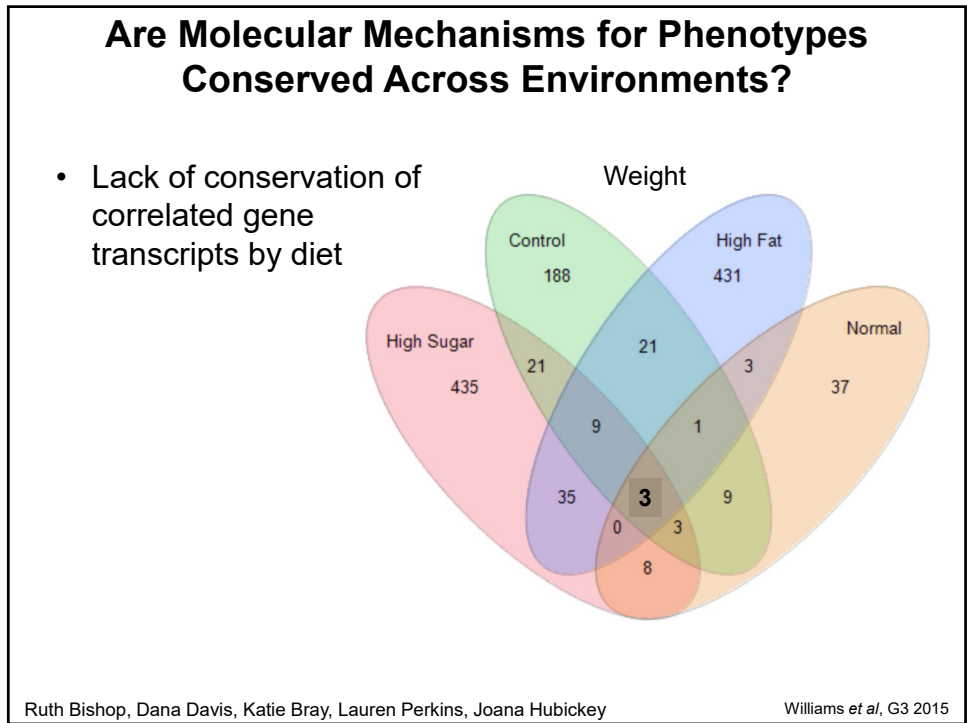
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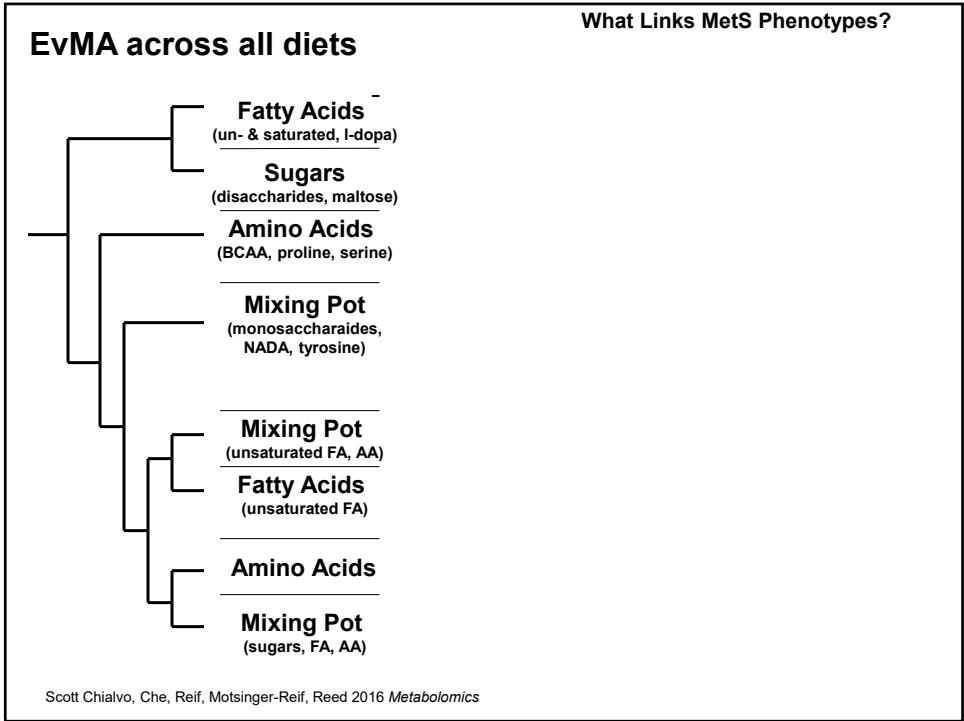
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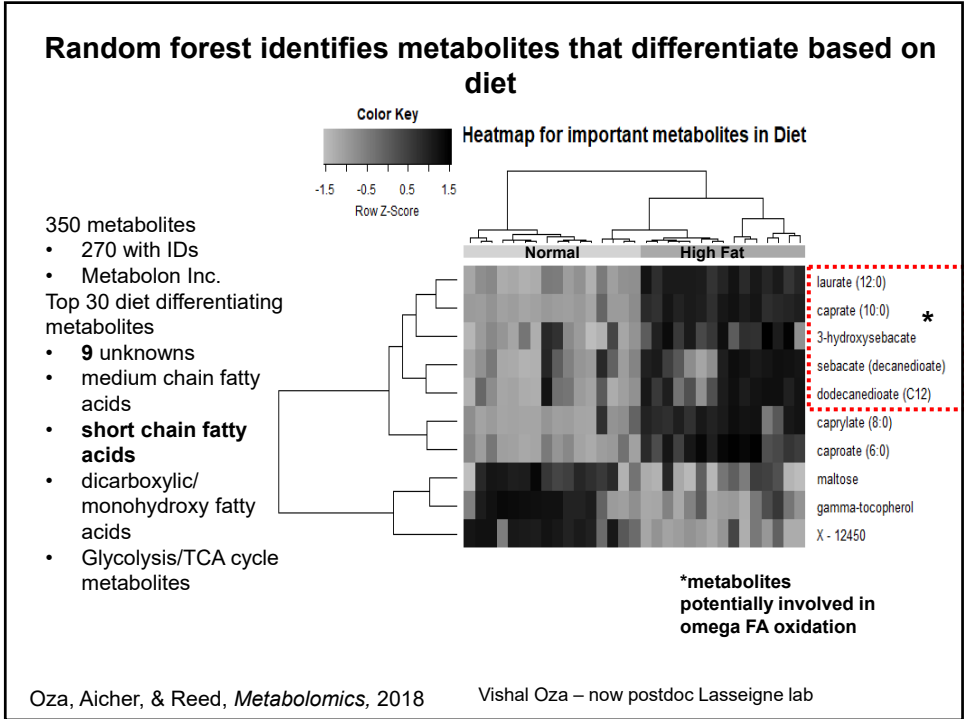
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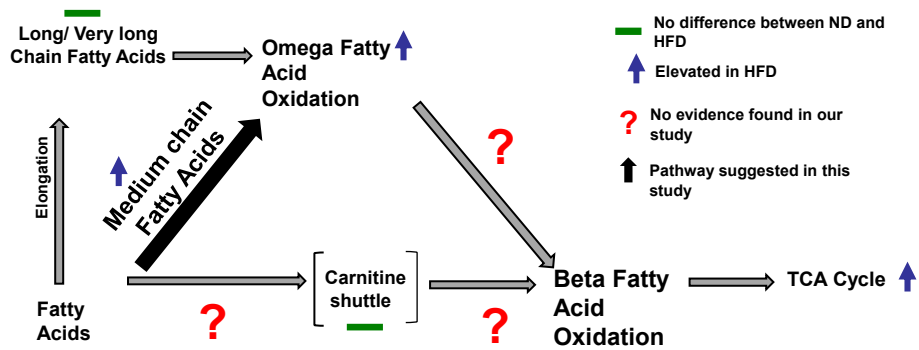


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Hypothesized shift toward Omega fatty acid oxidation on a High Fat Diet

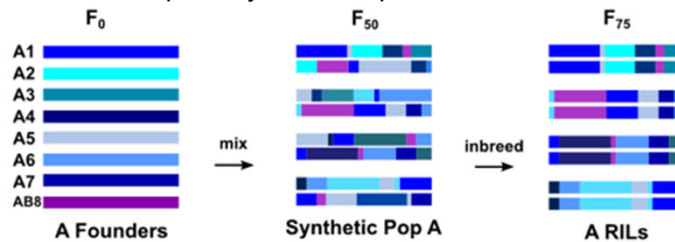


Oza, Aicher, & Reed, *Metabolomics*, 2018

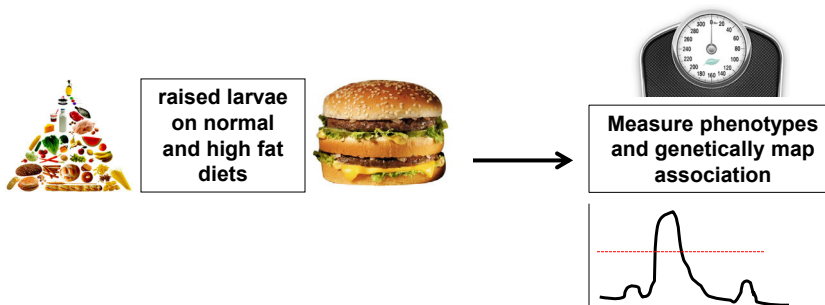
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What loci control genotype-by-diet interactions?

Drosophila Synthetic Population Resource



King, McDonald, Long, 2012

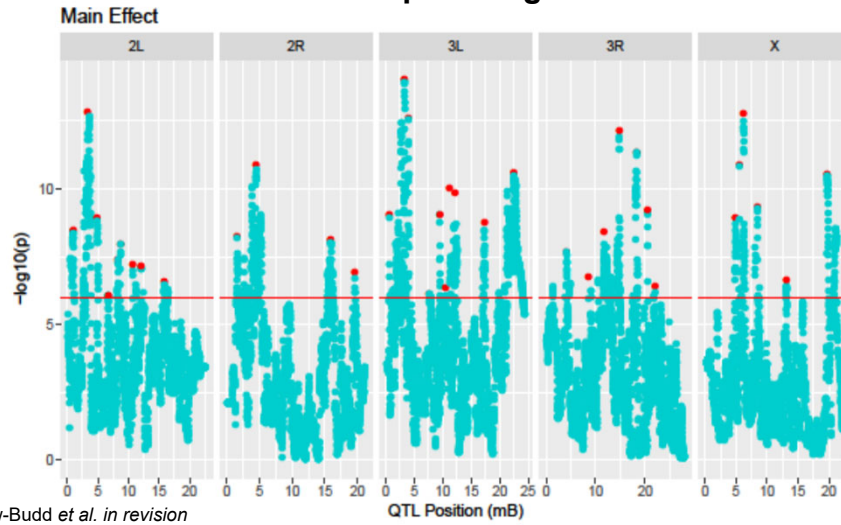


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What loci control genotype-by-diet interactions?

Main Genetic Effect QTLs

Male Pupae Weight



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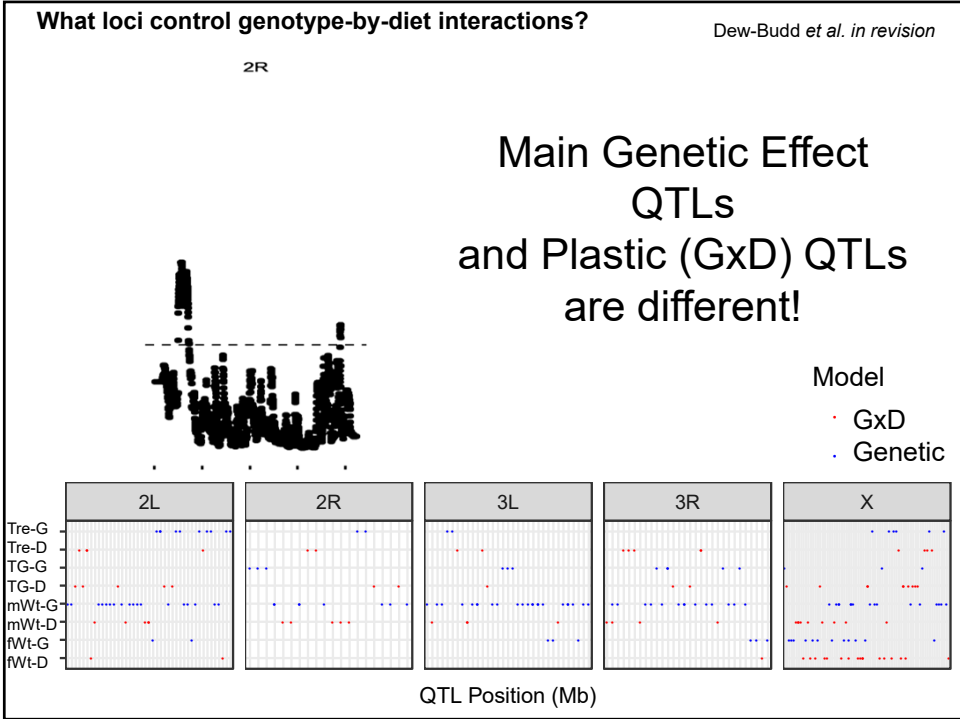
What loci control genotype-by-diet interactions?

Genotype-by-Diet Interacting QTLs (Plastic QTLs)

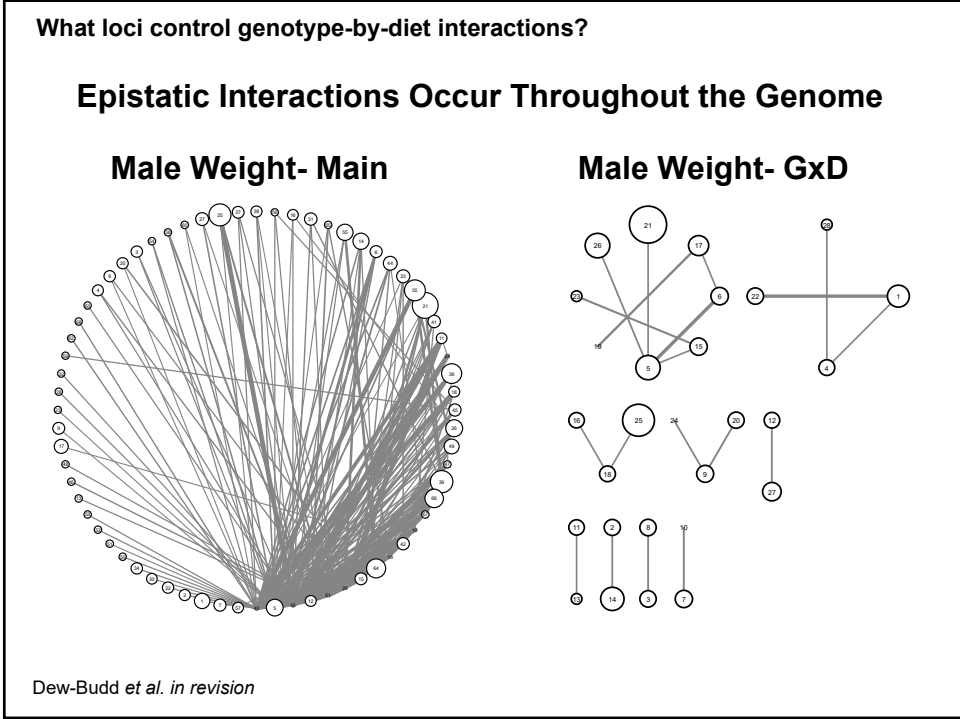
Male Pupae Weight



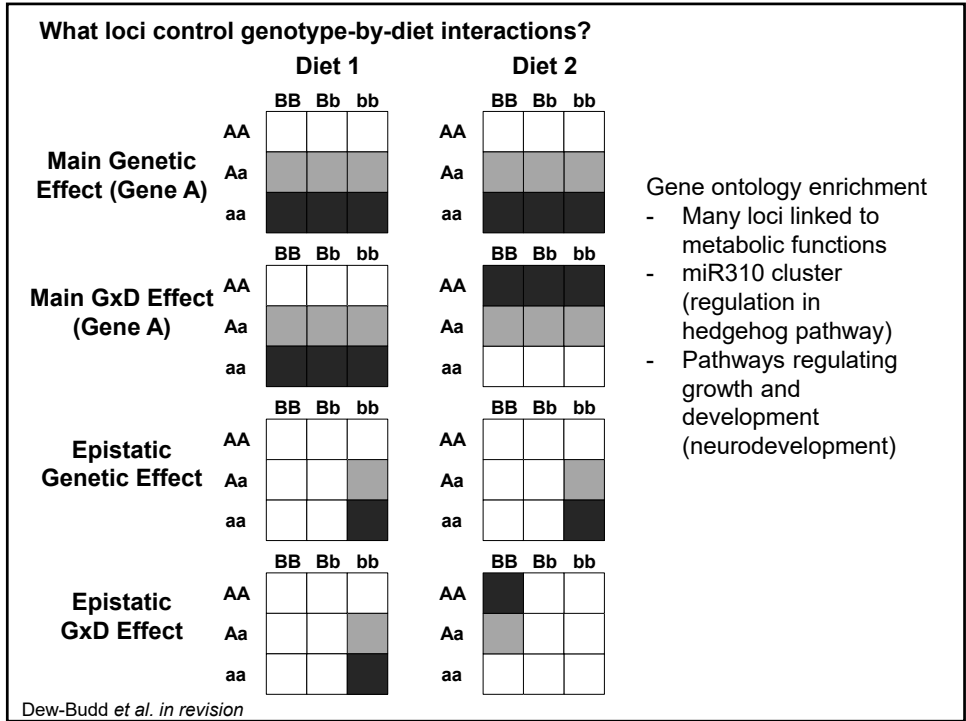
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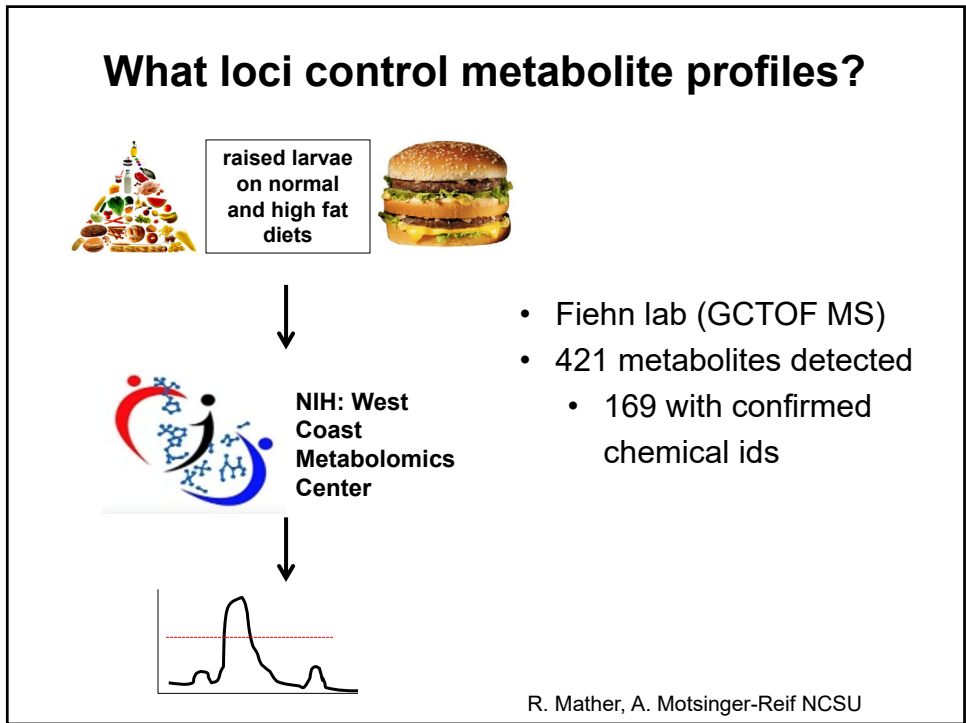
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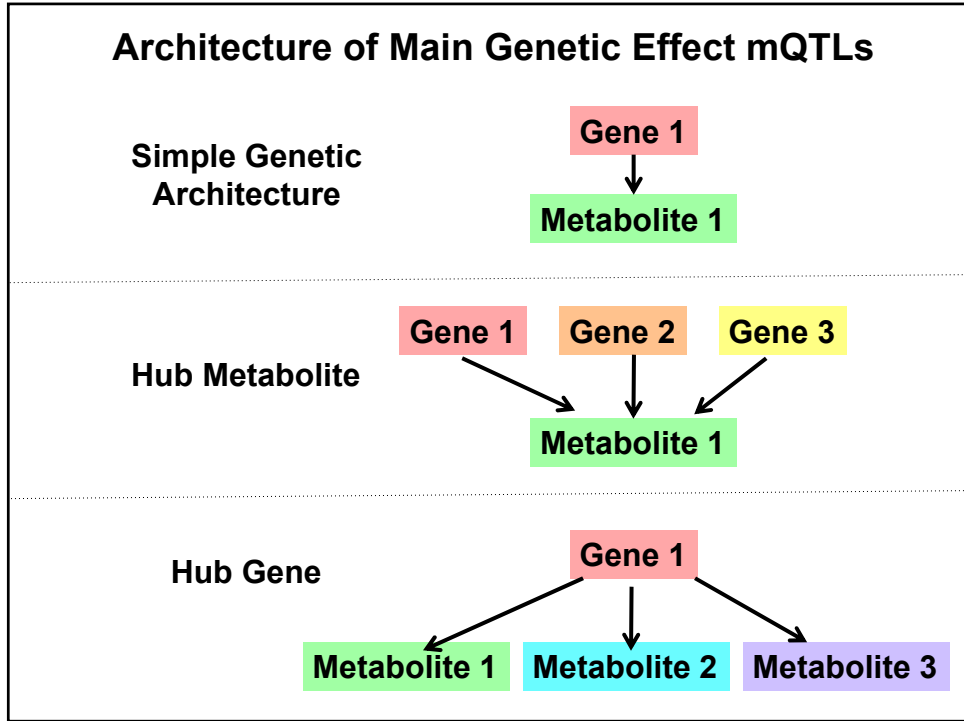
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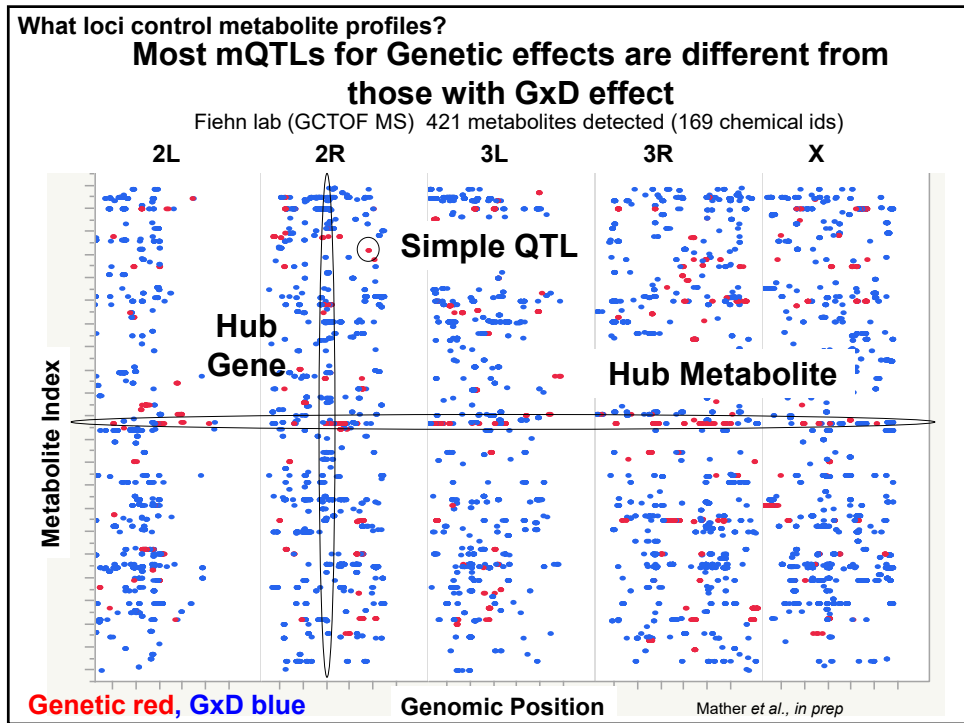
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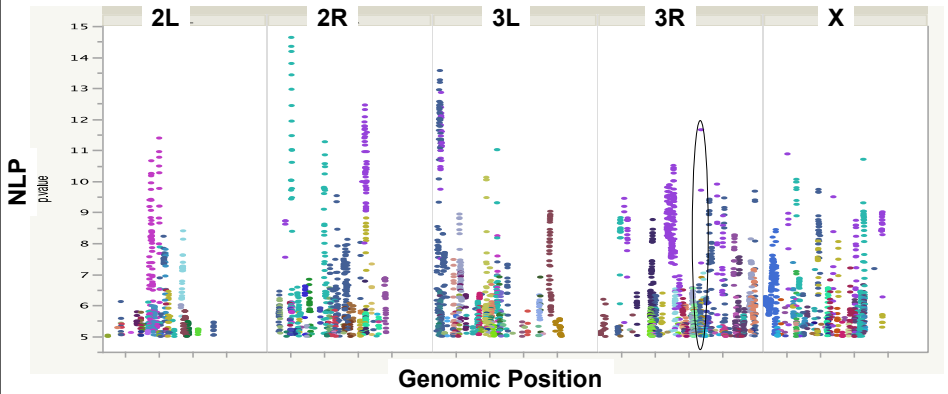


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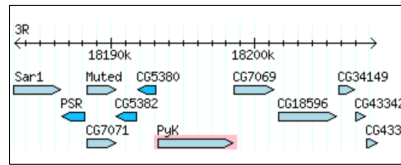


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Linking Metabolites through mQTLs



- mQTL shared between glycolic acid and citrulline
- pyruvate kinase rate limiting step in glycolysis



pyruvate kinase

glycolate → ▪ ▪ ▪ phosphoenolpyruvate → pyruvate ▪ ▪ ▪ → citrulline

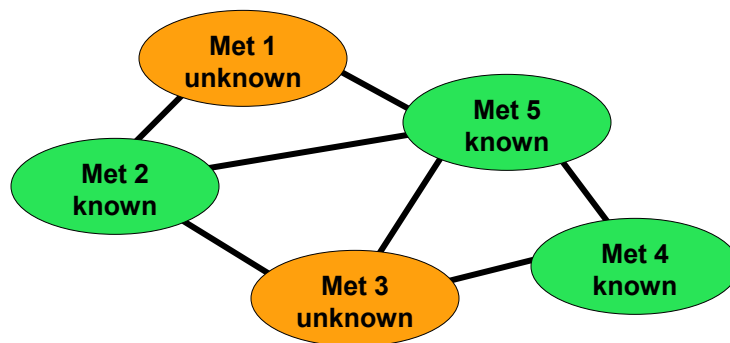
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Gaussian Graphical Model

Correlation Structure

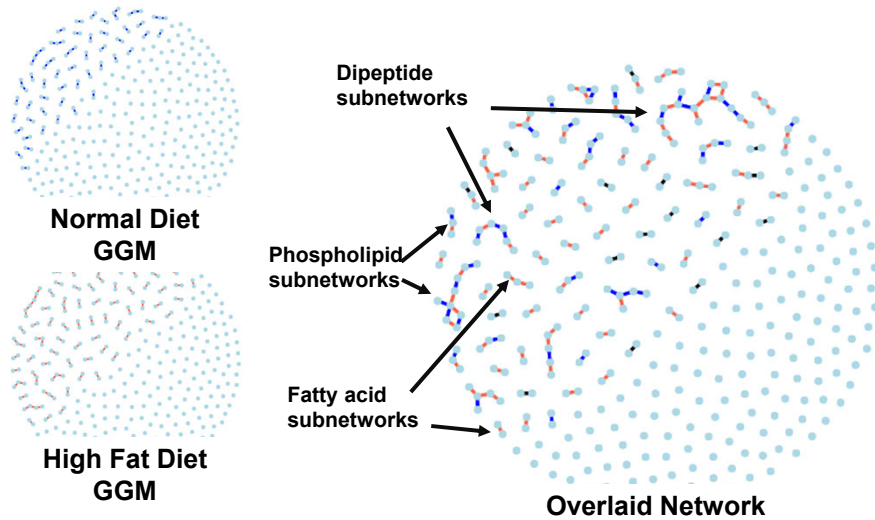


Conditional Dependence



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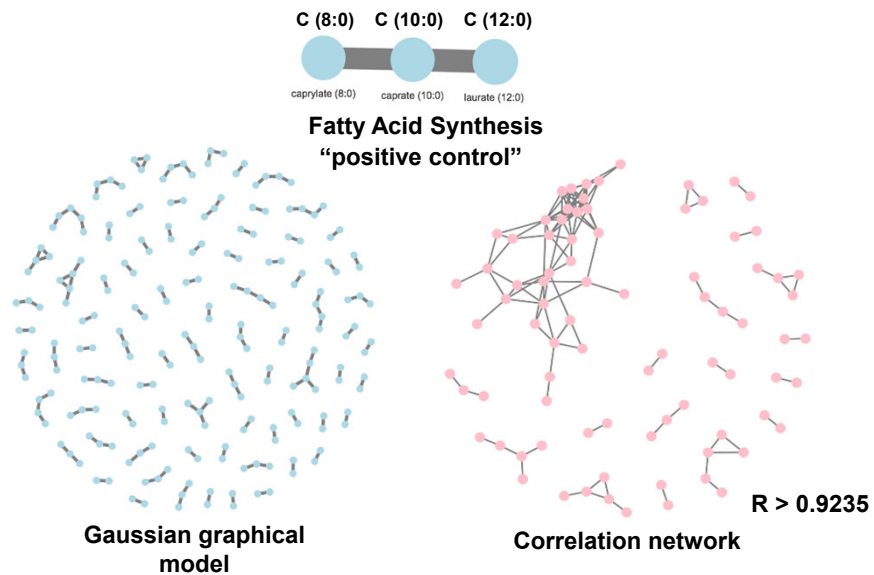
Gaussian graphical models by diet reveals distinct portions of sub-networks



Oza, Aicher, & Reed, *Metabolomics*, 2018

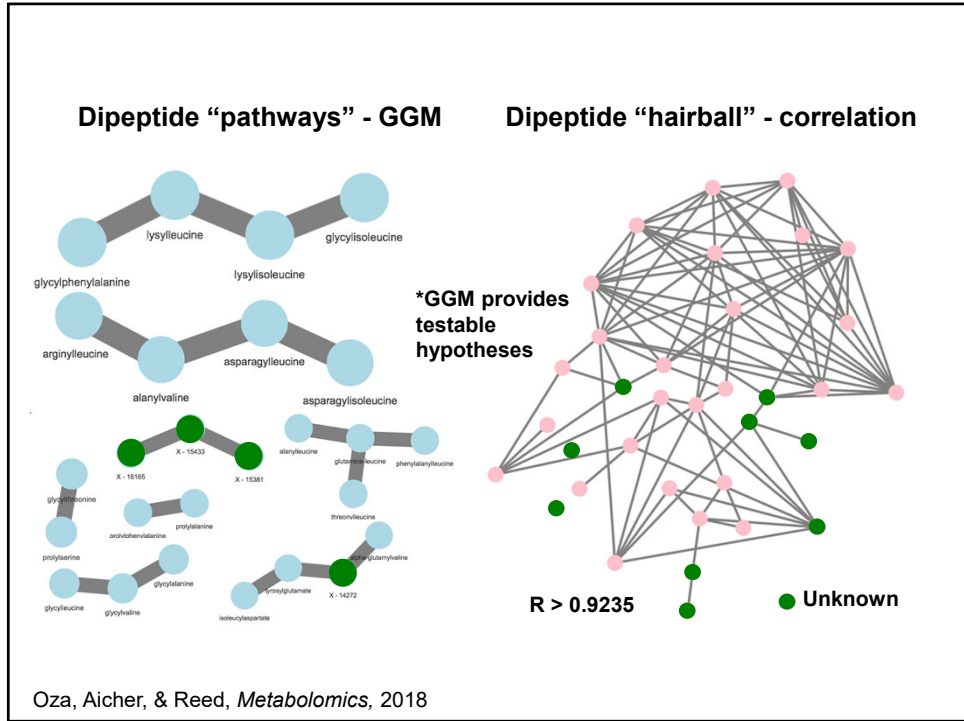
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Edges in the GGM are between biologically (and chemically) similar metabolites, but correlation network misses known biological relationships



Oza, Aicher, & Reed, *Metabolomics*, 2018

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Exercise TreadWheel

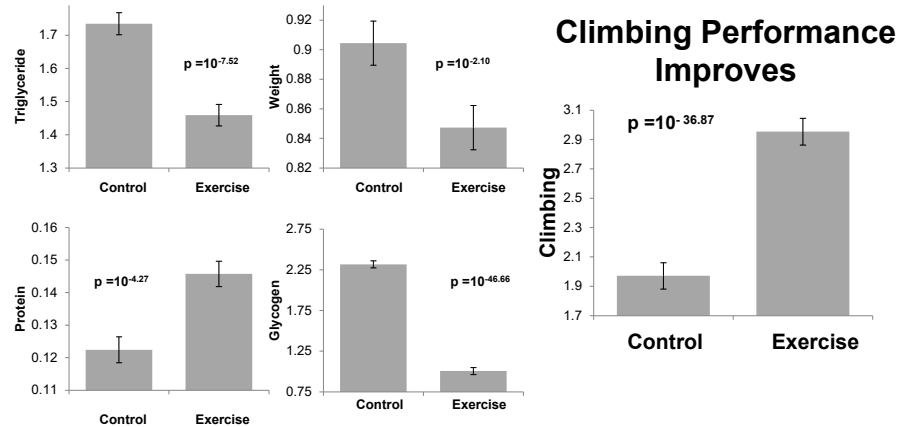
Uses negative geotaxis to exercise adult flies

Treatment Control

Mendez et al. 2016 *PlosOne* Sean Mendez Rachel Hill

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Exercise Works in Flies



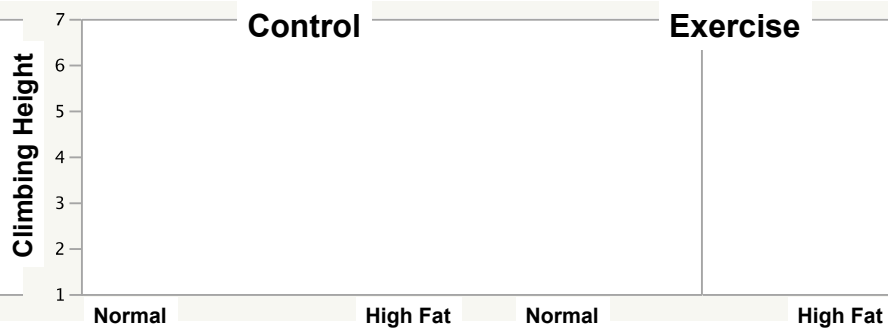
Mendez *et al.* 2016 *PlosOne*

Nicole Riddle, Louis Watanabe, Maria DeLuca UAB

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Exercise Works in Flies (for some better than others)

- Exercise interacts with genetic line and sex
- Mitochondrial function genes show exercise and genotype-by-exercise interactions
- Adult exercise interacts with larval diet and genotype



Lowman *et al.*, *in prep*

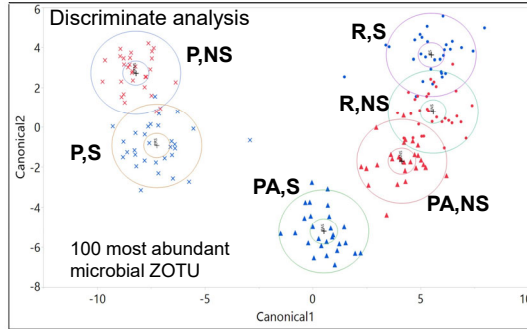
Mendez *et al.* 2016 *PlosOne*

Genotype x Diet x Exercise $p=5.7e-17$

Nicole Riddle, Louis Watanabe, Maria DeLuca UAB

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Larval bacterial communities from natural conditions are interact with genetic and dietary effects



1. Maternal microbes shape bacterial community
2. Community on natural peach diets differ from lab and autoclaved diets
3. Genotype-by-diet interactions on bacterial communities
4. Correlations between dominant taxa and metabolic traits (consistent with the literature)

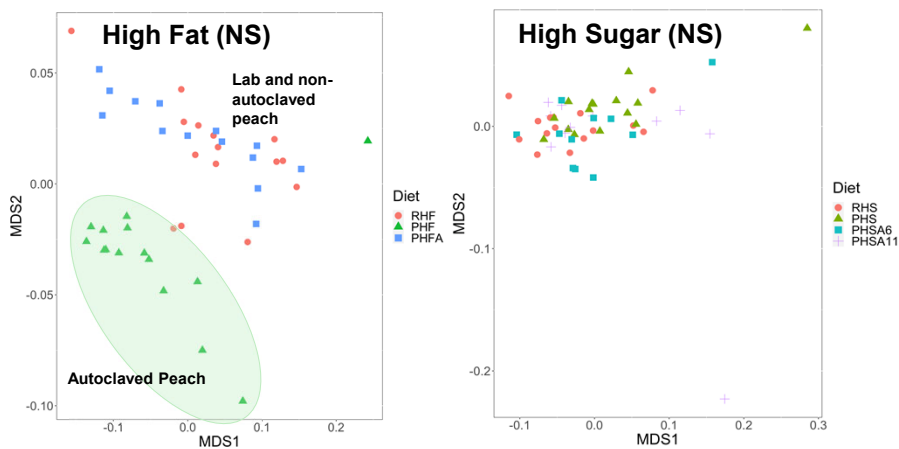


www.motherjones.com

Bombin *et al*, 2020, *Microorganisms* 8(12), 1972

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Bacterial communities more strongly influenced by environmental bacteria on a high fat diet



The bacterial species correlated with metabolic phenotype vary with diet and maternal microbes

Bombin *et al*, *in prep*

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The Take Home Messages

- Flies are great models!
- Genotype-by-diet interactions are a substantial contributor to MetS variation
- Metabolite profiles have predictive power for MetS phenotypes
- Quantitative data can be used to categorize unknown compounds and hypothesize new pathways
- Loci for genetic and genotype-by-diet interactions are different
- Additional environmental factors can be modeled in *Drosophila*



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Flies, More Flies, and Statistics....

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Cheyenne Paiva
Andrea Davidson
Steph Williams
Julie Brown
Ruth Bishop
Levi Miller
Olivia Sorrell
Alison Adams
Ashley Gilchrist
Julie Jarnigan
Cigdem Tunckanat

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Michael Moore
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Treavor Hearing
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Anna Grace Price
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Reed Lab Motto: When it comes to genes, our flies are always open.

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UA Office of Research
UA College of Arts and Sciences

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The Genomics Education Partnership:

A community of practice that enhances research opportunities for students and faculty at diverse institutions

 Washington University in St. Louis

THE UNIVERSITY OF
ALABAMA

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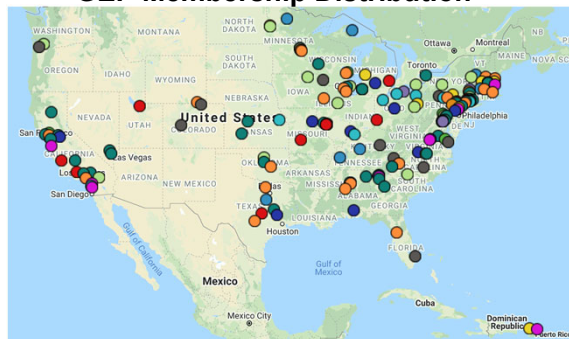
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Course-based Undergraduate Research Experience (CURE)

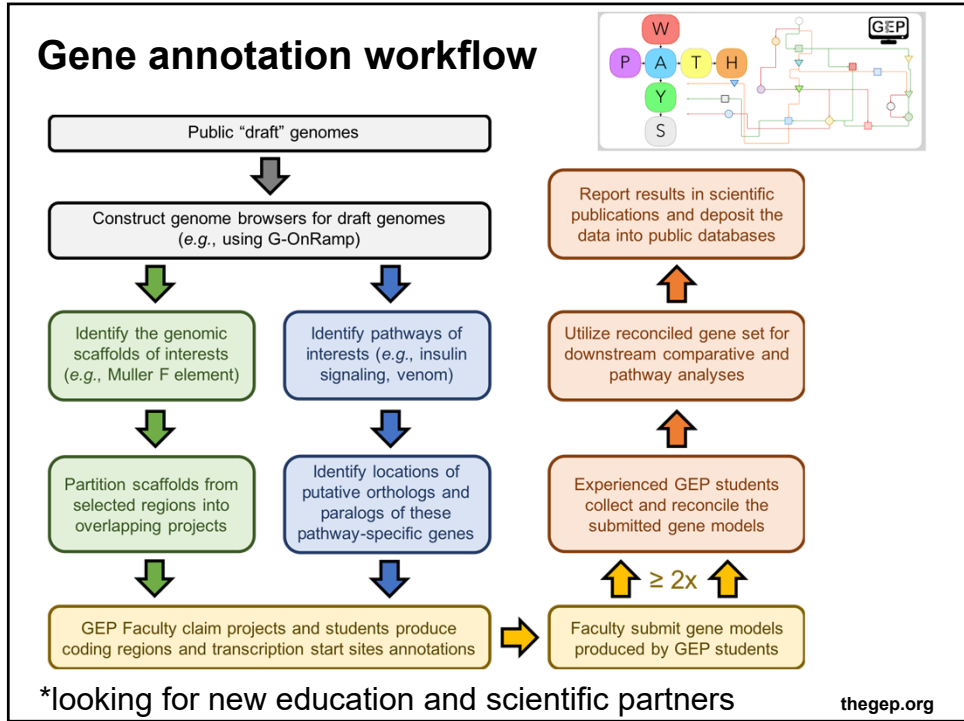
GEP Membership Distribution



- nationwide collaboration of 160+ institutions
- > 2000 students participate annually
- core team provides computational, scientific, and pedagogical support - facilitates implementation
- uses comparative genomics to study the evolution of genes and genomes
- implementation of takes many forms
 - Several-week modules to entire semester
- removes the technical barriers – all GUI and web-based
- students gain confidence in their ability to “do” science

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*Results not typical

PALEO

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