

# Complex metabolic traits are mediated by genes with distal heritability

Greg Carter

Professor ▫ Bernard & Lusia Milch Chair

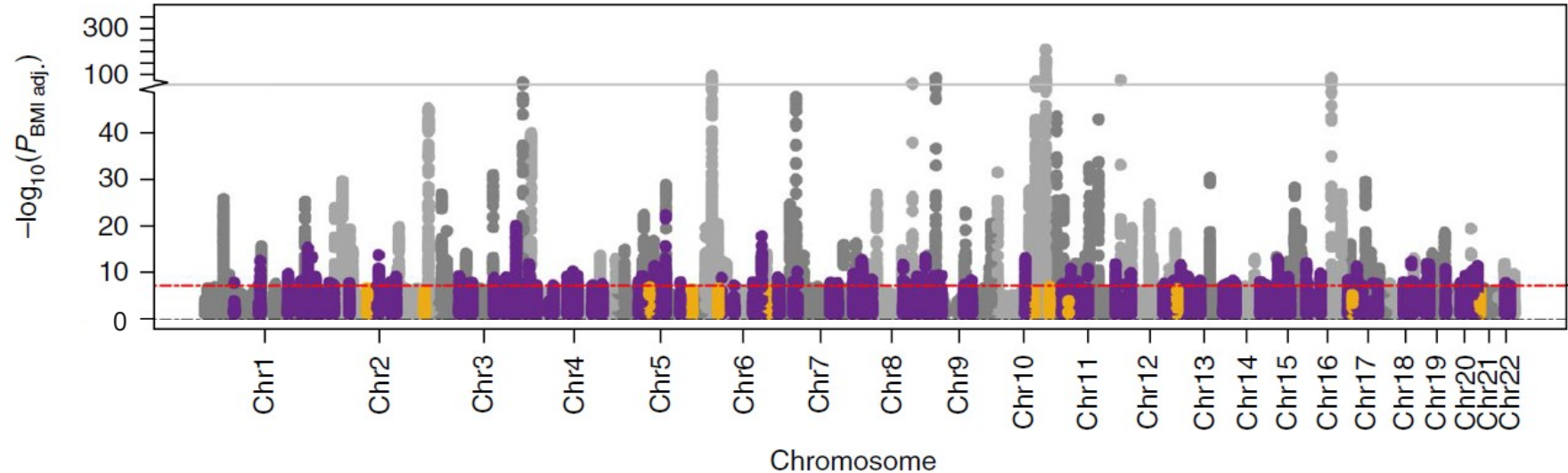
The Jackson Laboratory

Bar Harbor, ME ▫ Farmington, CT

CTC 2024 ▫ Milwaukee, WI



# TYPE 2 DIABETES HAS OVER 250 GWAS ASSOCIATIONS

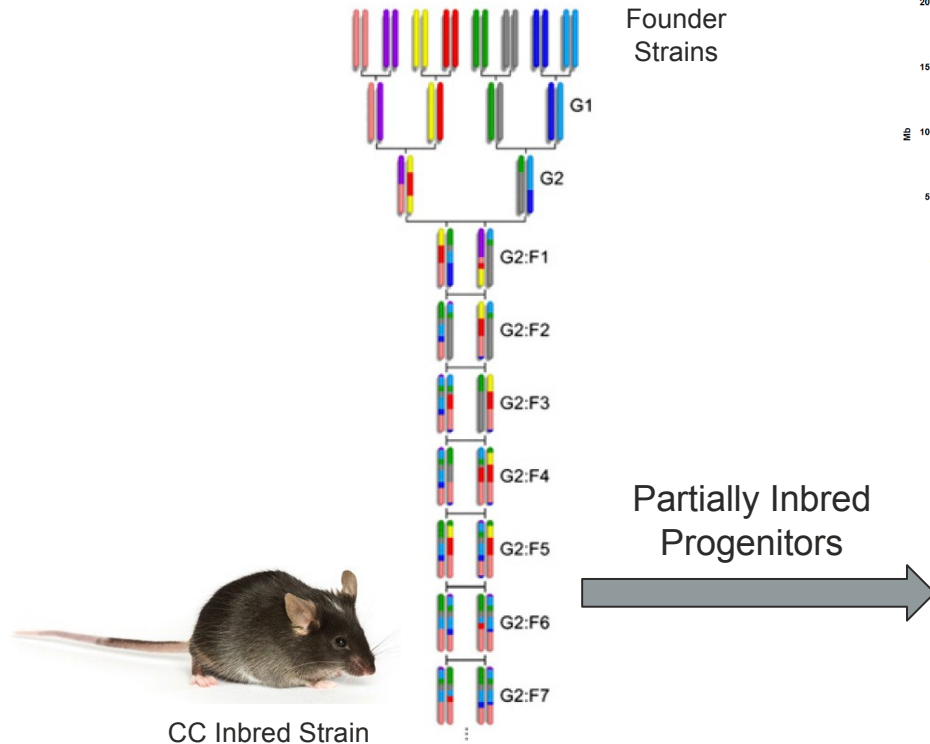


# USING INBRED MICE TO CREATE COMPLEX POPULATIONS

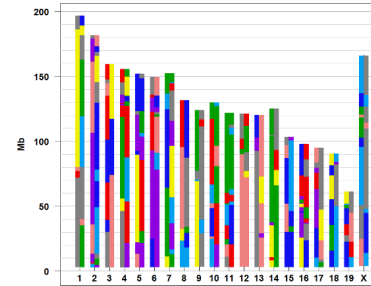


# DIVERSITY OUTBRED

## Collaborative Cross



## Diversity Outbred



Multiparental  
Population  
(DO)

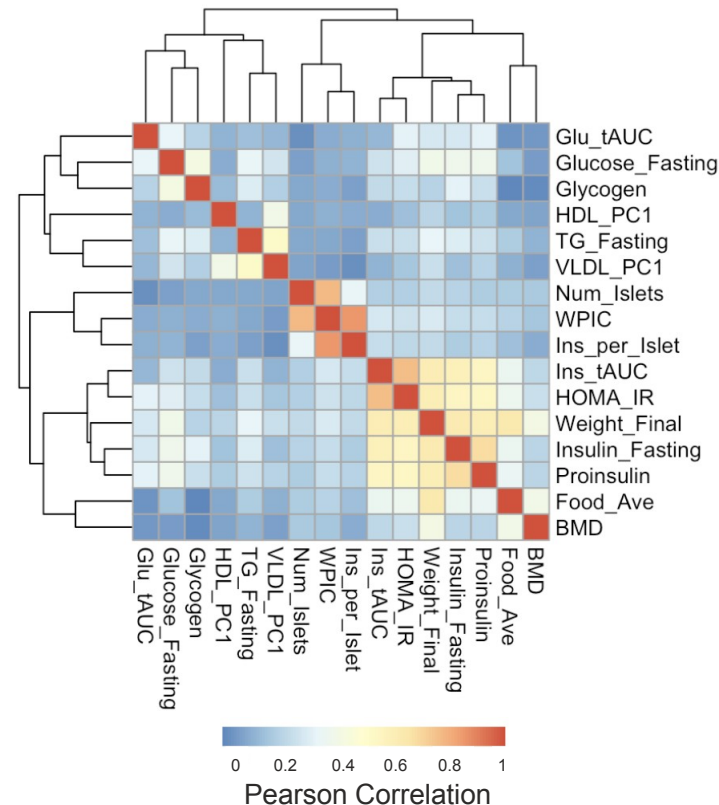
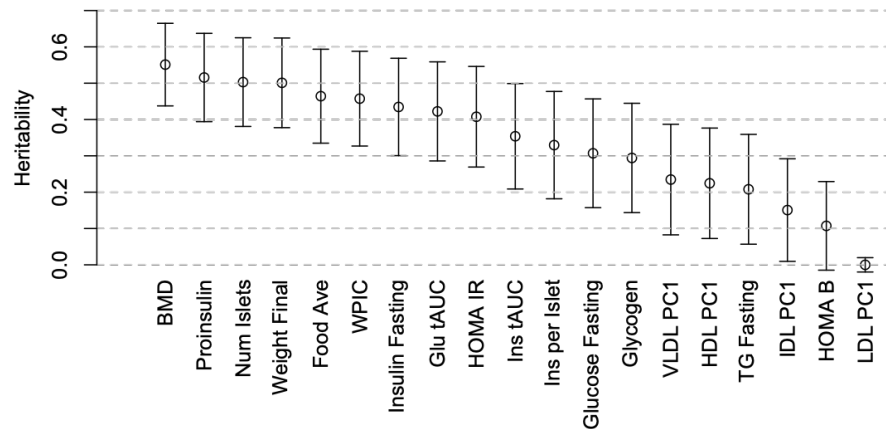


Randomized  
Breeding



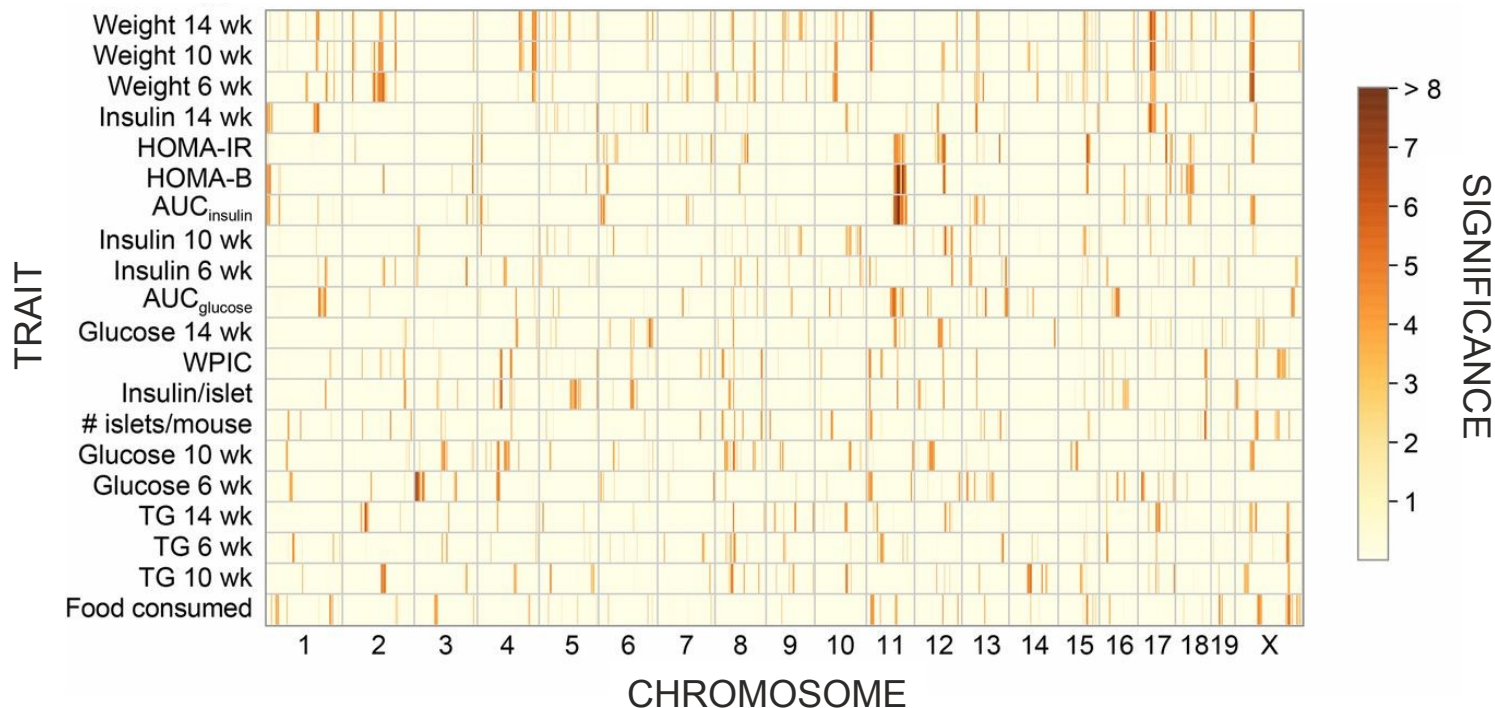
# DIVERSITY OUTBRED MICE AS A GENETIC MODEL

Metabolic health traits are heritable and correlated



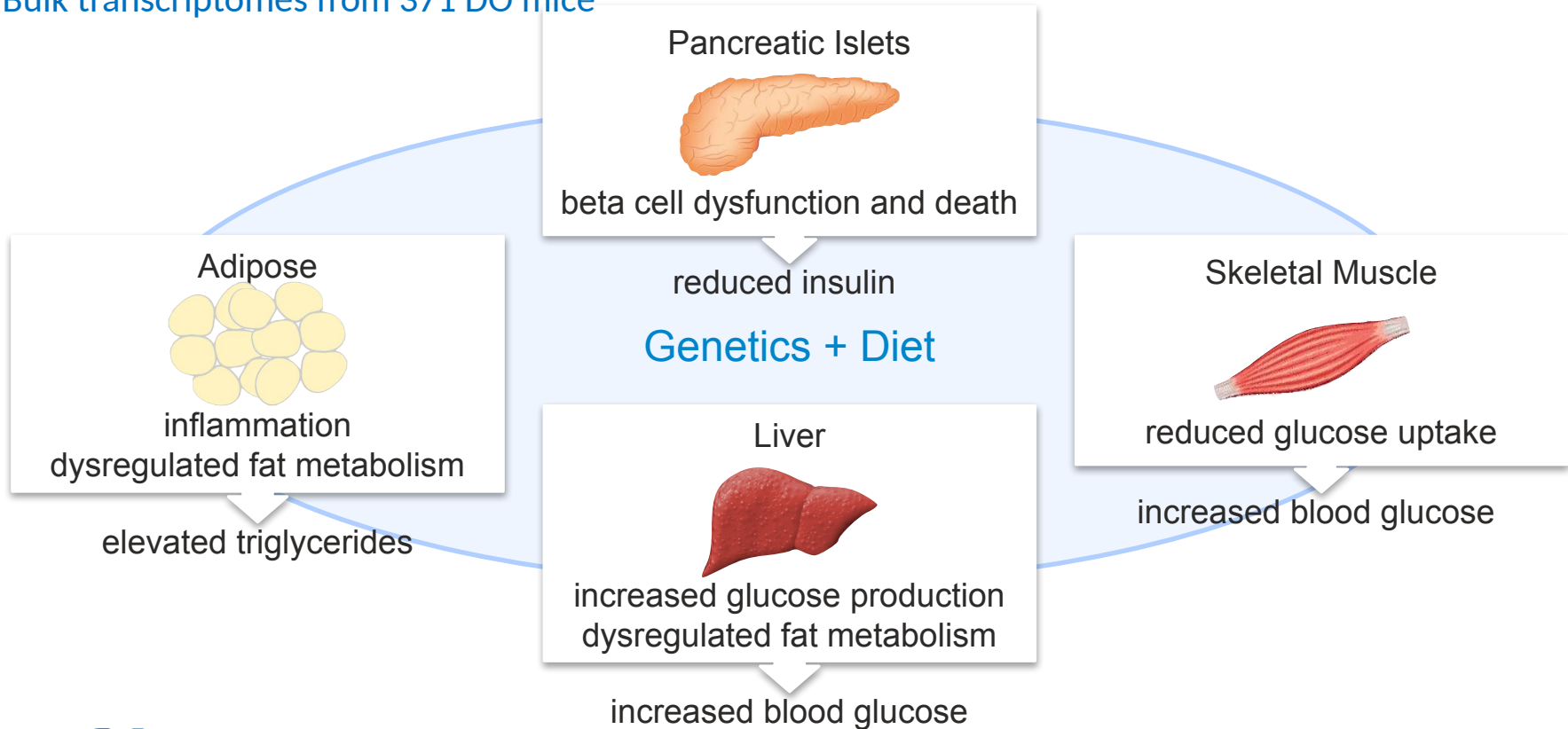
# DIVERSITY OUTBRED MICE AS A GENETIC MODEL

Metabolic health traits mapped in a DO population



# DISSECTING TRAITS VIA ORGAN-SPECIFIC TRANSCRIPTOMES

Bulk transcriptomes from 371 DO mice

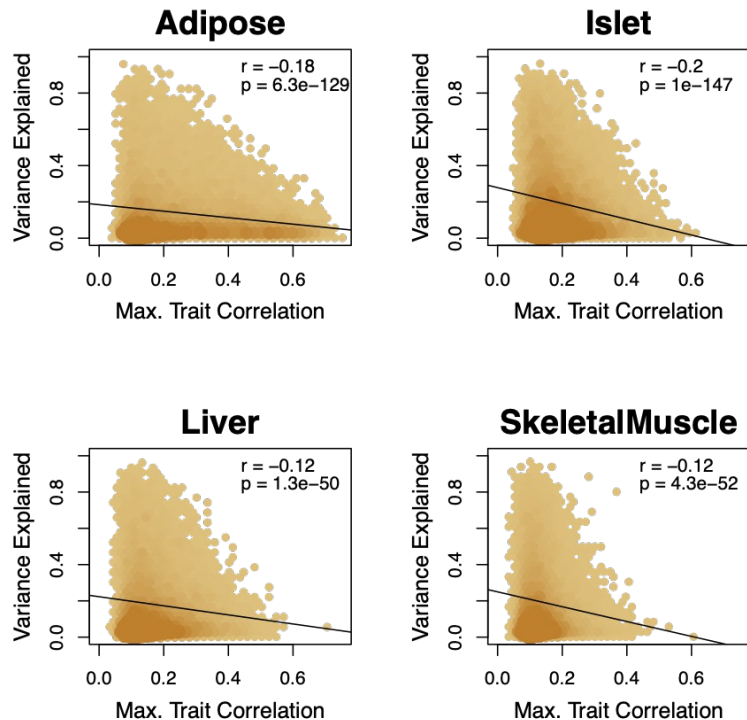




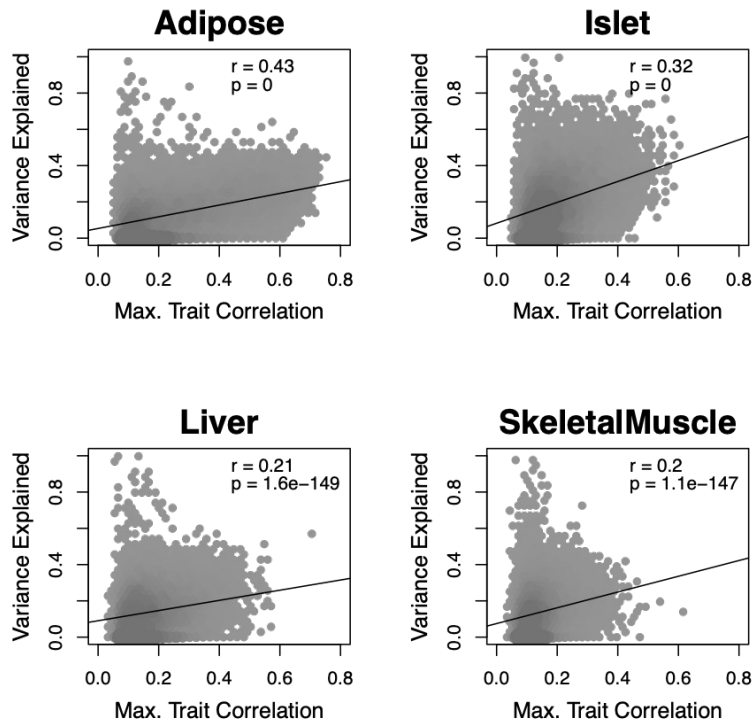
# DISTAL EQTL ARE MORE CORRELATED WITH TRAITS

Strongest local eQTL are not correlated with traits; “expression drift”?

## Local eQTL



## Distal eQTL

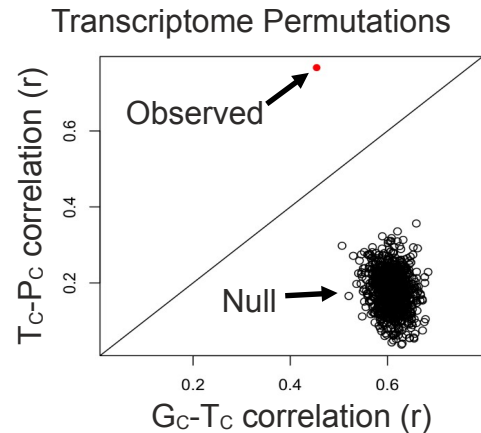
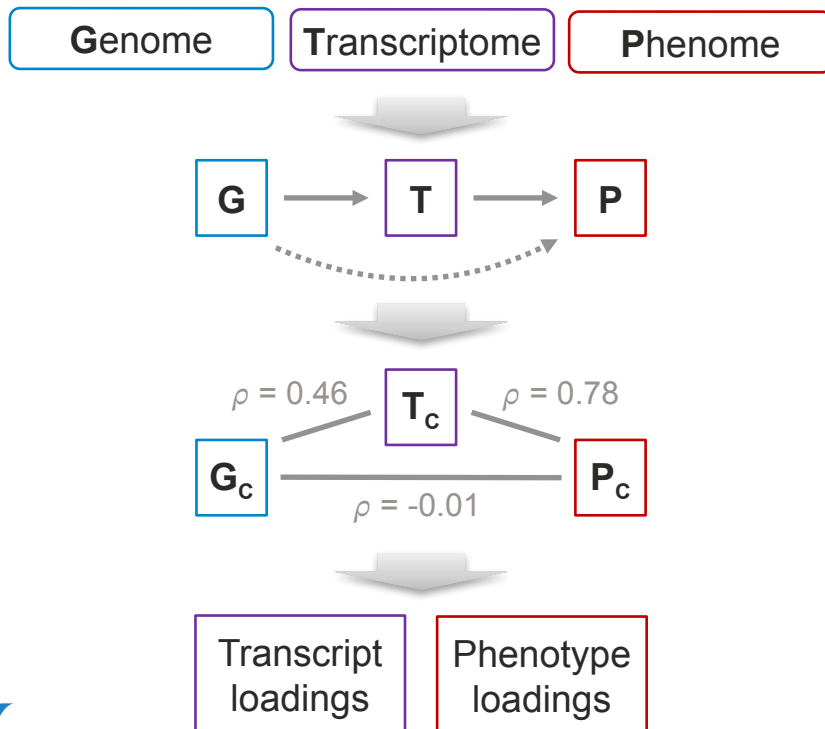




# CONNECTING GENETICS, TRANSCRIPTOMICS, AND TRAITS

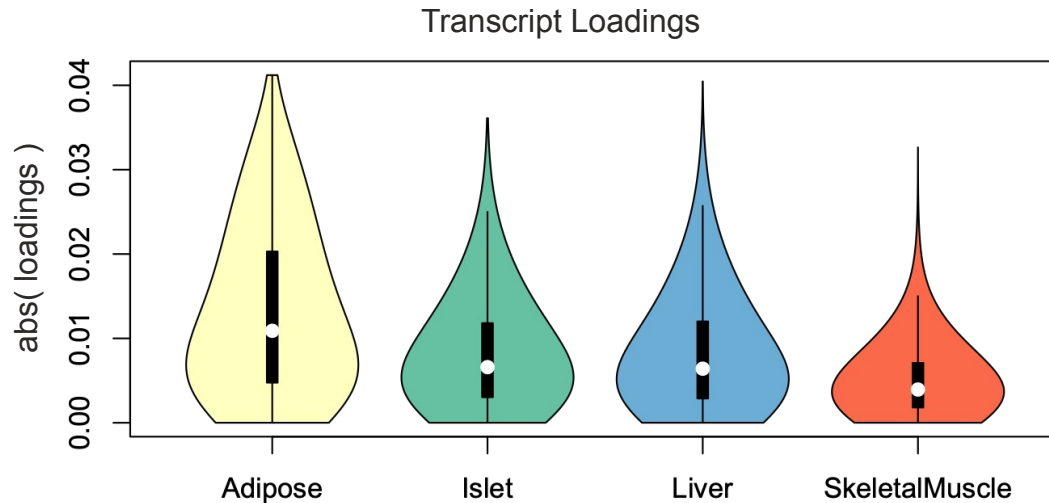
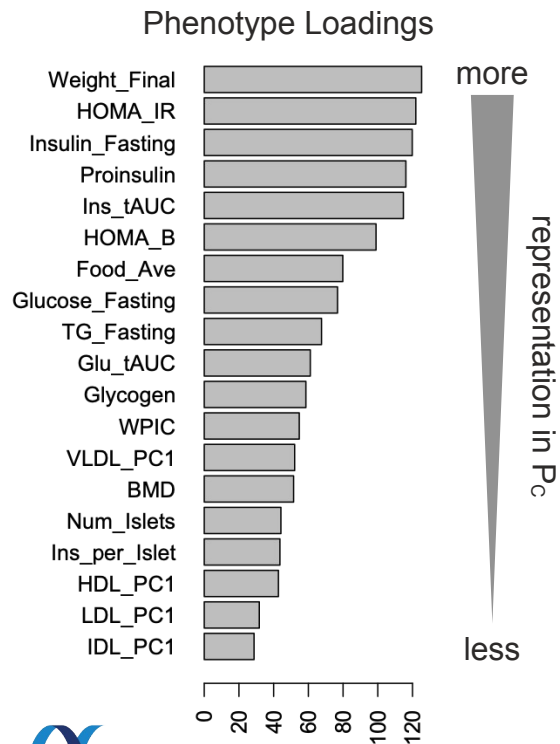
## High-dimensional mediation analysis

- determines transcriptome loadings that optimally link genotype and phenotype



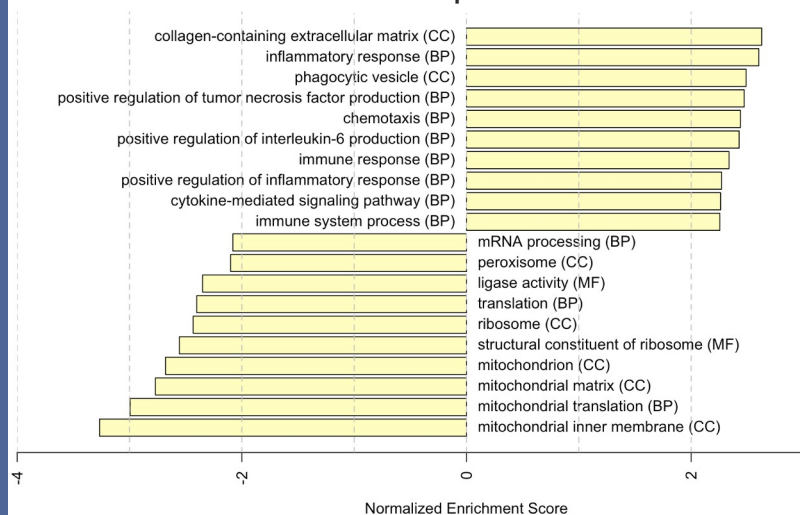
# TISSUE AND GENE CONTRIBUTIONS TO TRAIT MEDIATION

Matched trait loadings and transcript loadings for each tissue

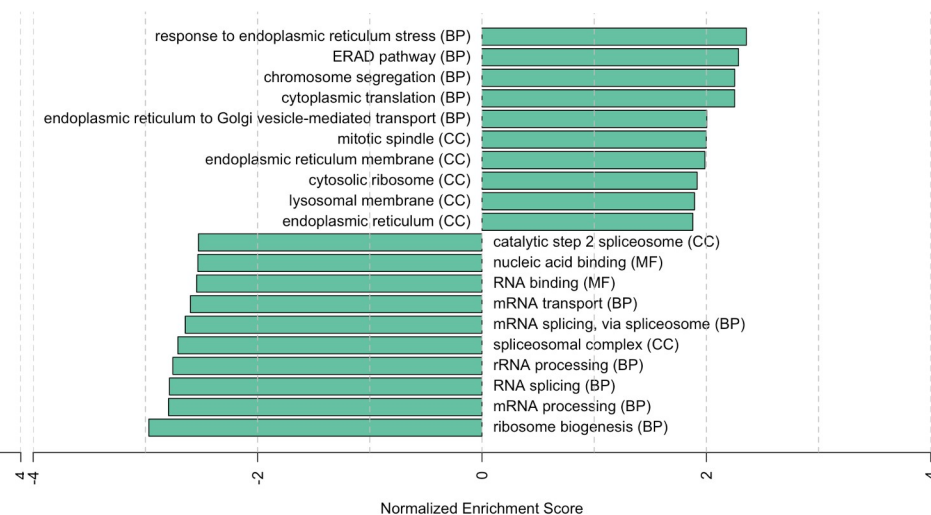


# TISSUE-SPECIFIC TRANSCRIPTIONAL RESPONSES

## Adipose



## Liver



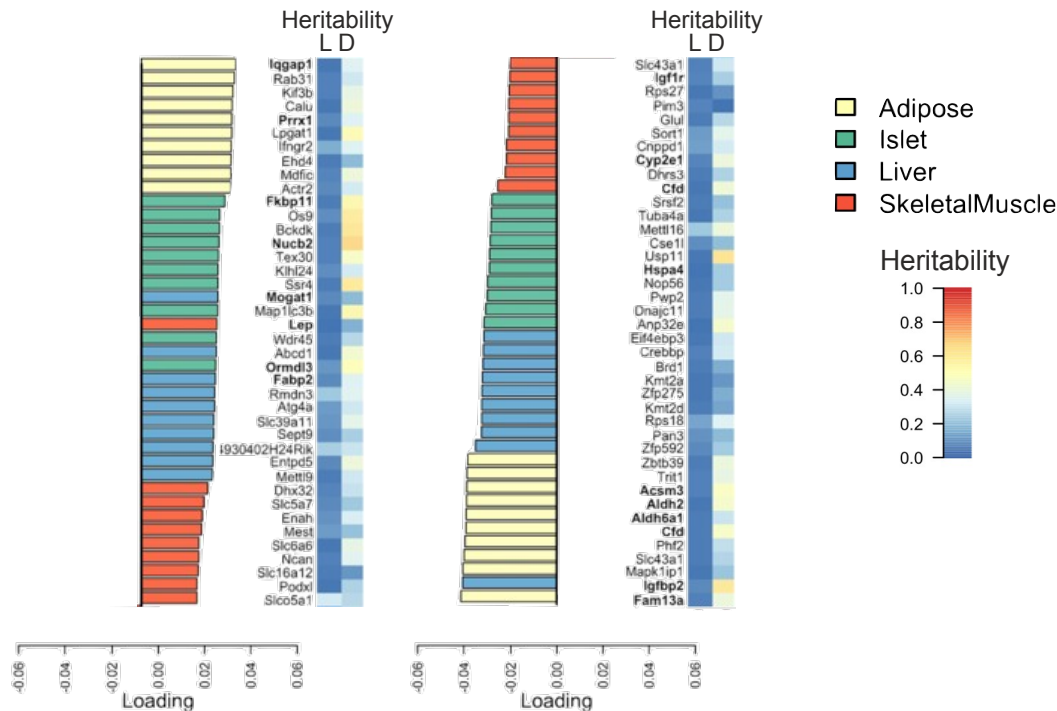
## Transcript Loading



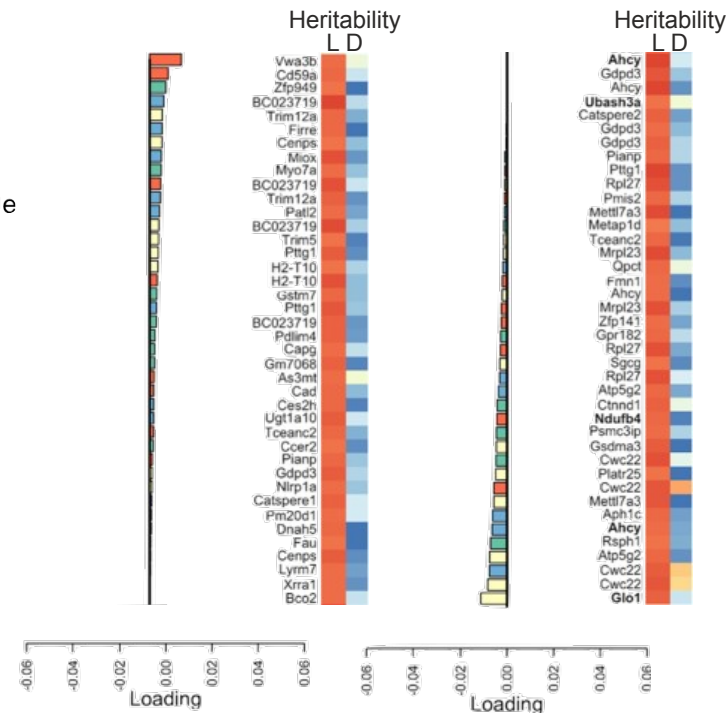
# TRAIT-RELEVANT TRANSCRIPTOMES ARE CONSTRAINED

Genes most informative of traits have distal genetic regulation and are tissue-specific

Genes with Largest Loadings

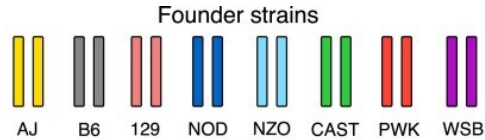


Genes with Largest Local Heritability



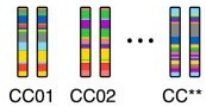
# TRANSCRIPTS ARE PREDICTIVE OF TRAITS BUT GENOTYPE IS NOT

Model validation in a separate population derived from the same genetics (CC-RIX)



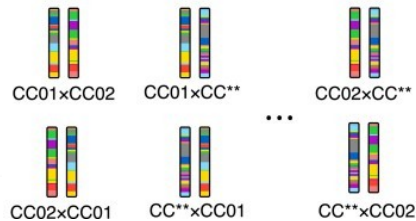
Inbreed

Collaborative Cross (CC)



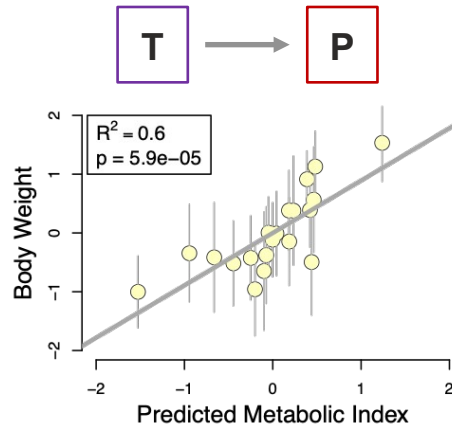
Cross

CC-Recombinant Inbred Intercross (CC-RIX)

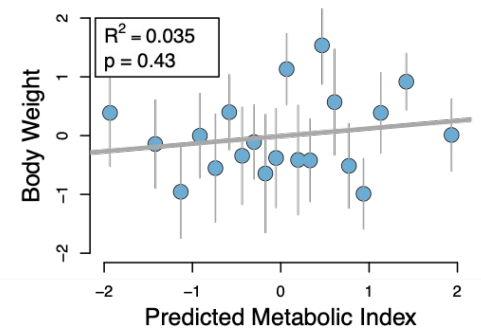
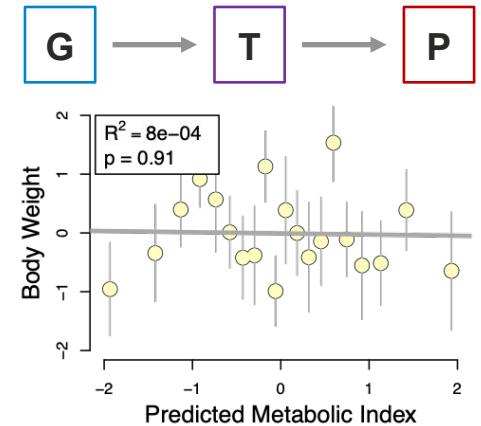
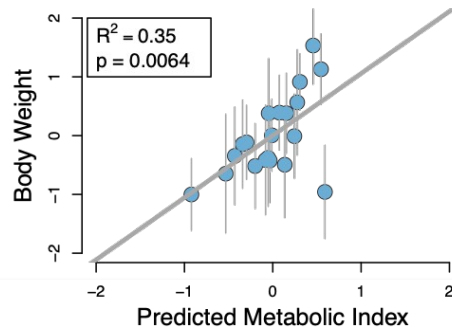


From Keele G, G3, 2023

Adipose

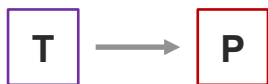


Liver

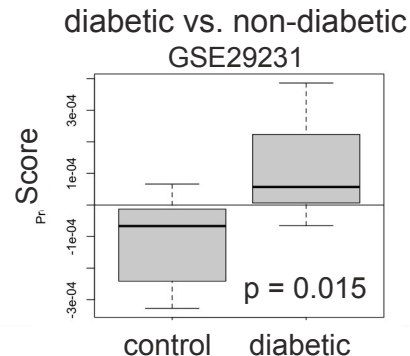
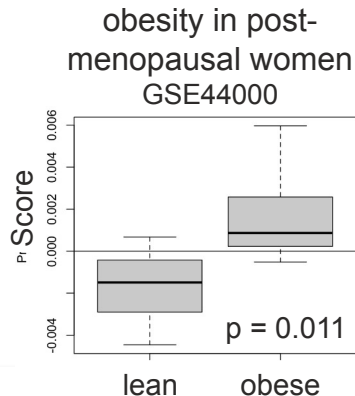
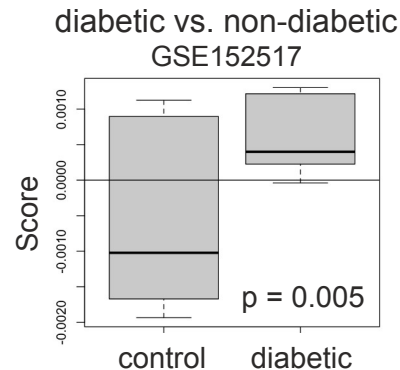
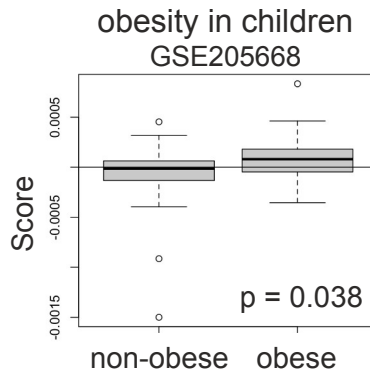


# HOMOLOGOUS TRANSCRIPTS ARE PREDICTIVE IN HUMANS

Used transcript loadings to predict metabolic traits in four human data sets with paired adipose transcriptomes and outcome traits.



As with mice, adipose transcriptomes were more predictive than islet or liver.





# SUMMARY

- *Transcripts that drive metabolic outcomes are constrained by complex distal genetics*
- *Genotype, local eQTL, and TWAS are poor trait predictors for independent populations*
- *Genotype-phenotype mediator transcripts from DO are predictive for independent CC-RIX and human populations*



# ACKNOWLEDGEMENTS

## Carter Lab

Anna Tyler  
Lauren Kuffler  
Catrina Spruce  
Annat Haber  
Ann Wells  
Alex Fine  
Robyn Ball  
Wendy Pittman  
Robert Valenzuela  
Zoe Vittum  
Alex Daines  
Asli Uyar  
Yi Juin Liew  
Avijit Podder  
Tamar Abel  
Greg Cary  
Stephen Keegan  
Sonal Kumar

## Collaborators

Gary Churchill  
Matt Mahoney  
Isabela Gerdes Gyuricza  
Margaret Gaca  
Anuj Srivastava  
Nadia Rosenthal  
Jake Emerson  
Candice Baker  
Madeleine Braun  
Mark Keller (UWisc)  
Allan Attie (UWisc)

## Funding

NIGMS K25 GM079404  
NIGMS P50 GM076468  
NIGMS R01 GM115518  
JAX Innovation Fund

[gregory.carter@jax.org](mailto:gregory.carter@jax.org)



@gwcarter





# ORGAN-SPECIFIC EXPRESSION EFFECTS

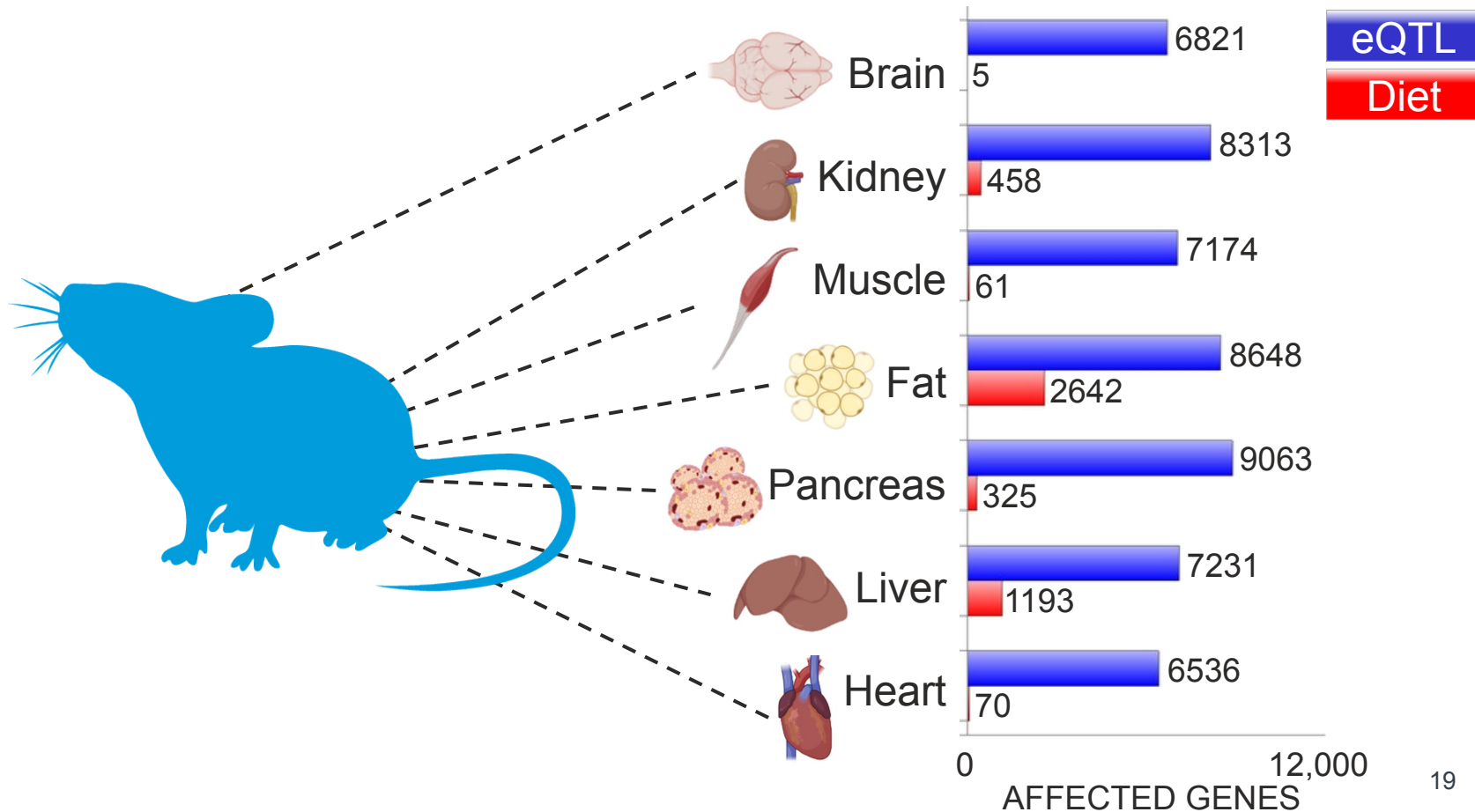
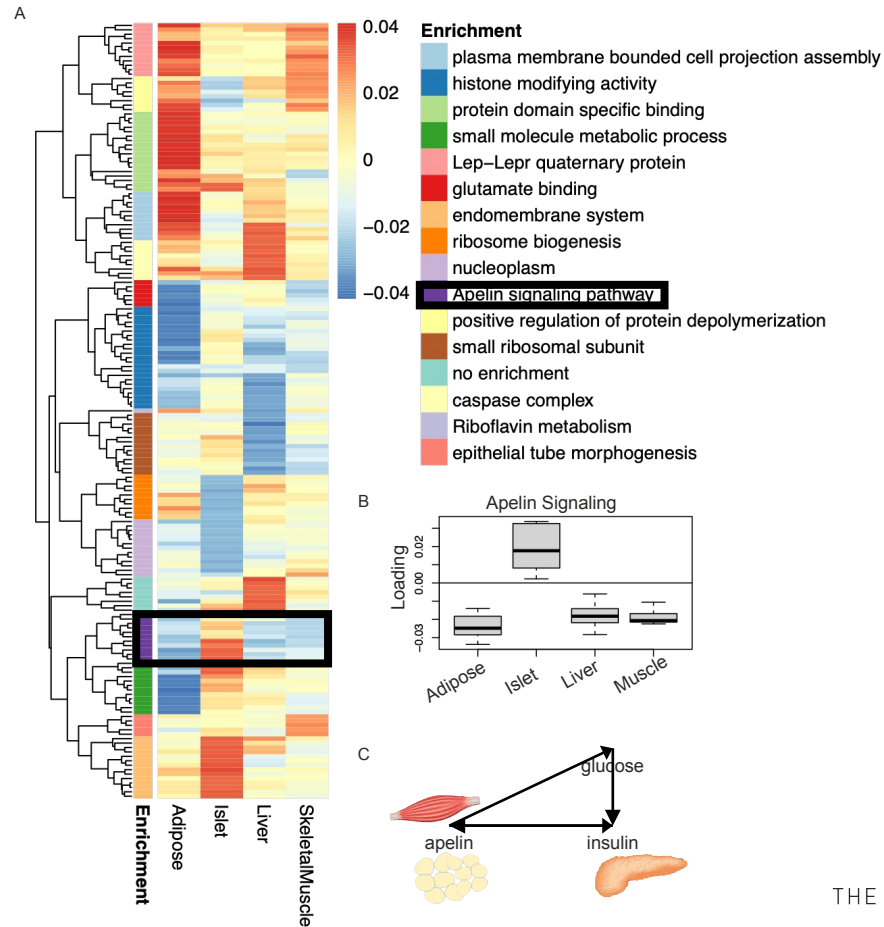


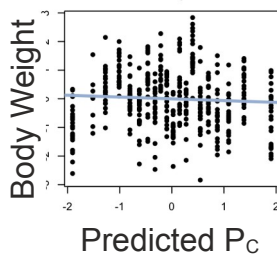
Figure 6: Tissues of action





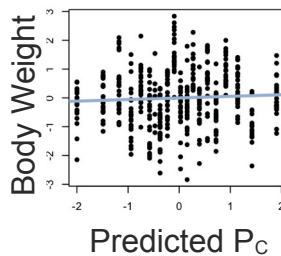
## Adipose

$r = -0.061, p = 0.21$



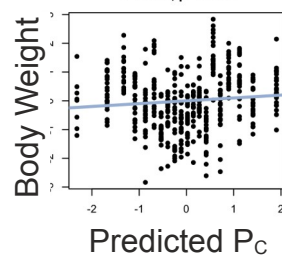
## Liver

$r = 0.054, p = 0.26$

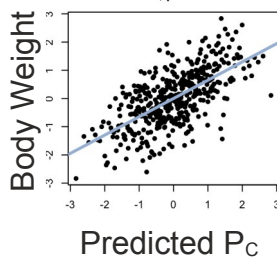


## Muscle

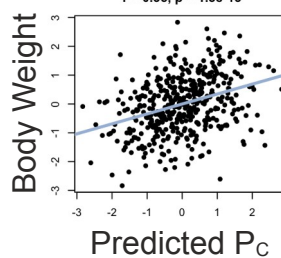
$r = 0.097, p = 0.042$



$r = 0.65, p = 2.9e-53$



$r = 0.35, p = 1.3e-13$



$r = 0.32, p = 9.7e-12$

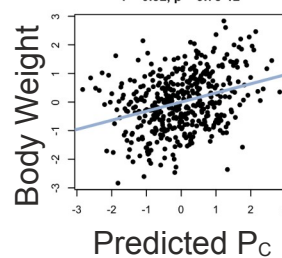
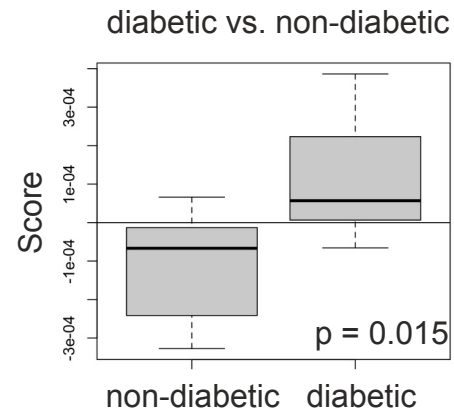
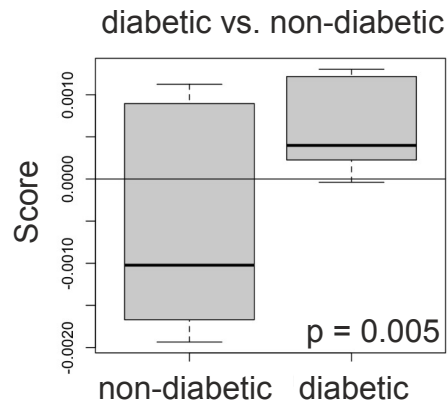
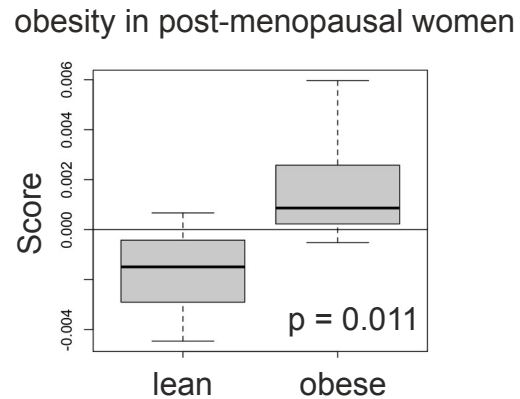
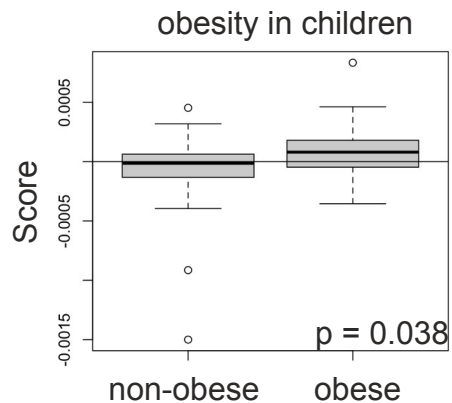
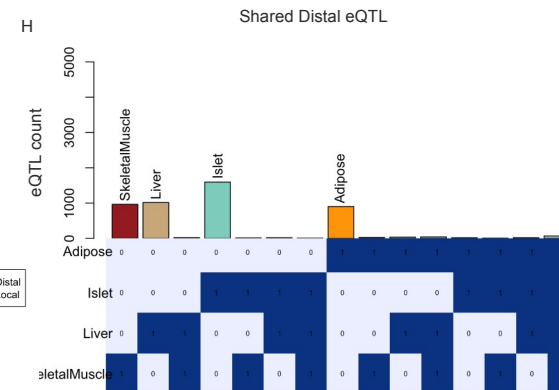
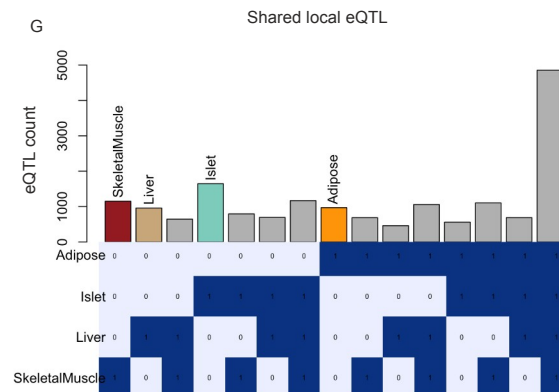
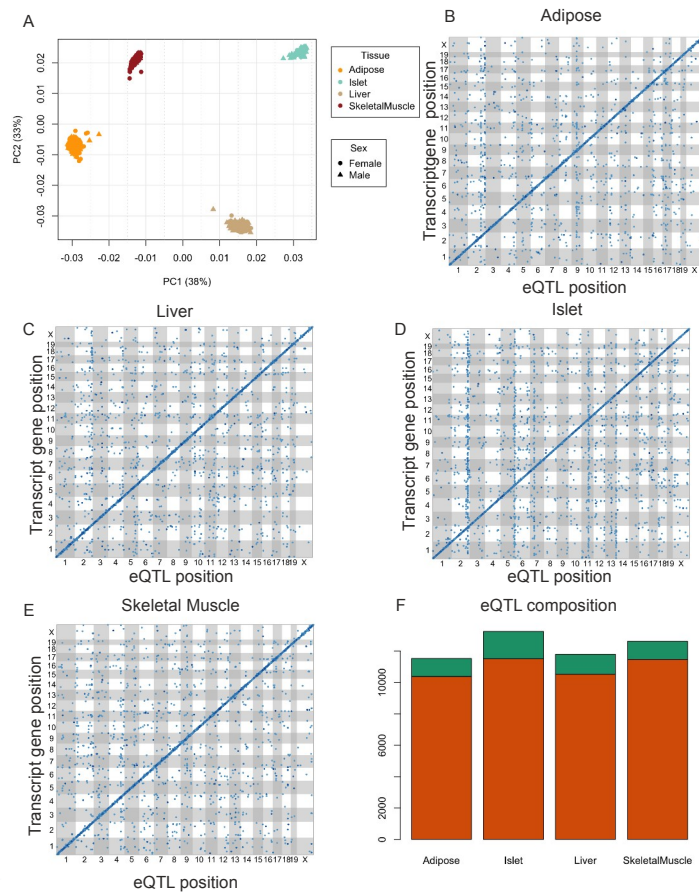


Figure 8: Human Translation

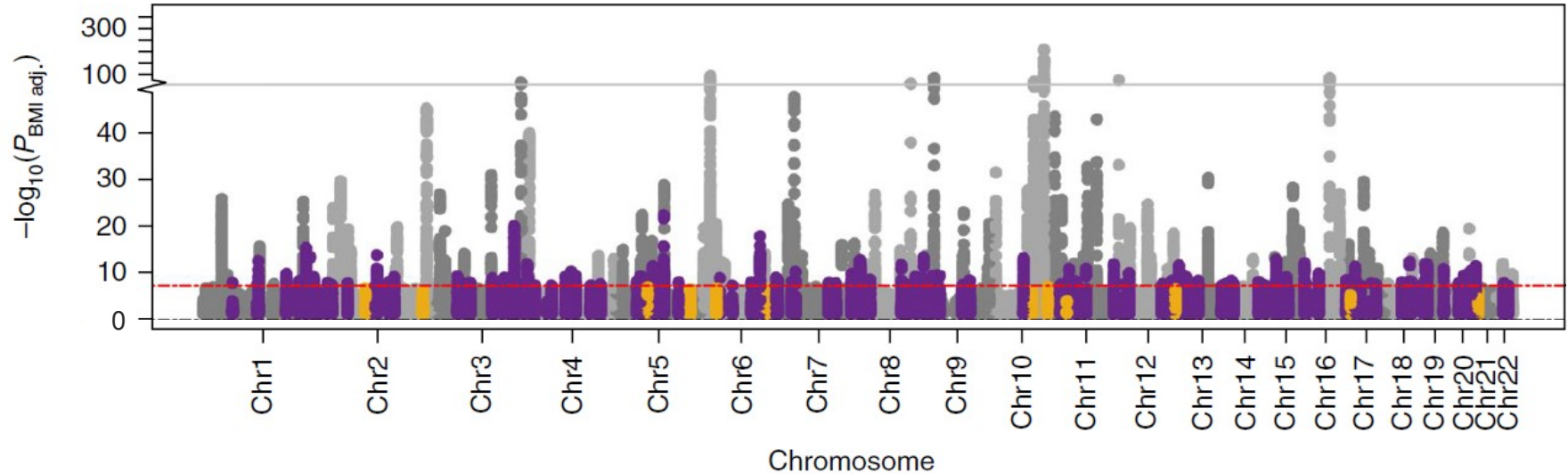




# Supplemental eQTL figure

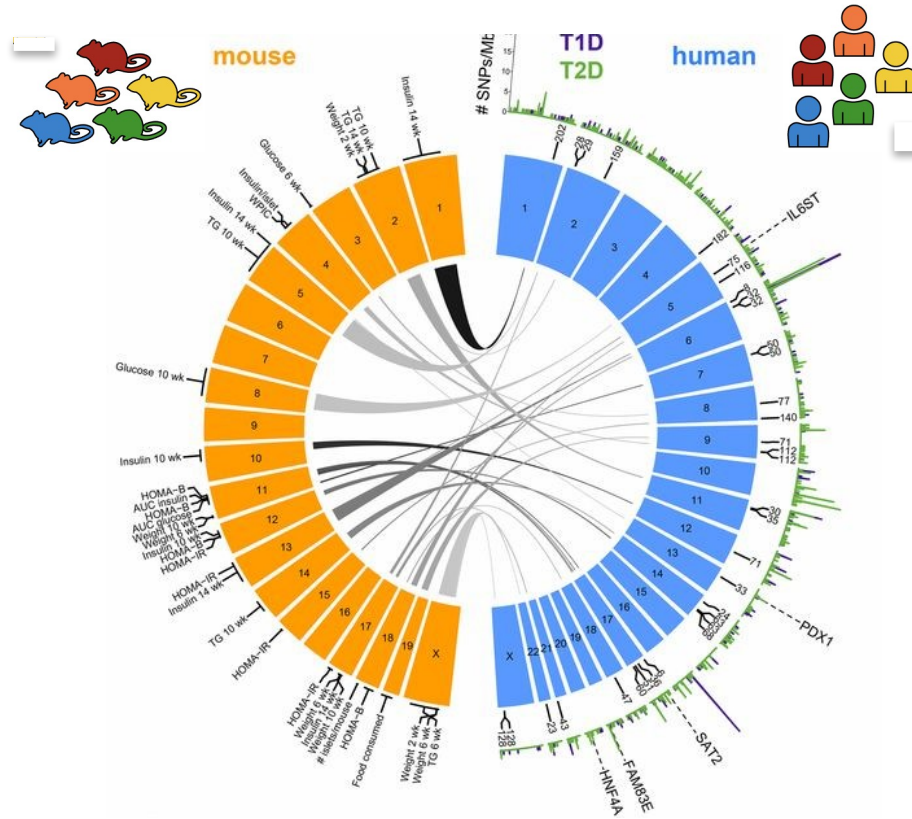


# HUMAN GENETICS OF TYPE 2 DIABETES

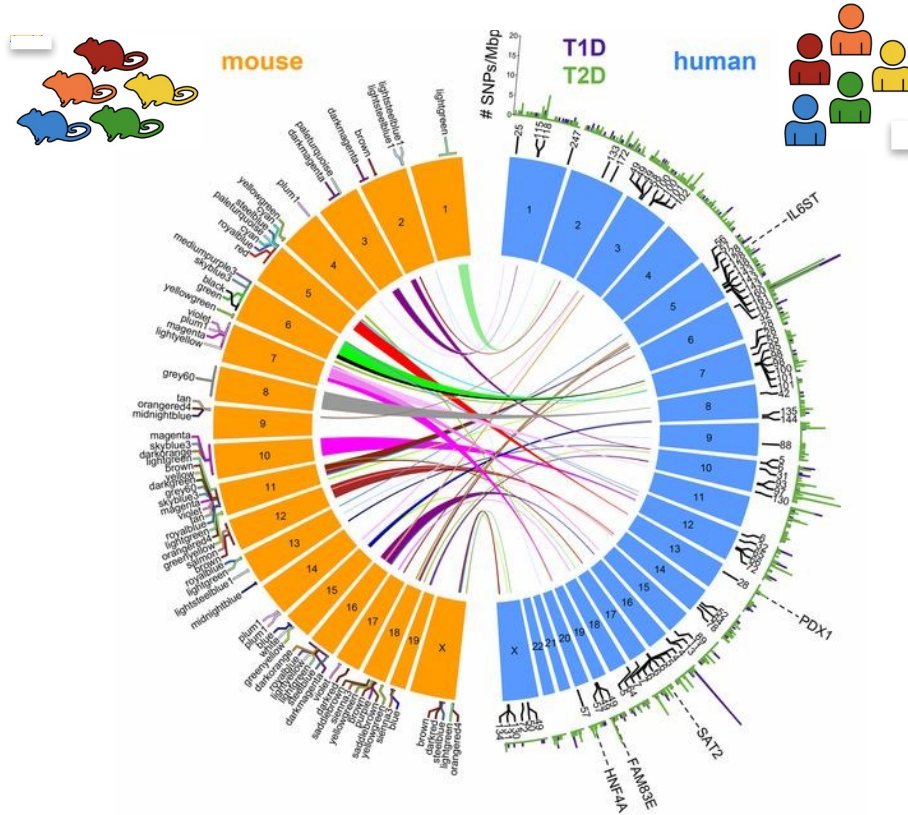


Mahajan A, et al *Nat Genet* **50**, 1505–1513 (2018)

# HUMAN-MOUSE GENETIC ALIGNMENT

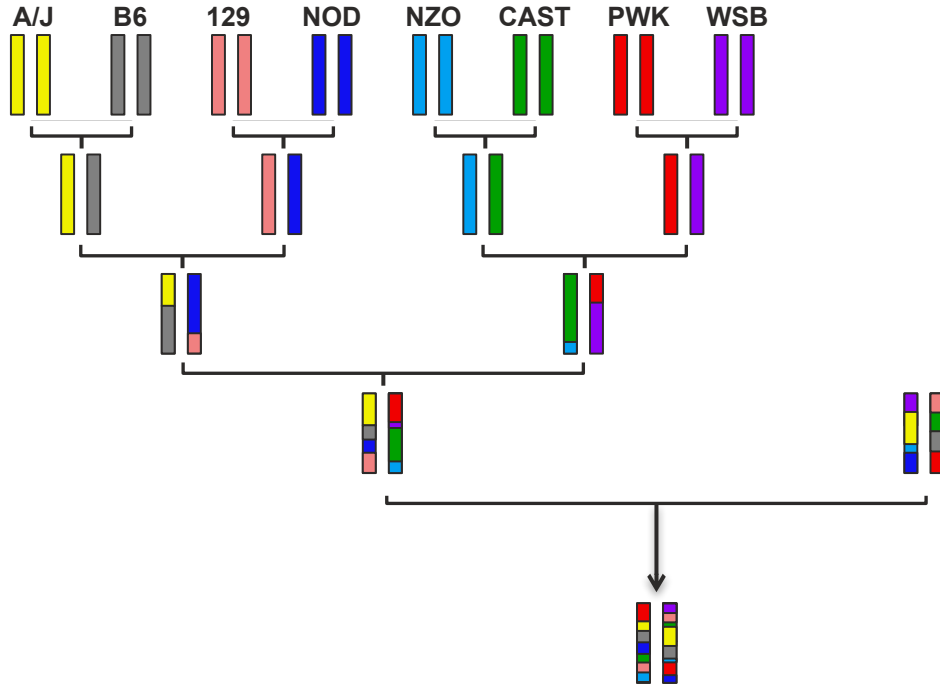


# HUMAN-MOUSE TRANSCRIPTOMIC ALIGNMENT

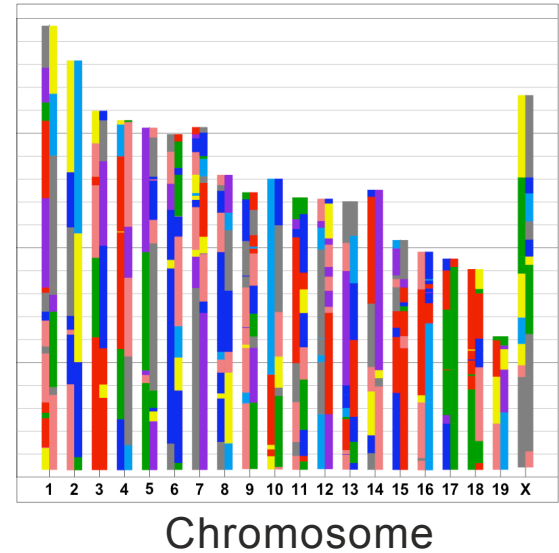


# We've Created Mice for Modern Genetics

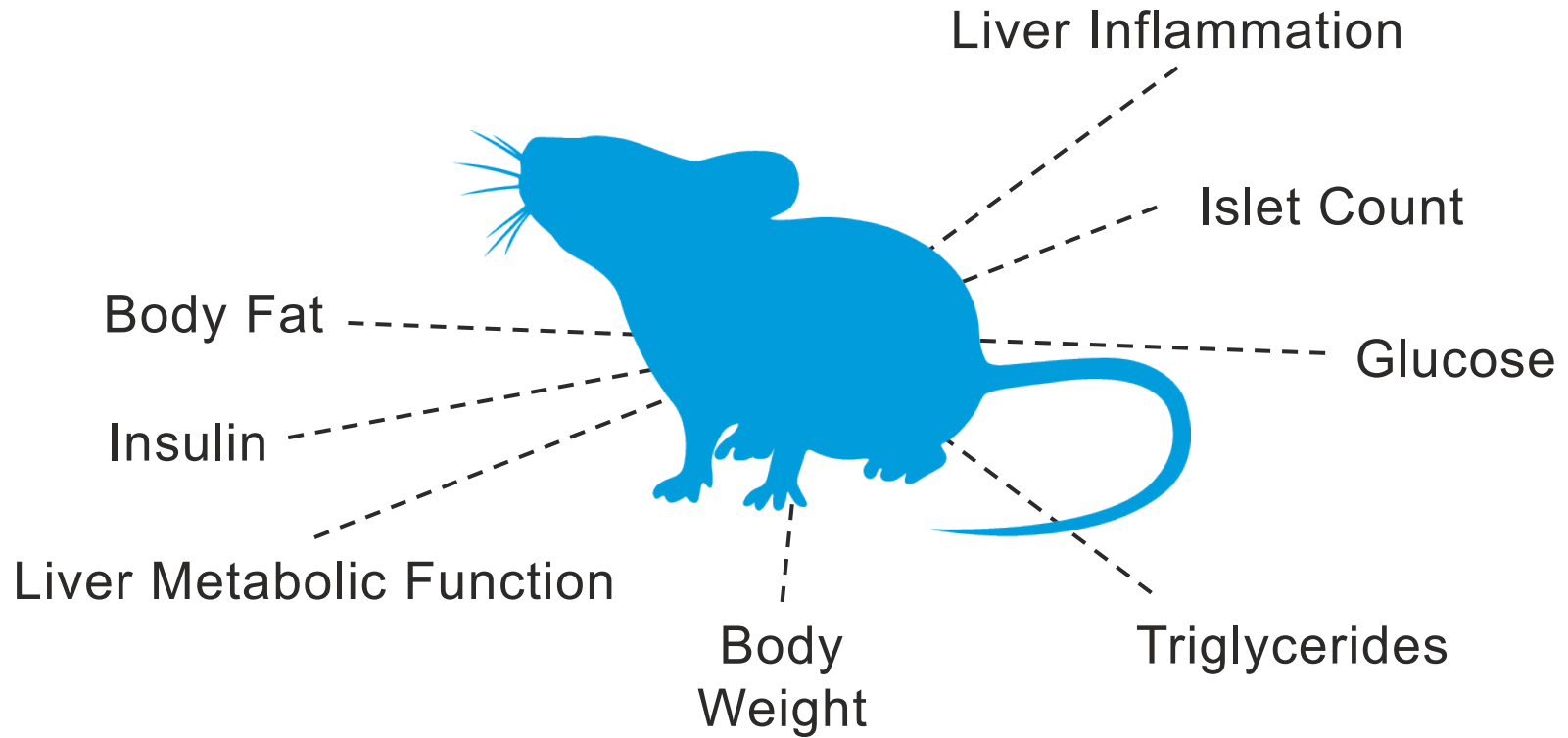
## ORIGINAL INBRED MICE



## DIVERSITY OUTBRED MOUSE



# A Comprehensive Platform for Genetics



# QUESTIONS?

