Gut Microbiota Regulates the Interplay Between Diet and Genetics to Influence Glucose Tolerance

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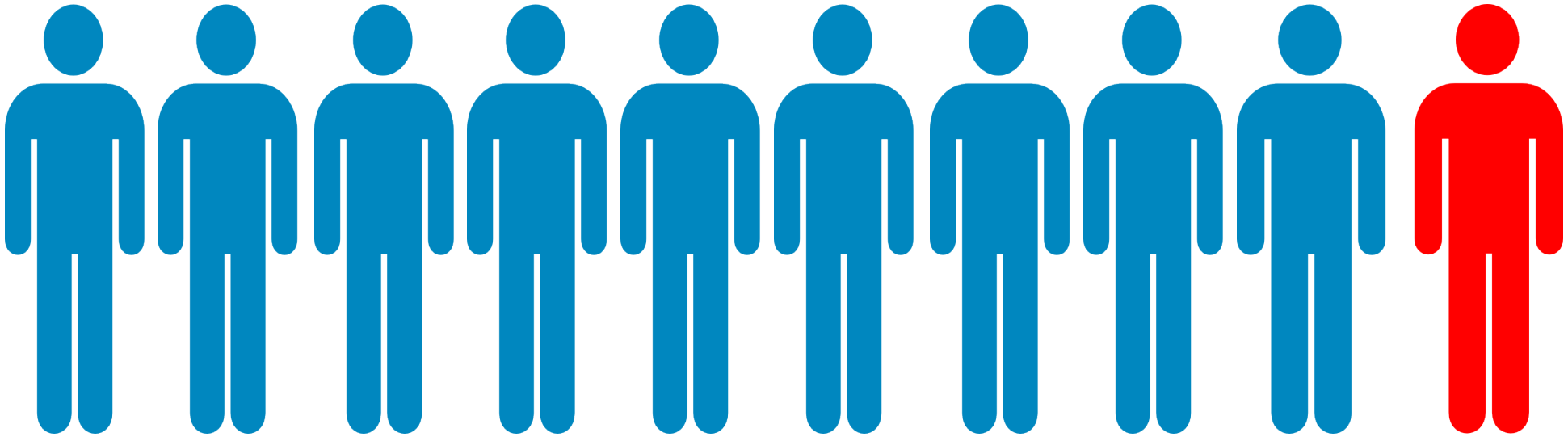
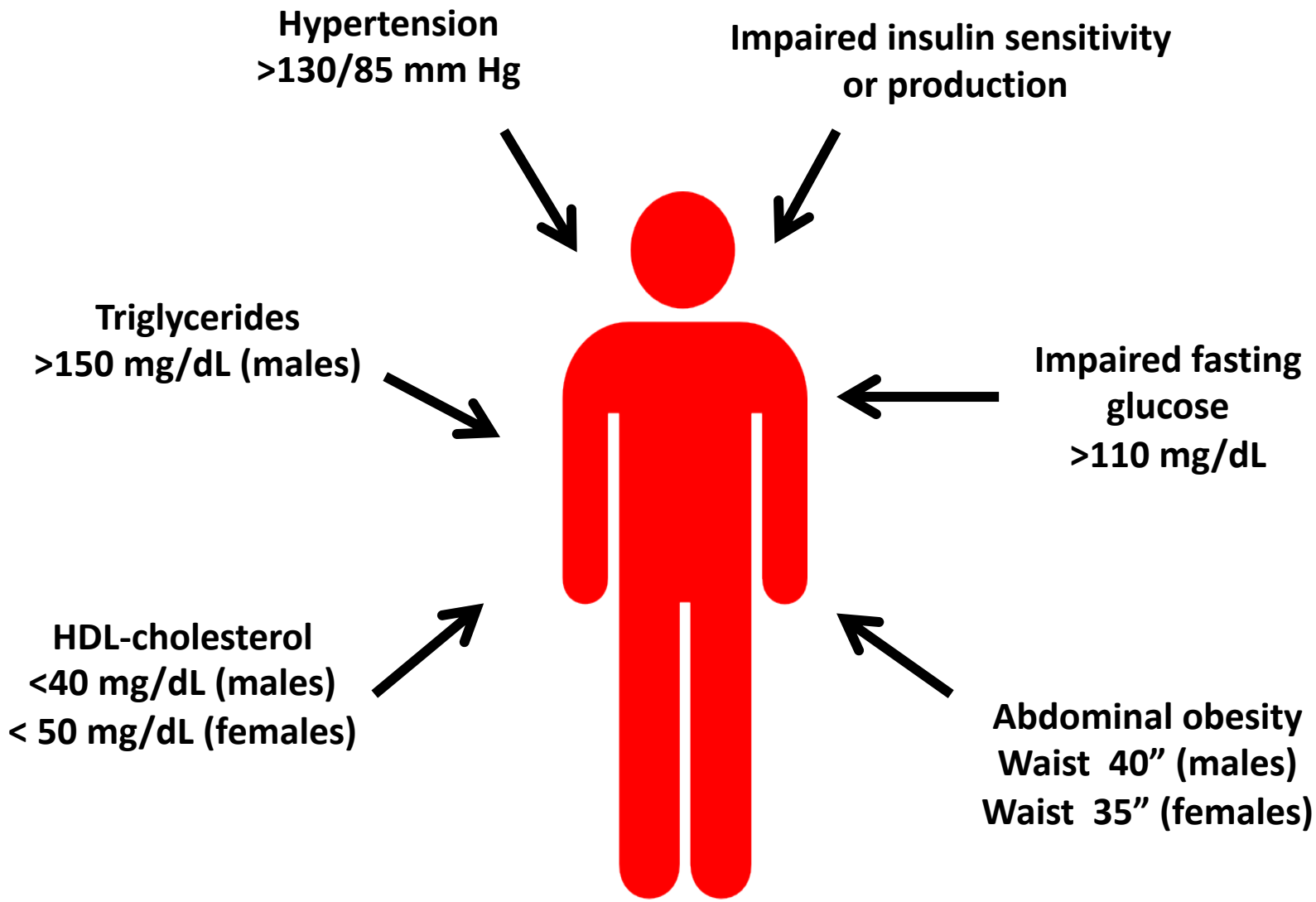
Background

Metabolic Disease, an Increasing Health Crisis

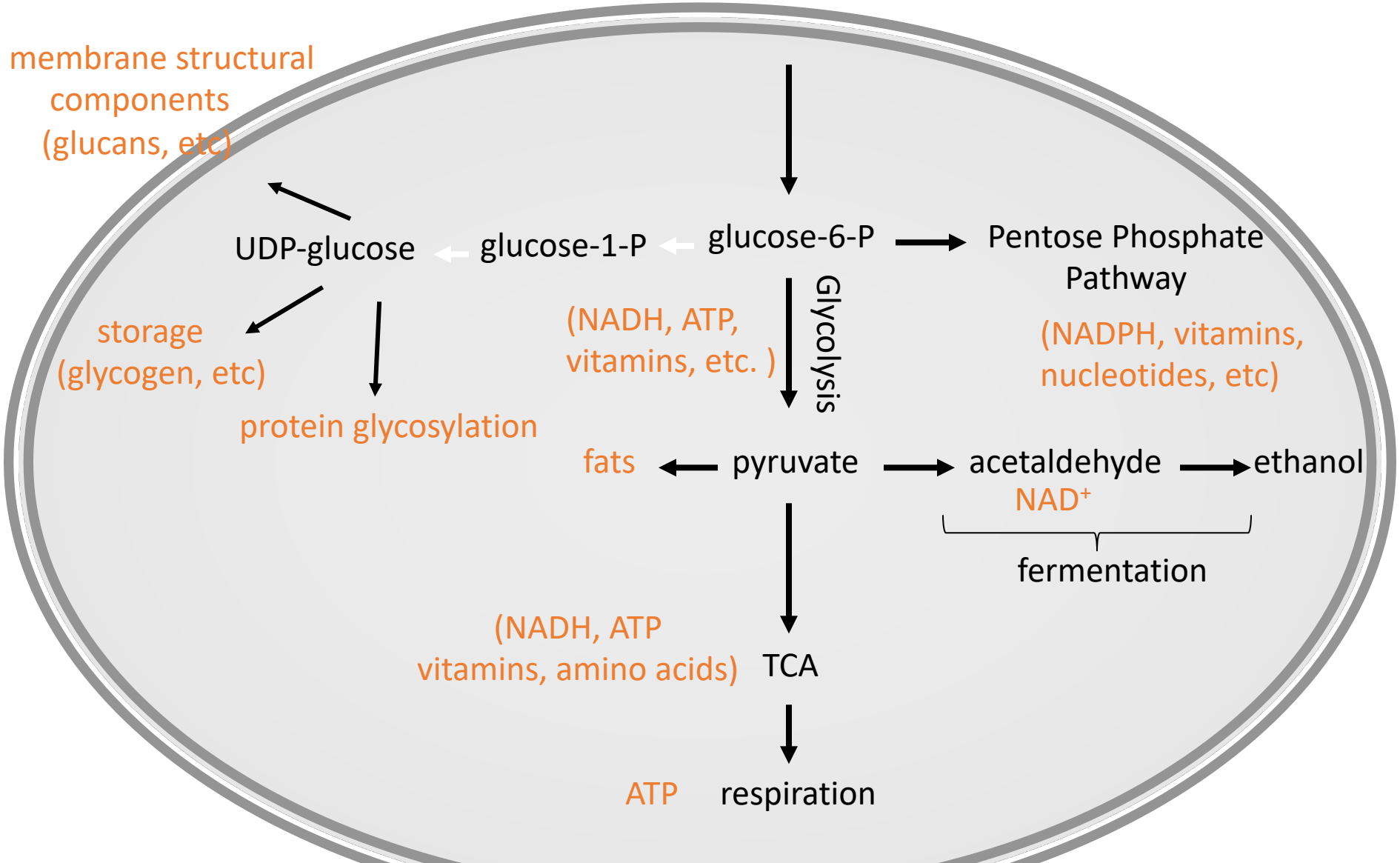


10.5% of the US population has diabetes, 26.8% of seniors (>65%)
>300 billion/year to diabetes

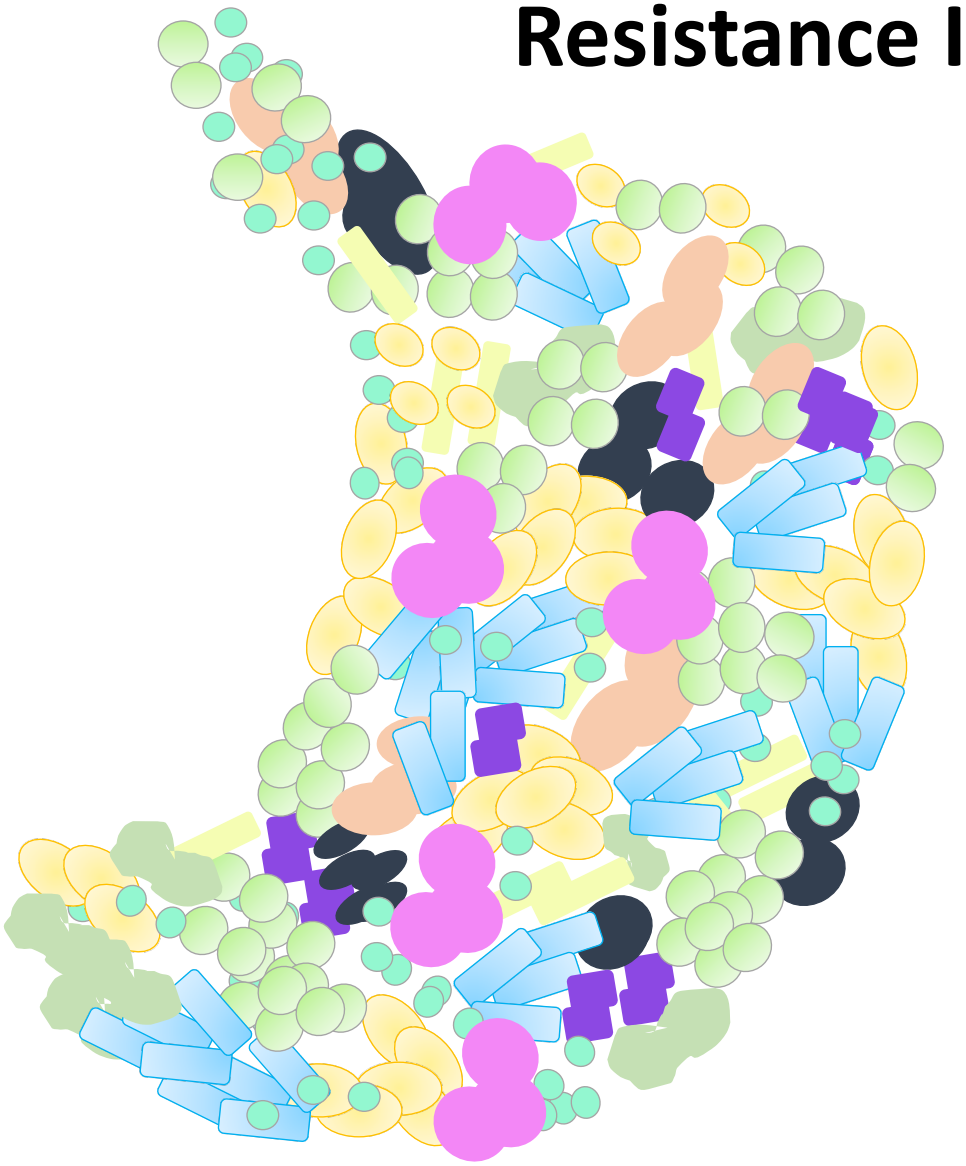
Diabetes is a Complex Disease, with Many Interrelated Phenotypes



Metabolism Is Complex, with Many Competing Pathways That Are Regulated by Both Diet and Genetics



The Microbiome Has Been Shown to Play a Key Role in Weight Gain, Triglyceride Accumulation and Insulin Resistance In Response to Diet

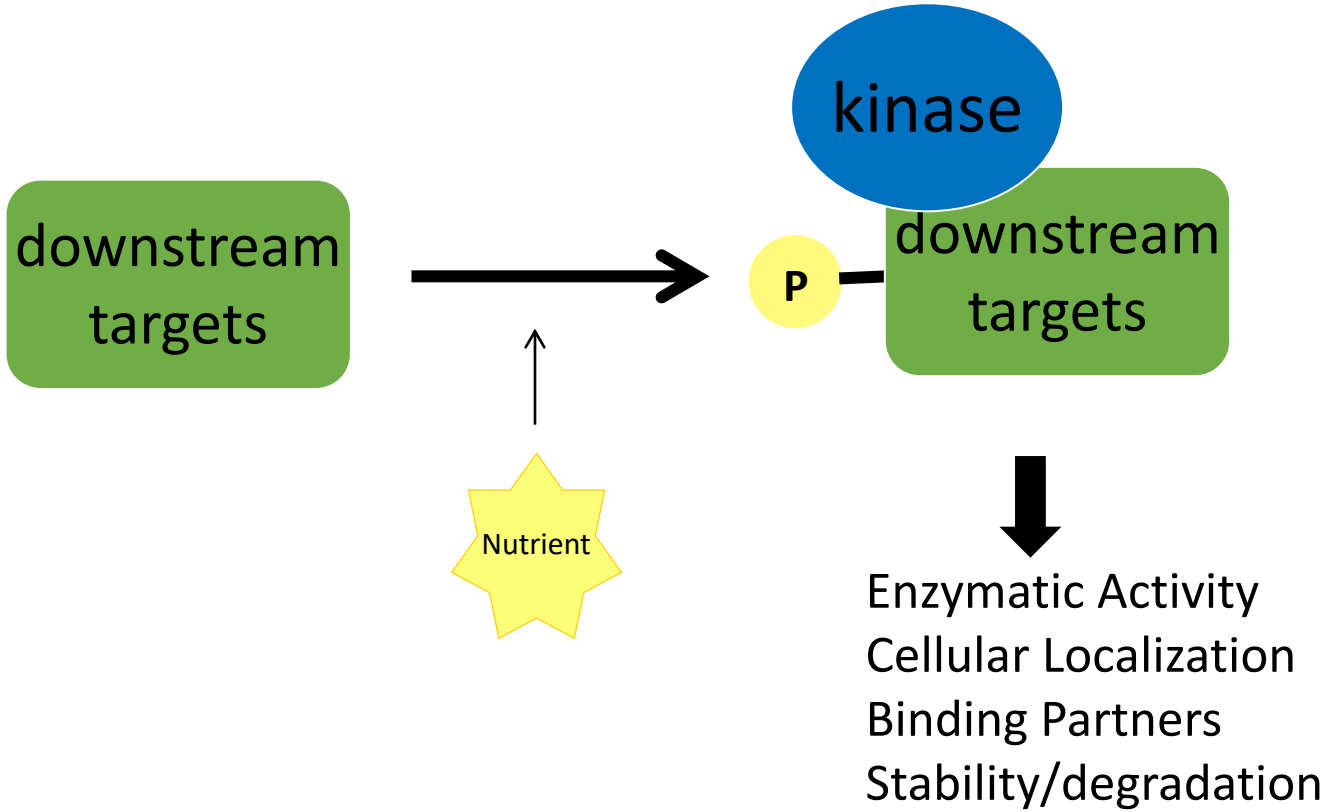


Duodenum: 10^3 bacterial cells/gram tissue
Jejunum: 10^4 bacterial cells/gram tissue
Ileum: 10^7 bacterial cells/gram tissue
Colon: 10^{12} bacterial cells/gram tissue

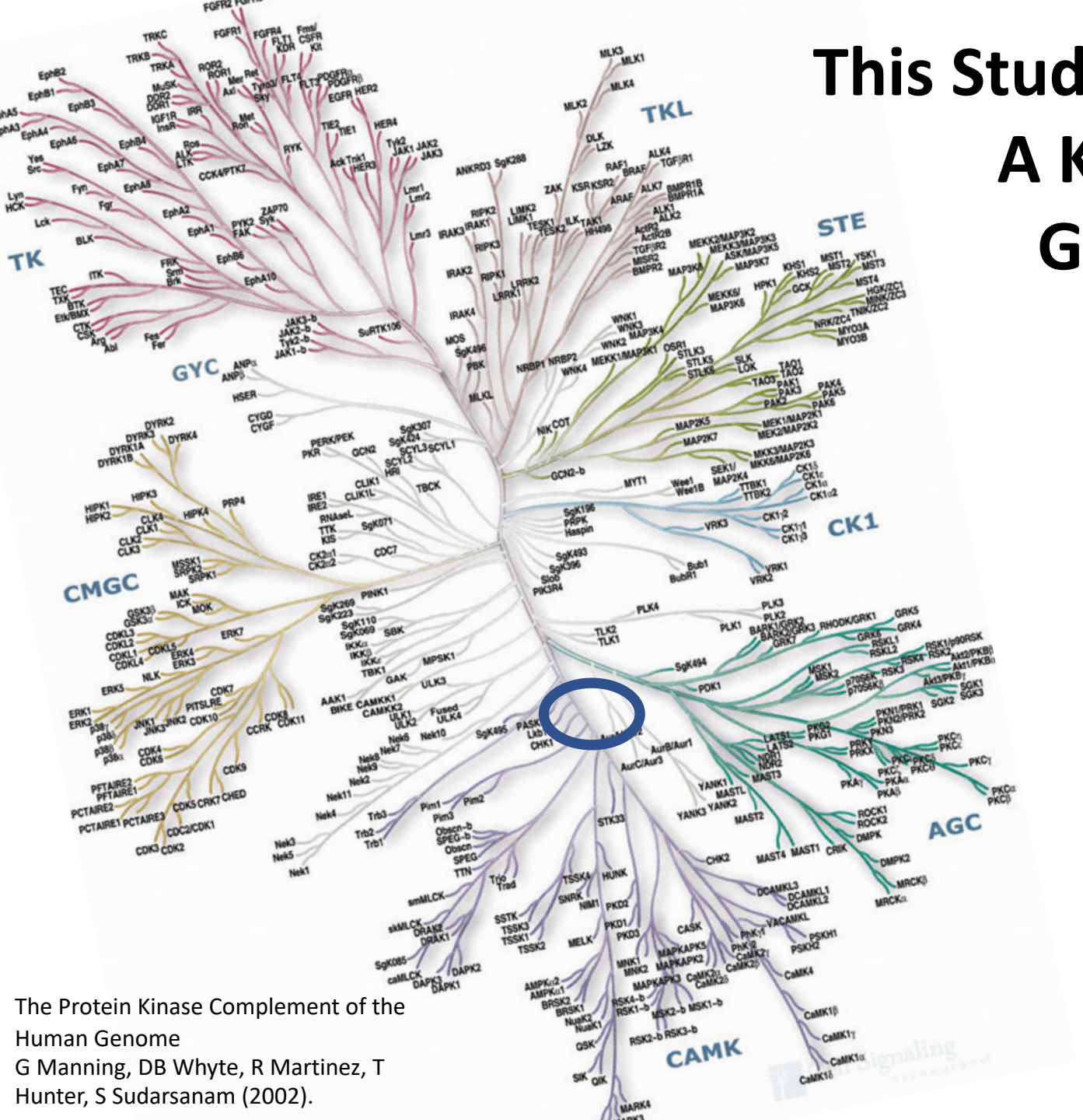
Obesity and Insulin Resistance (Bacteriodetes & Firmicutes)

Ley, et al, *PNAS, 2005*
Moreno-Indias, et al, *Am. J. Trans.Resl.* 2016
Cani, et a., *Diabetes* 2008
Martinez-Medina, et al, *Gut* 2014
Bäckhed, et a., *PNAS* 2007
Fei, et al, *The ISME journal* 2013,
Turnbaugh, et al. *Nature*, 2006
Shin, et al *Gut* 2014.
Zhao, et al. *Science*, 2018
Everard, et al. *PNAS,* 2013
Karlsson, et al., *Obesity* 2012

Protein Kinases Are Some of our Key Drug Targets for Metabolic Disease Due To Their Ability to Coordinate Interrelated Processes Protein Phosphorylation of Tens of Protein Substrates



This Study Will Focus on PAS Kinase, A Kinase That Regulates Glucose Homeostasis

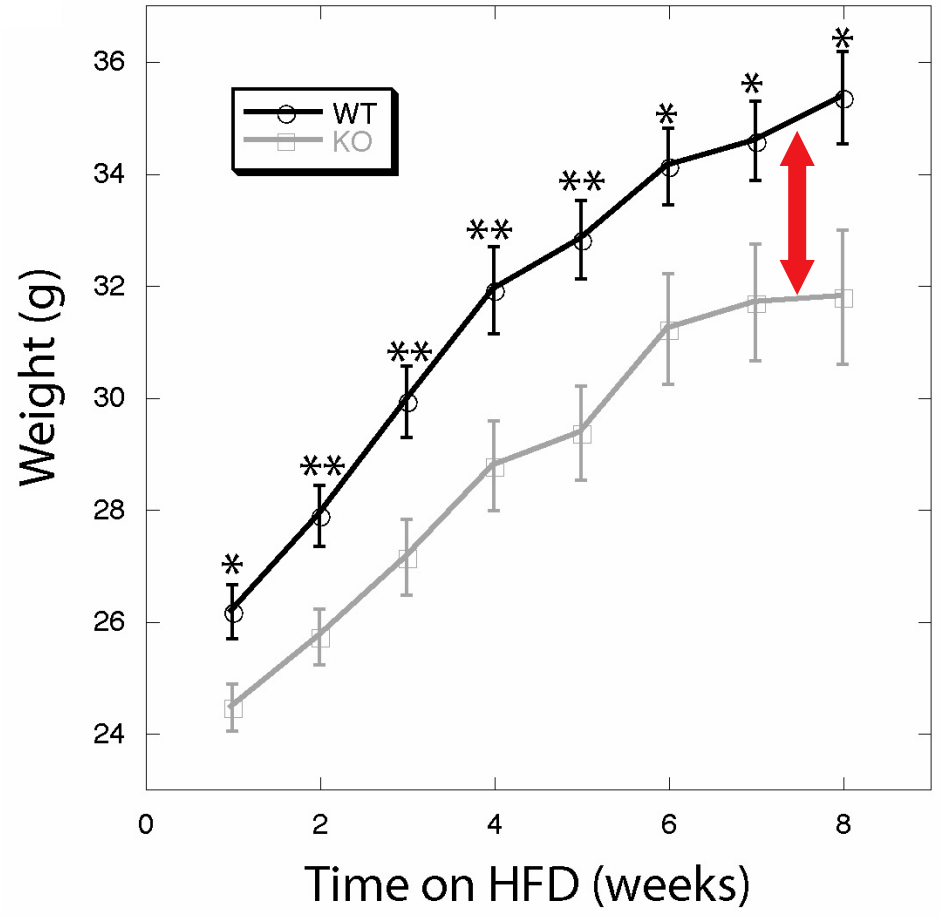


The Protein Kinase Complement of the Human Genome
G Manning, DB Whyte, R Martinez, T Hunter, S Sudarsanam (2002).

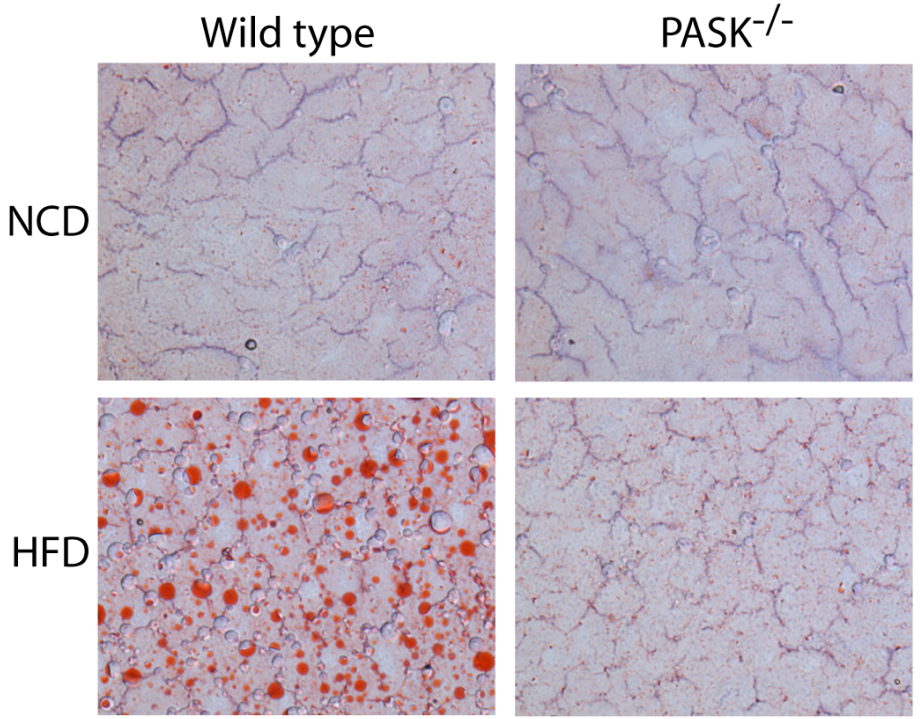
- The human kinome is complex and overlapping
- Over 100 serine/threonine protein kinases
- Tens of substrates per kinase
- Overlapping substrates

PAS Kinase-deficiency Protects Against Weight Gain and Liver Triglyceride Accumulation on a High Fat Diet

Decreased weight



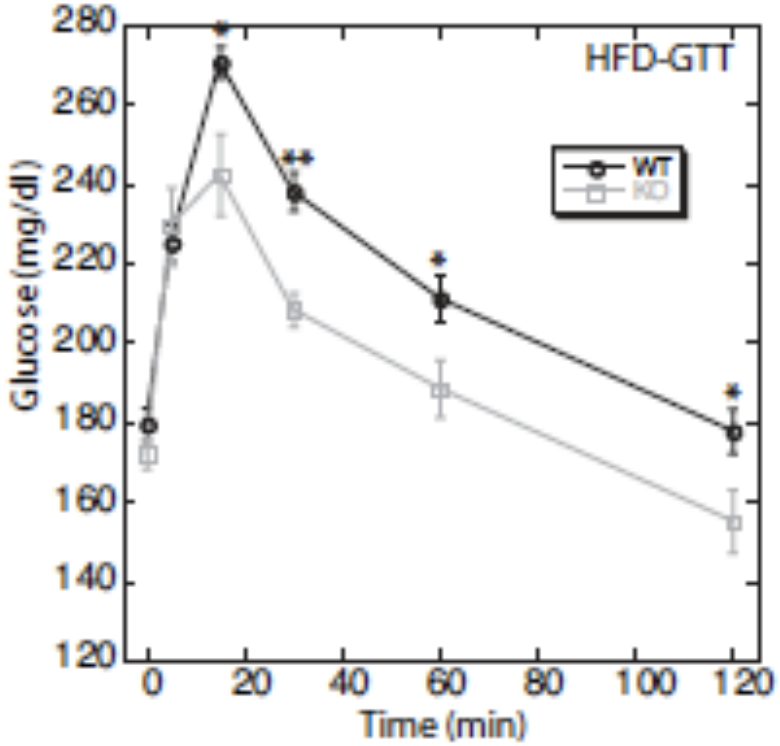
Decreased liver triglyceride



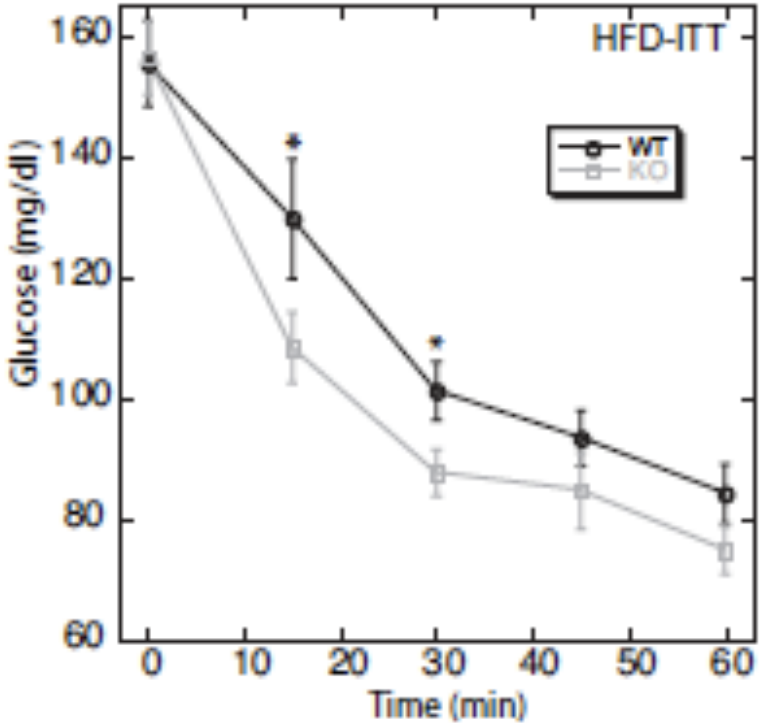
Hao et al, PNAS (2007)

PAS Kinase-deficient Mice Are Protected from High Fat Diet-induced Glucose Intolerance and Insulin Resistance

Glucose tolerance

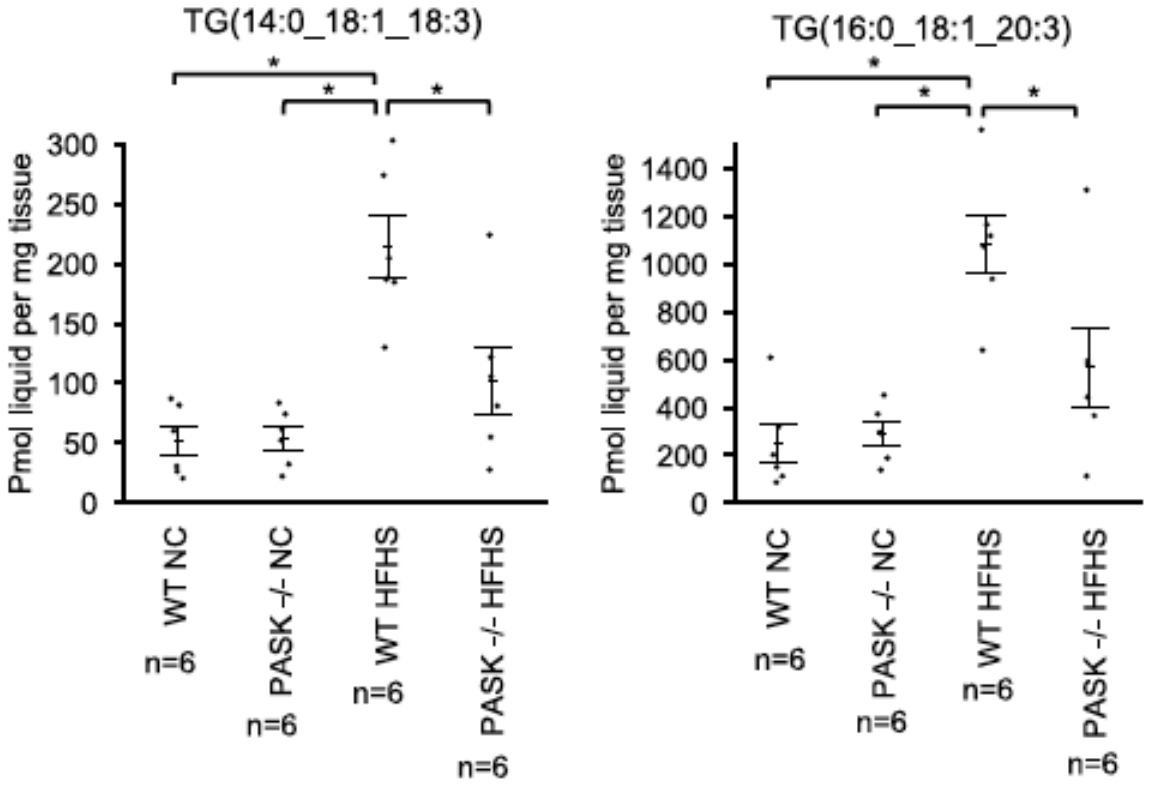


Insulin tolerance



Hao et al, PNAS (2007)

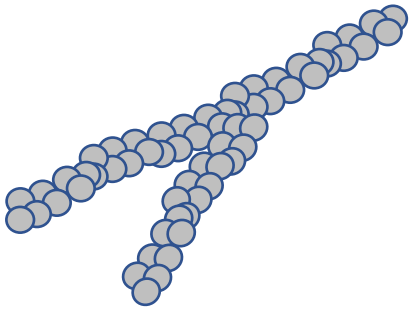
The Resistance To Triglyceride Accumulation was Characterized on a High Fat High Sugar (HFHS) Diet



PAS Kinase Protects Against SFA Accumulation

Pape et al., Nutrients (2019)

Where is the glucose going?



glucose

↓

glucose-6-P

↓

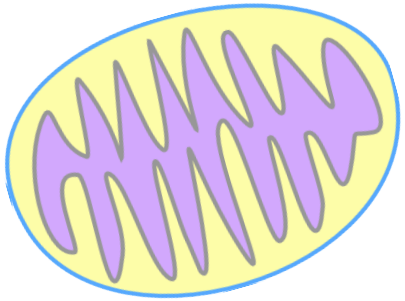
pyruvate

↓

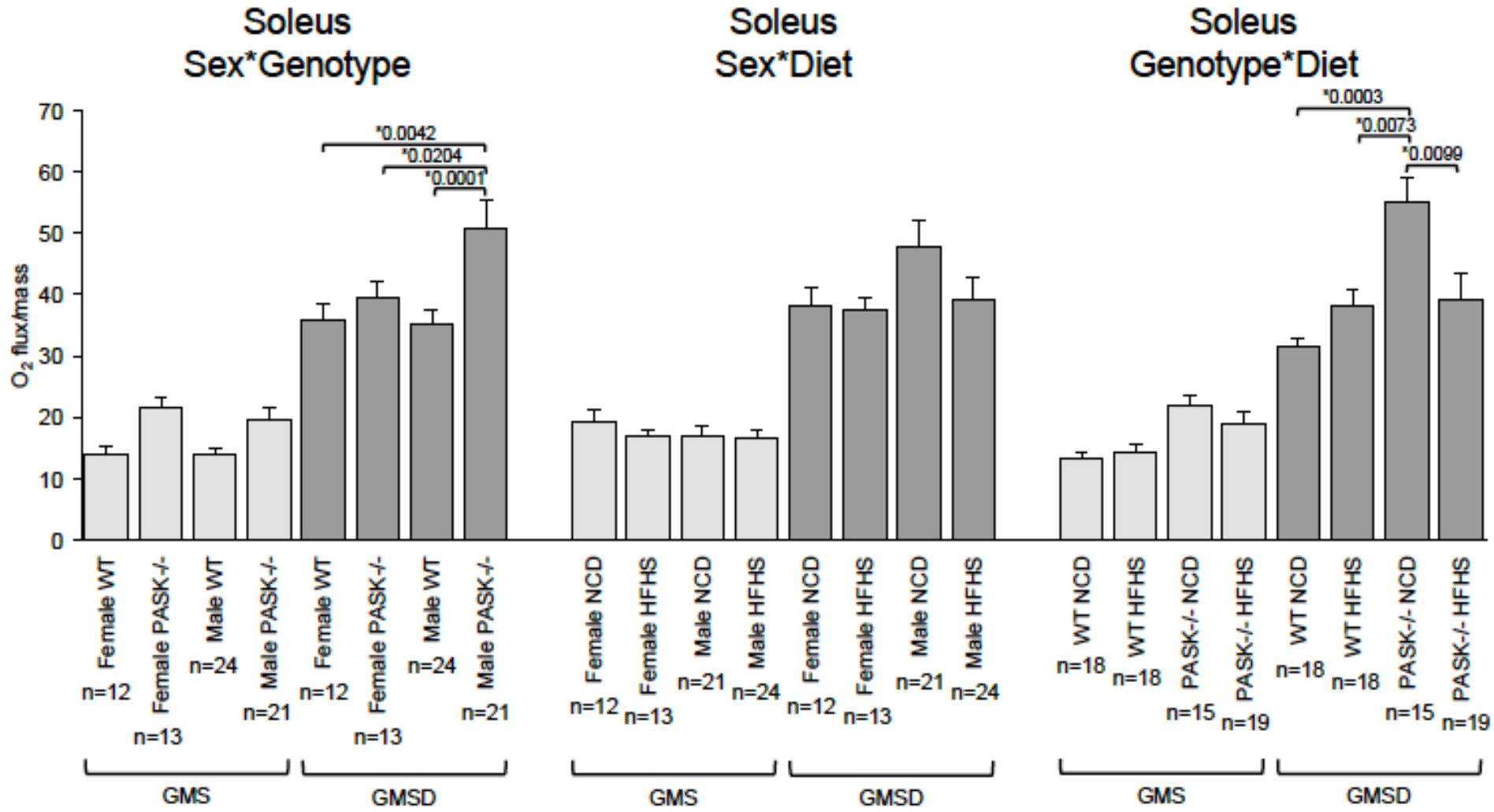
lipids ✗ Acetyl-coA

↓

respiration

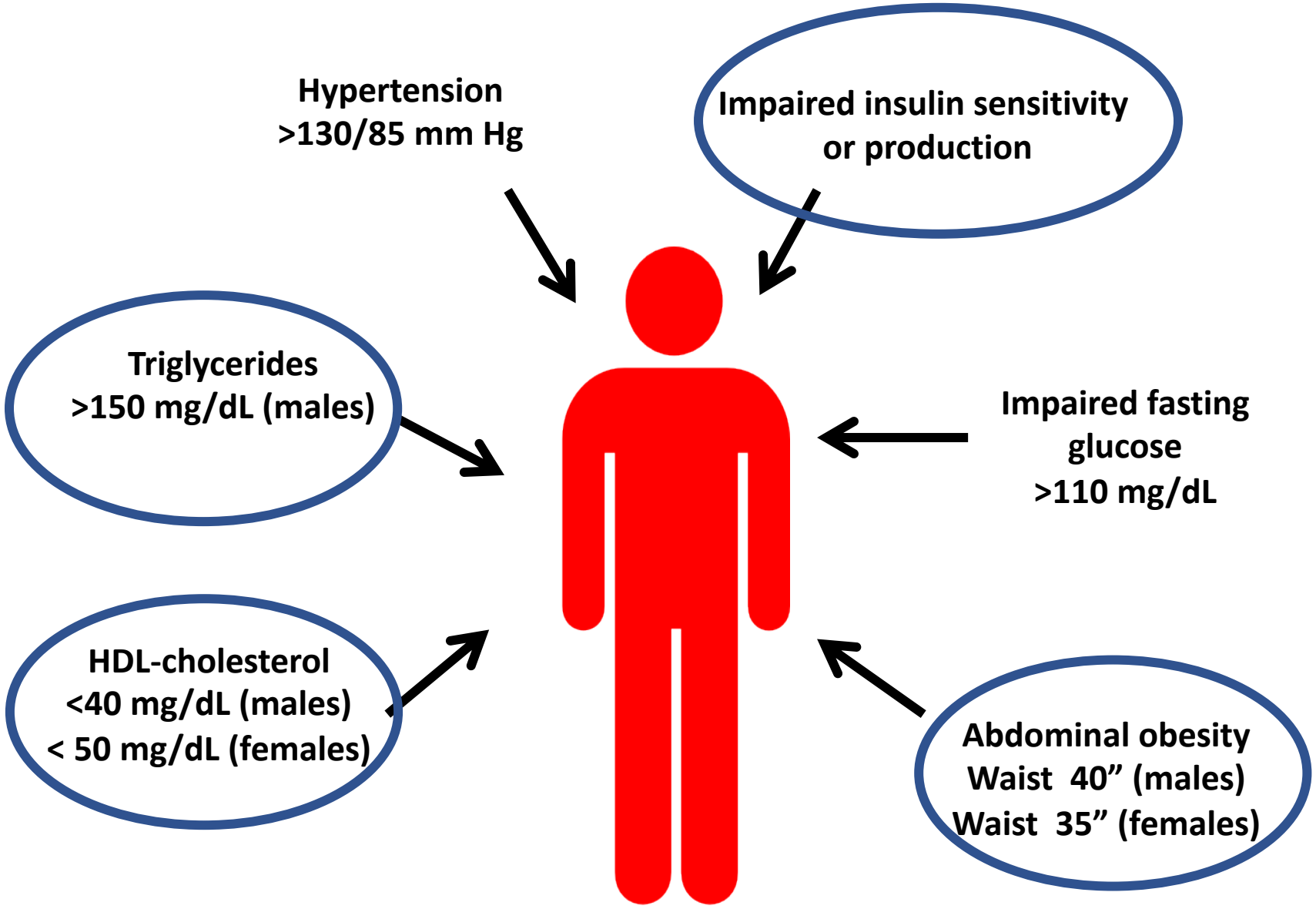


PAS kinase-deficient Mice Display Increased Respiration on a HFHS Diet



Pape et al., Nutrients (2019)

PAS Kinase is Associated with Diabetes-related Phenotypes



Goals Of This Study

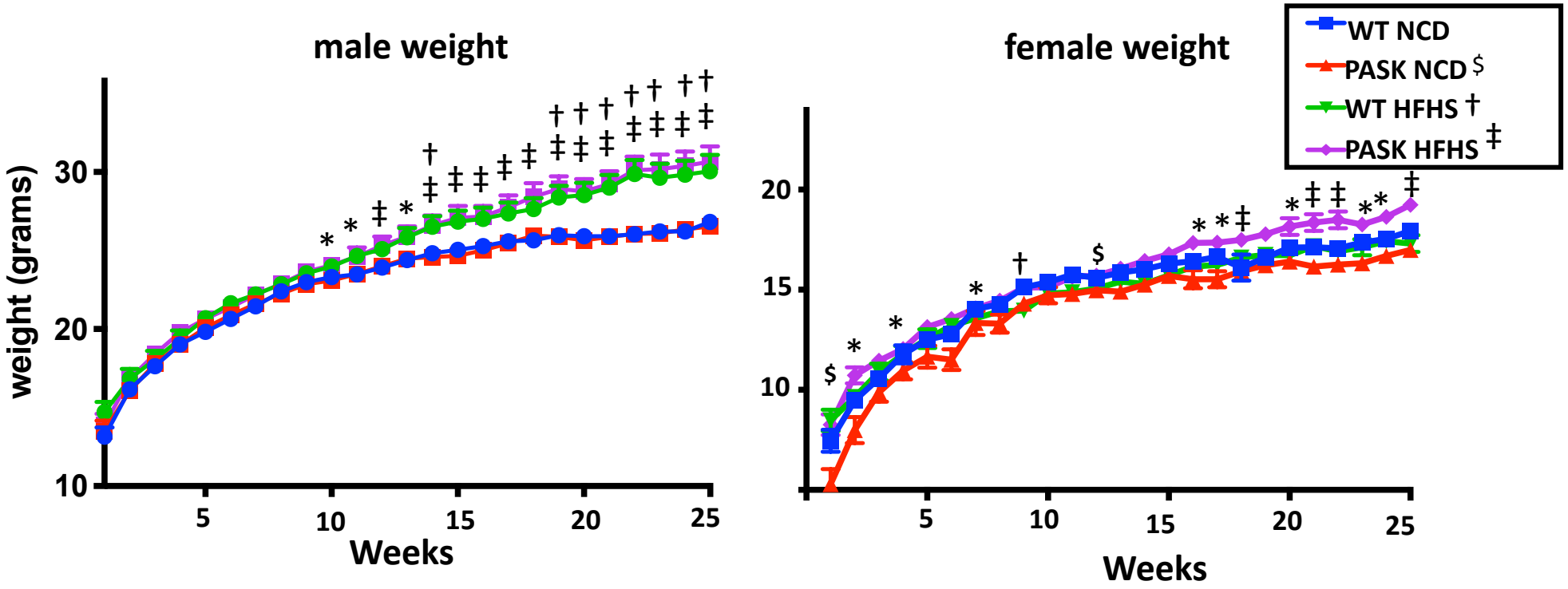
HYPOTHESIS: The Microbiome Will Influence Metabolism in Response to A High Fat High Sugar Diet, Including the Effects of PAS Kinase Deficiency

1) Further Characterize the Role of PAS Kinase in Response to a HFHS Diet, Including Weight Gain, Liver Triglyceride Accumulation, as well as Insulin and Glucose Sensitivity

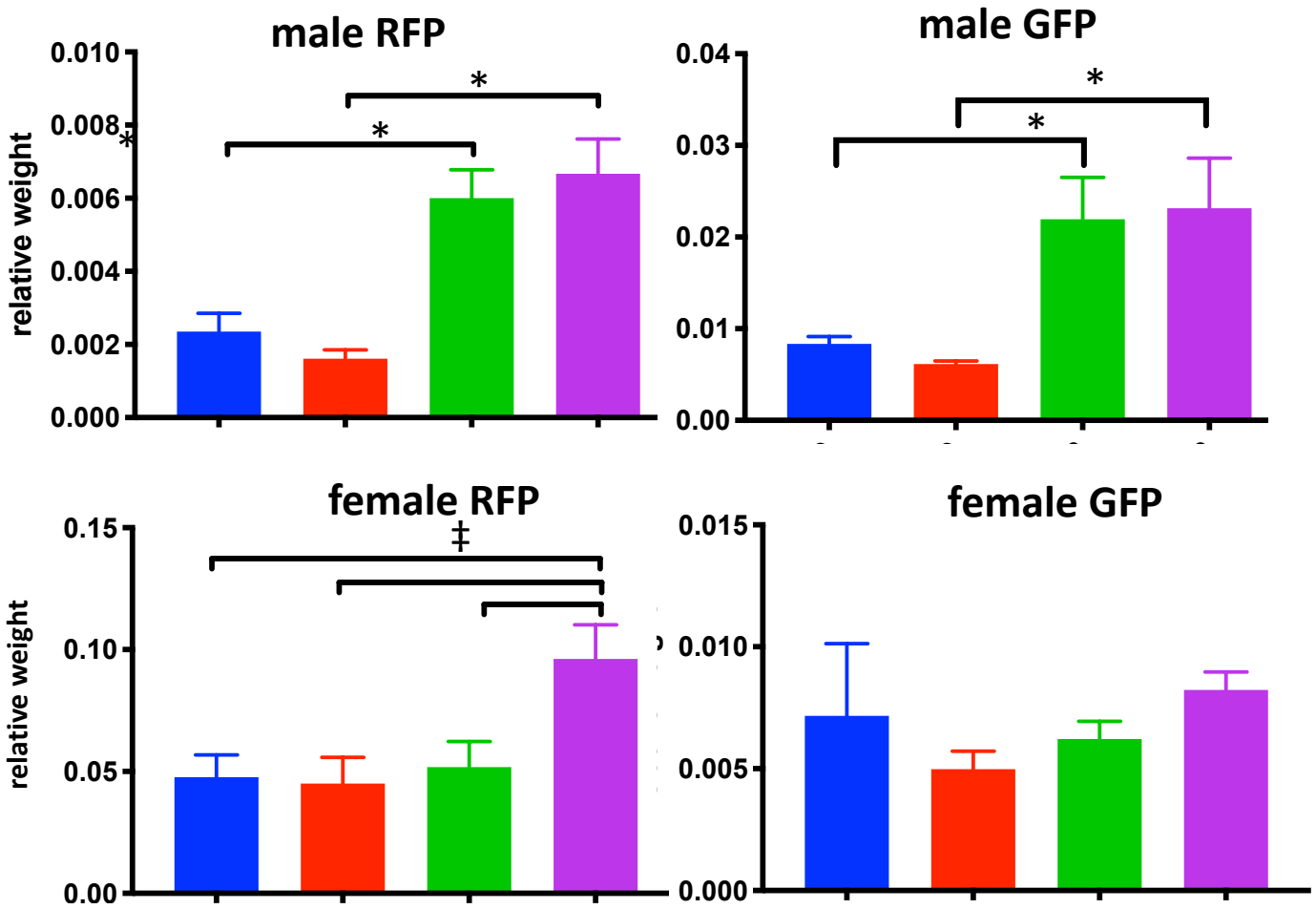
2) Investigate the Interplay Between the Microbiome and PAS Kinase-deficiency In T. hese Phenotypes

Results

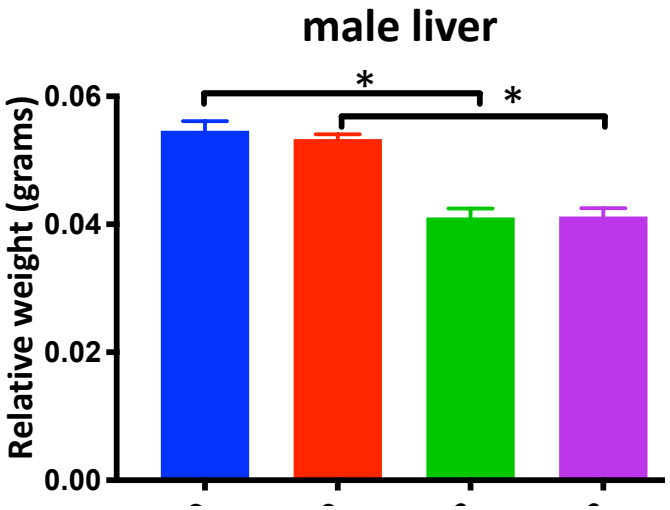
PAS Kinase Did Not Protect Male or Female Mice From Weight Gain on a HFHS Diet

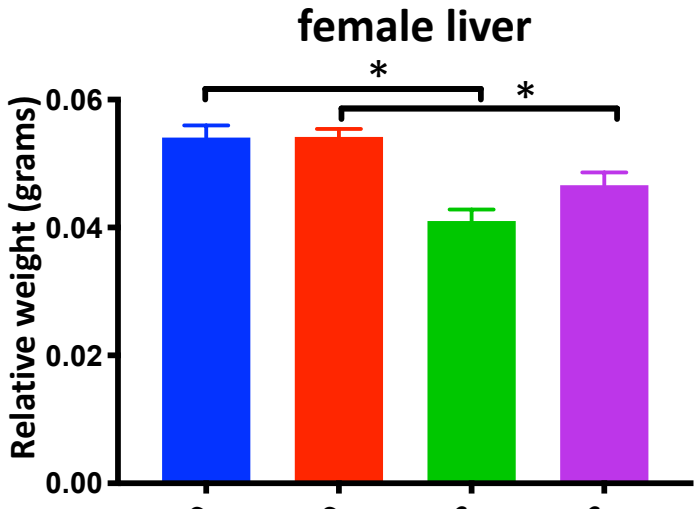


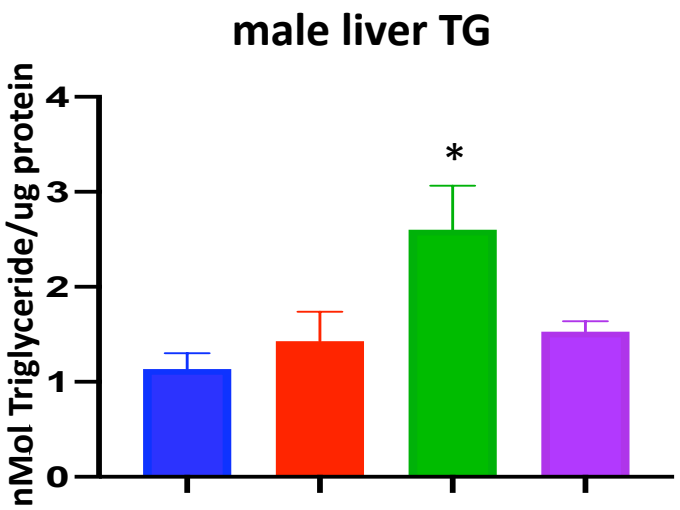
PAS Kinase-deficiency Did Not Protect Against Fat Accumulation In Response to a HFHS Diet



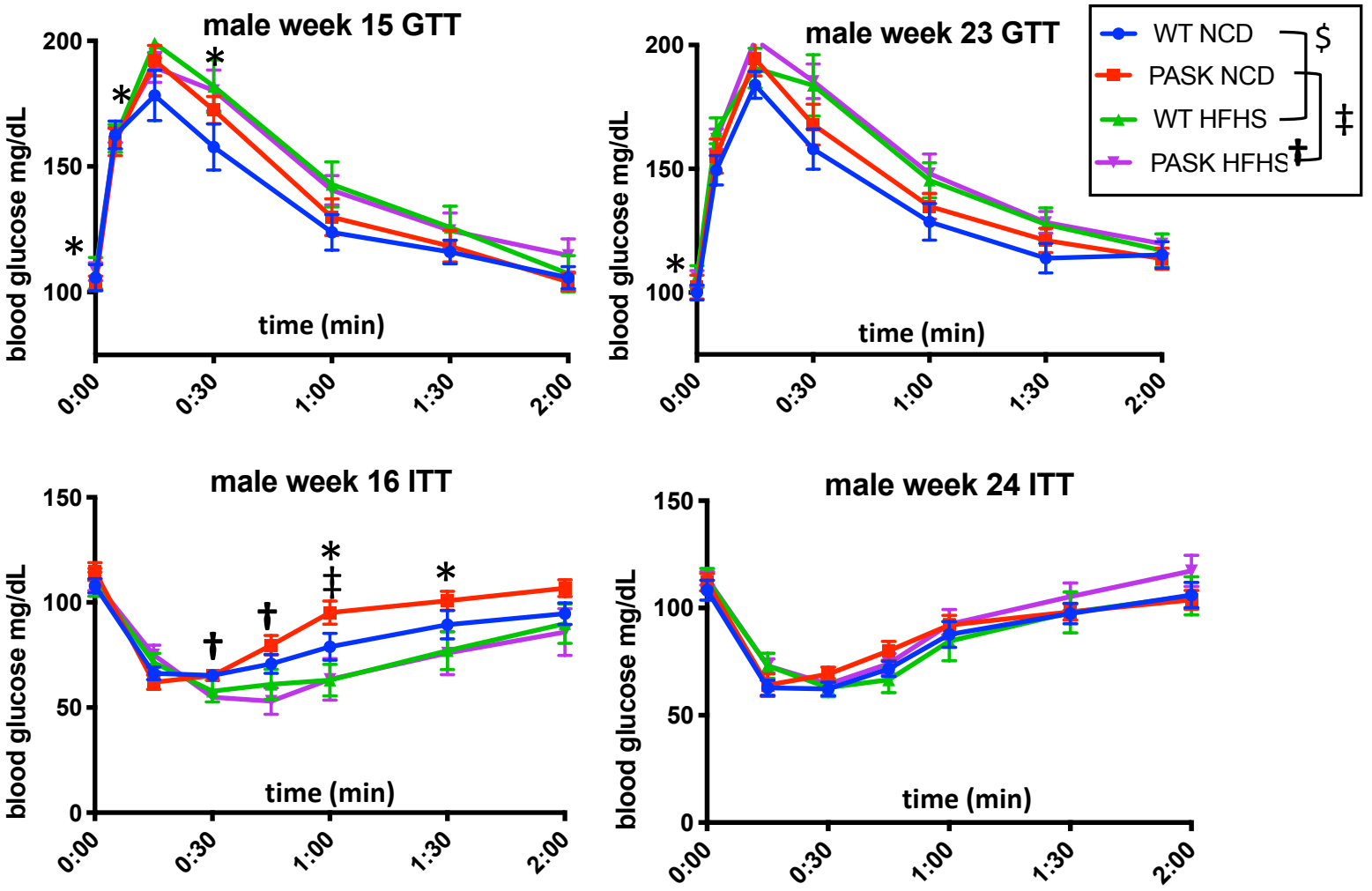
PAS Kinase-deficiency Did Protect Male Mice Against Triglyceride Accumulation In Response to a HFHS Diet



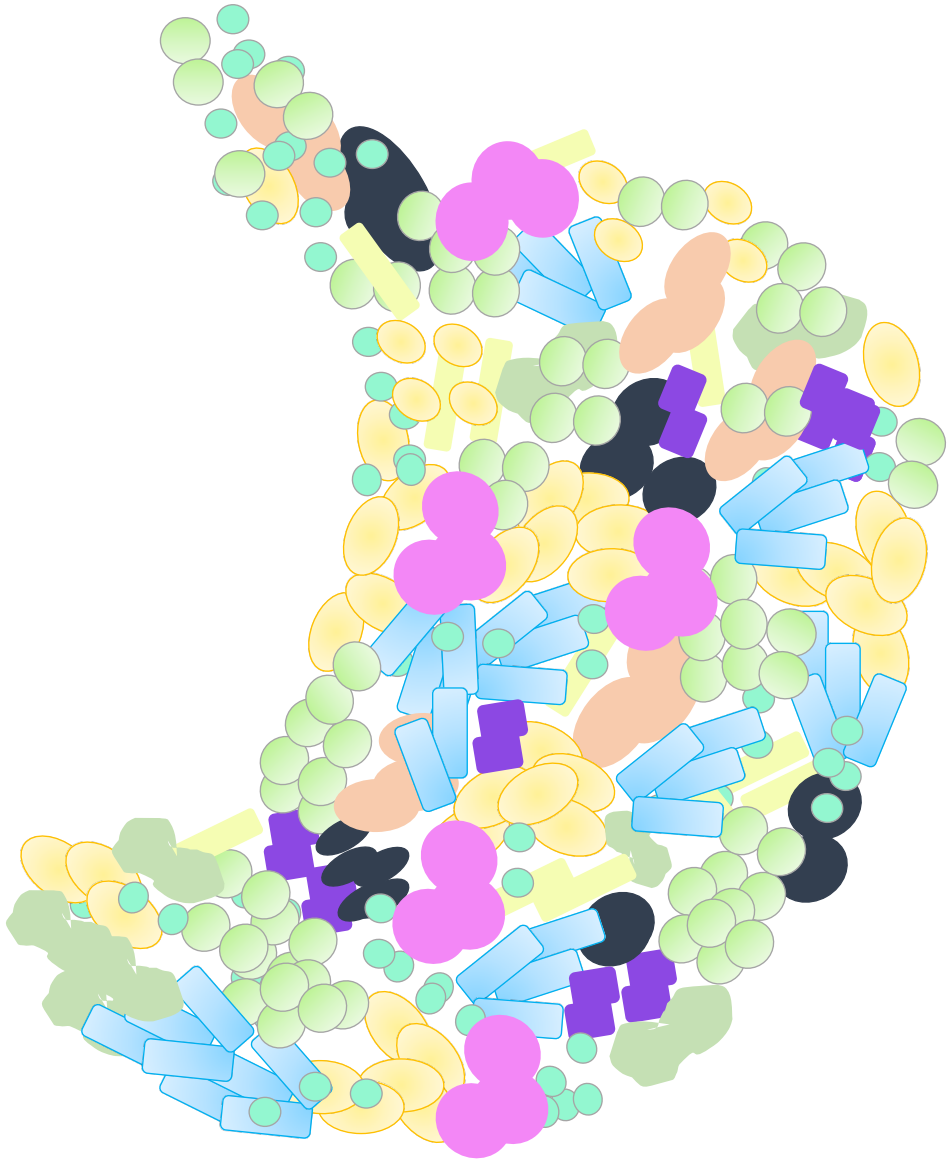




PAS Kinase-deficiency Did Not Appear to Protect Male Mice Against Glucose Intolerance or Insulin Resistance



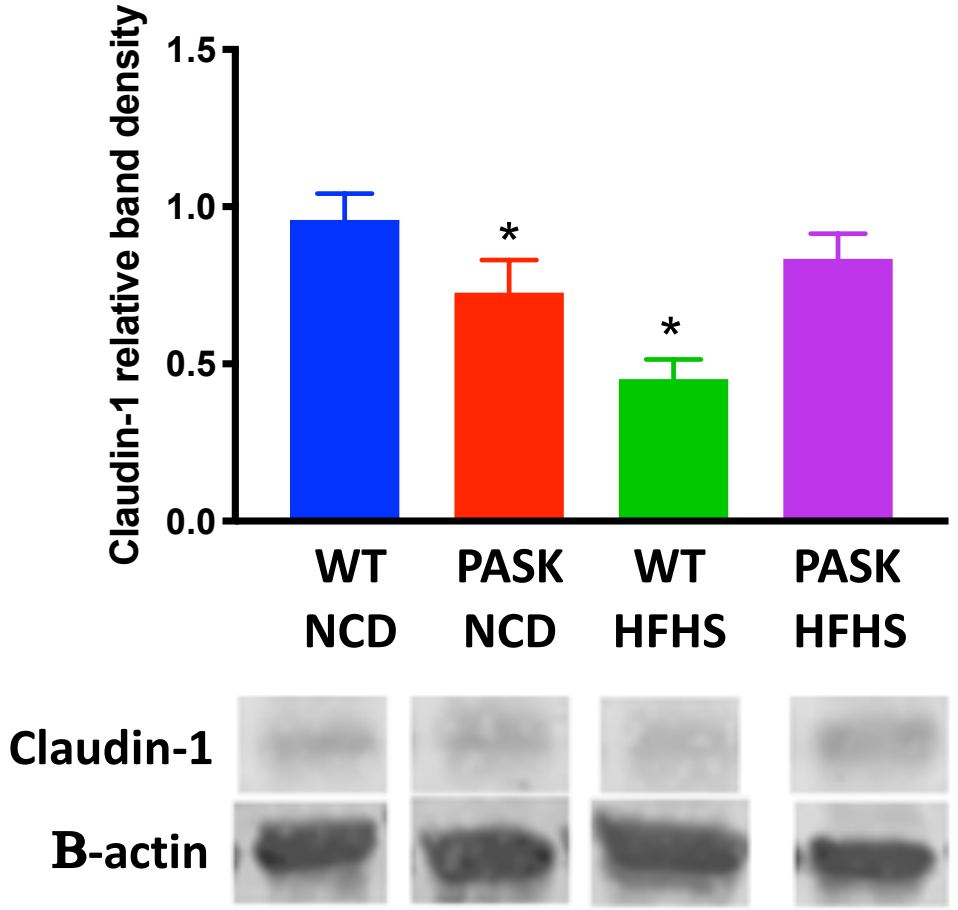
Leaky Gut And Inflammation Contribute to Insulin Resistance



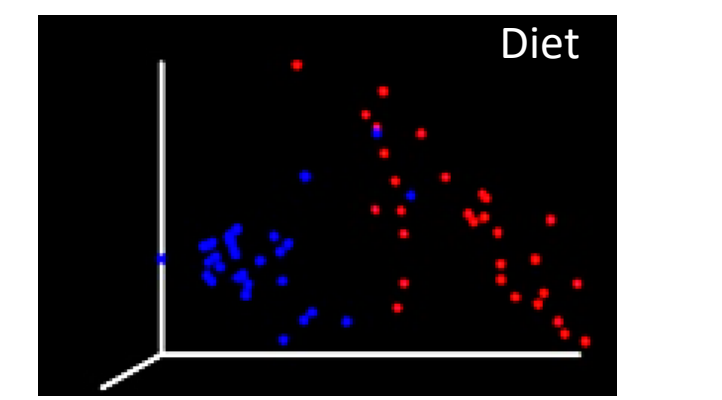
LPS → INFLAMMATION

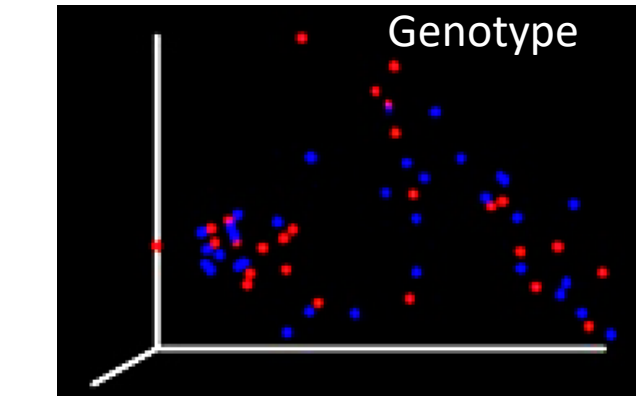
Ashida et al, *Nature chemical biology* 2011
Bergheim et al*, Journal of hepatology* 2008
Cani et al, *Diabetes*, 2008
Lim et al, *Nutrition Research* 2016,
Martinez-Medina et al, *Gut*, 2014

PAS Kinase-deficiency did Protect Against Claudin-1 Decreases, a Marker for Leaky Gut

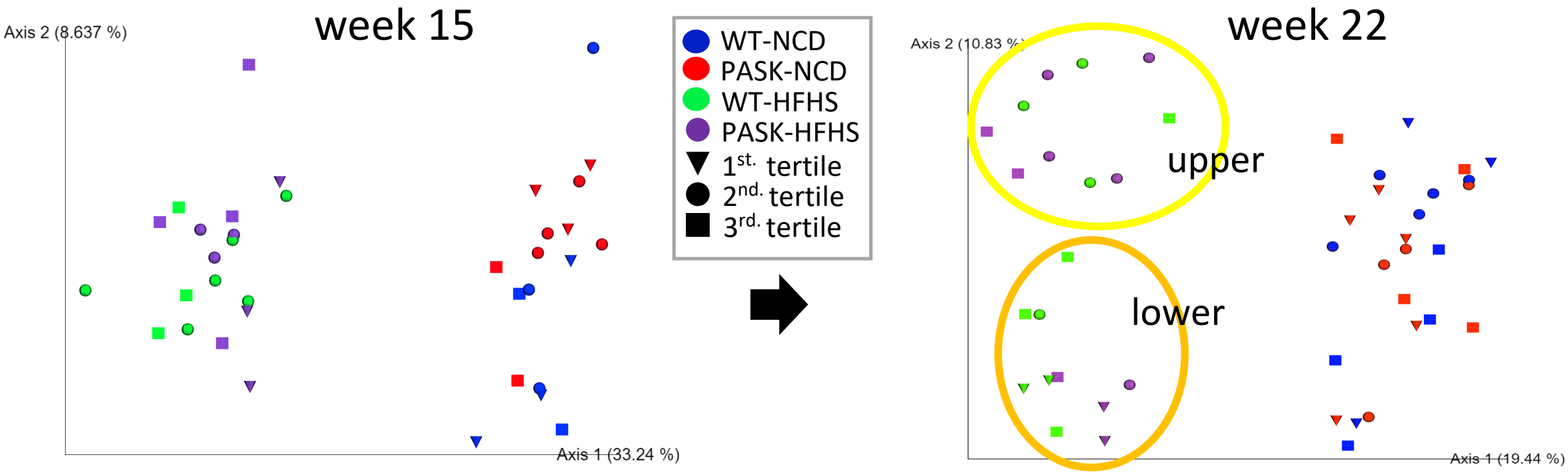


The HFHS Diet Caused a Genotype-Independent Shift in the Gut Microbiome at 22 weeks

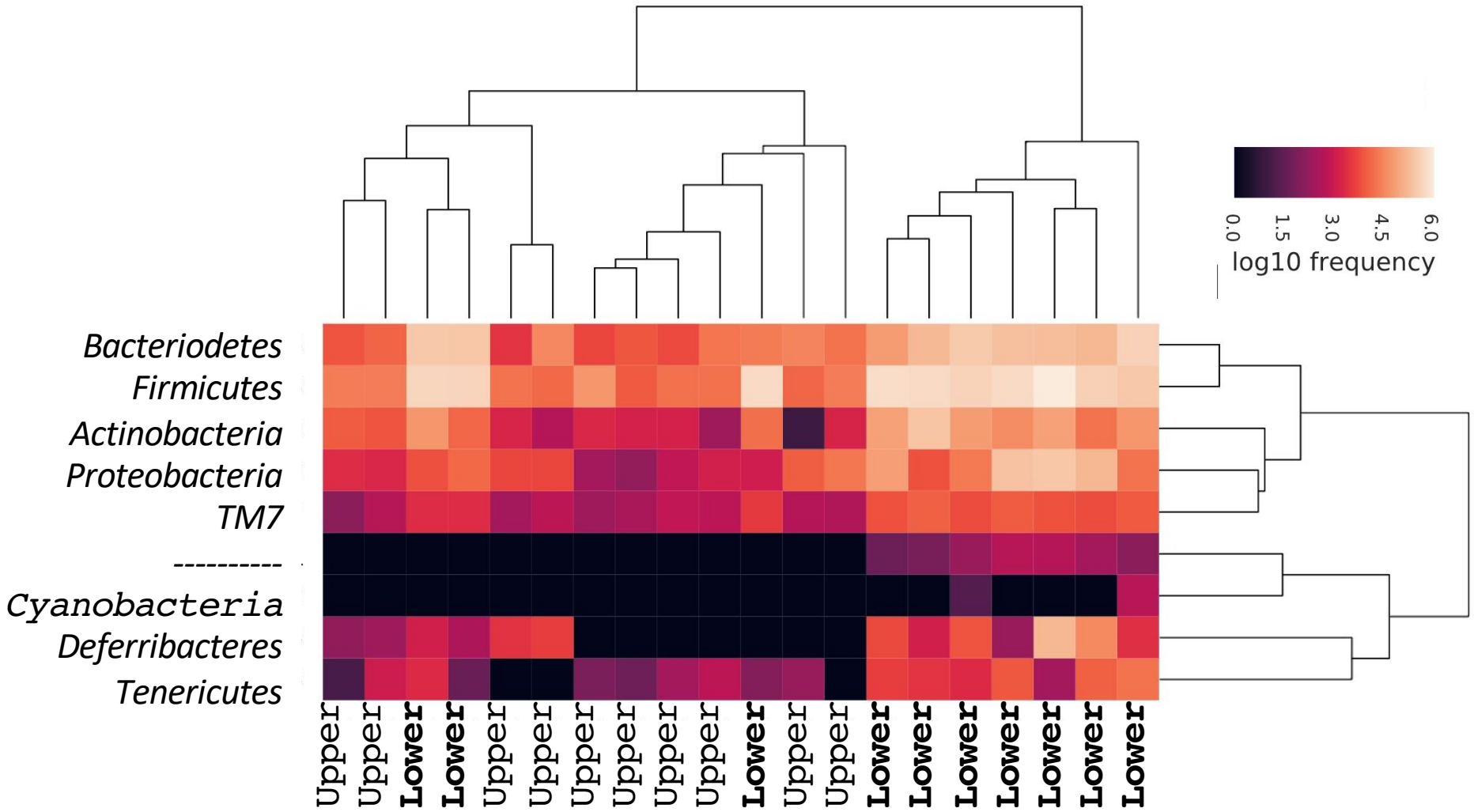




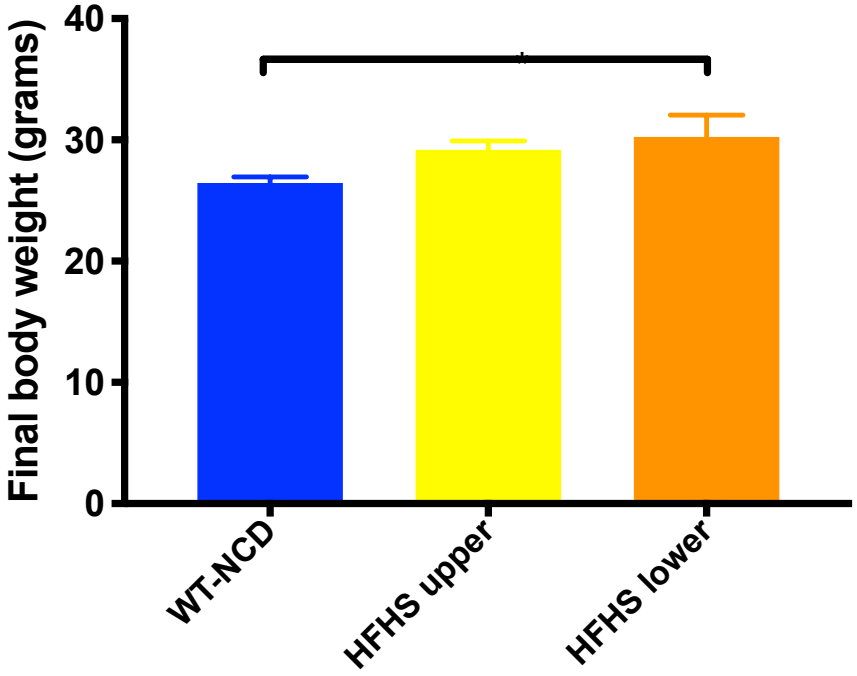
This Shift Resulted in Two Discrete Microbiome Clusters

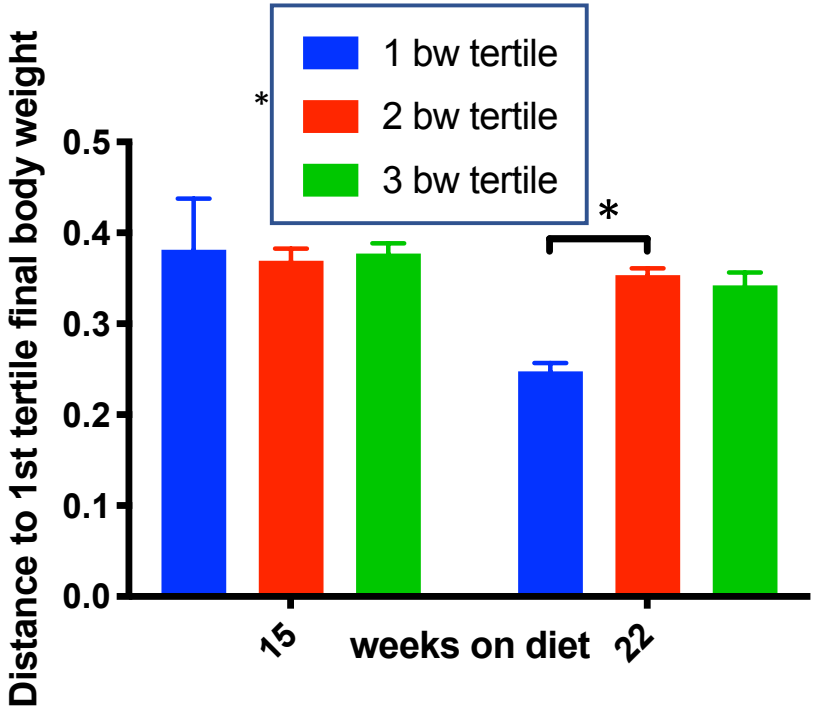


The Lower Cluster was Associated with Increased Bacteriodetes, Firmicutes, Actinobacteria, Proteobacteria

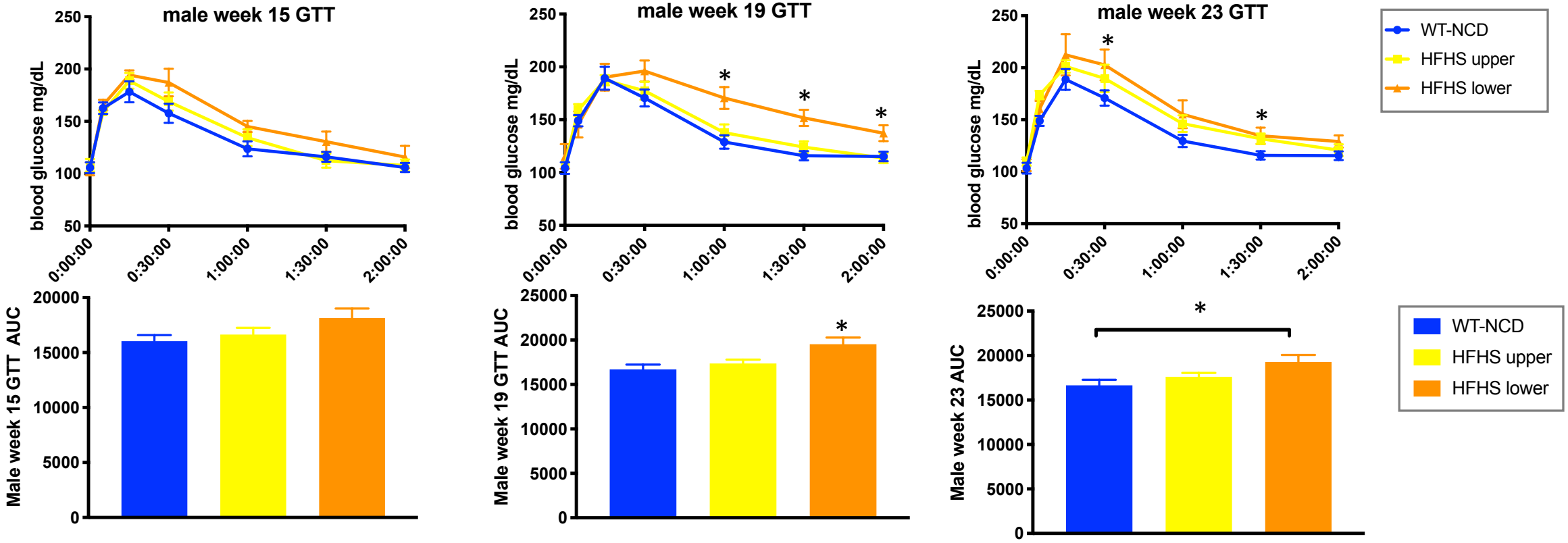


The Lower Cluster was Associated with Increase Weight Gain and Glucose Intolerance

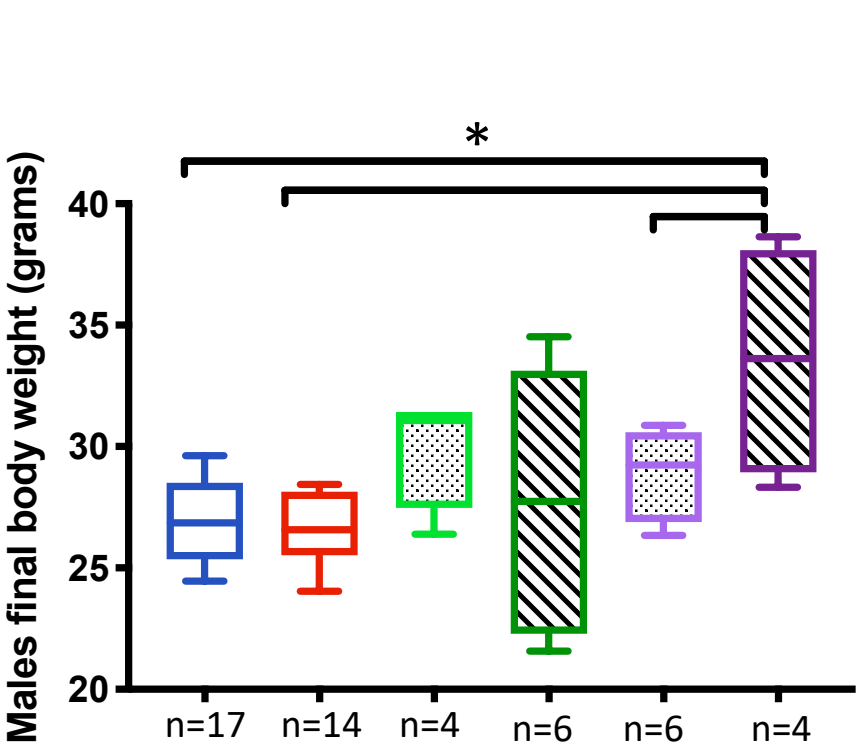


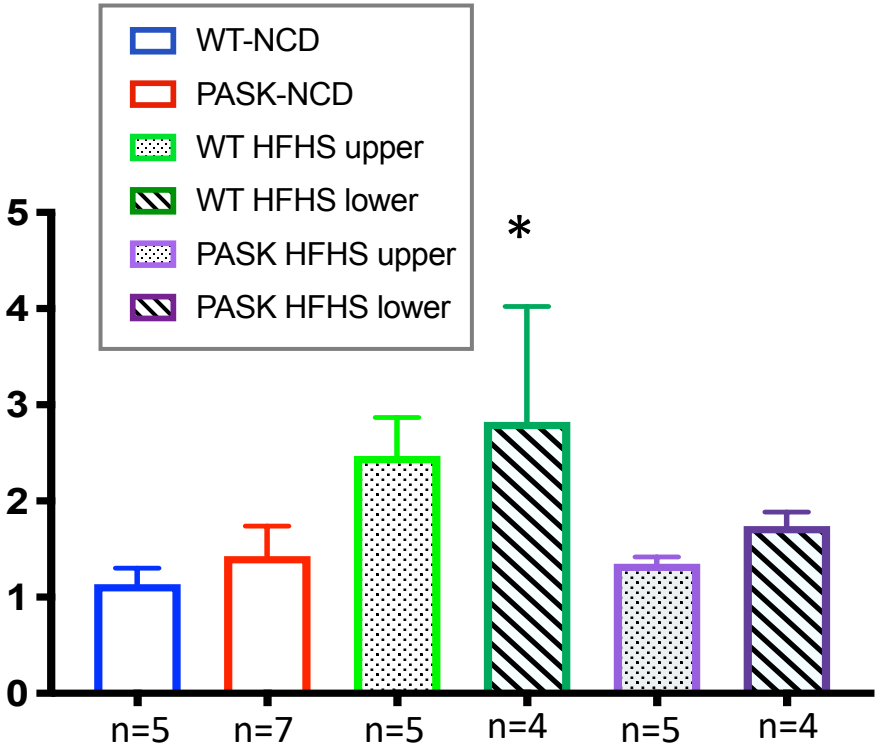


The Lower Cluster was Associated with Increased Glucose Intolerance

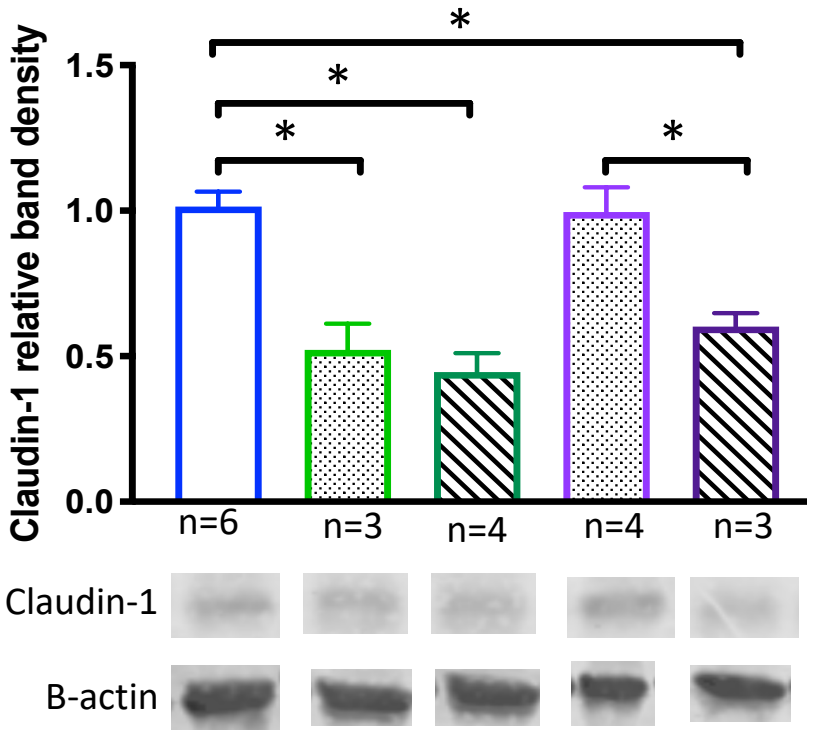


PASK$^{-/-}$ Lower Cluster Mice Display Increased Weight Gain, While WT Lower Cluster Mice Display Increased Liver Triglycerides

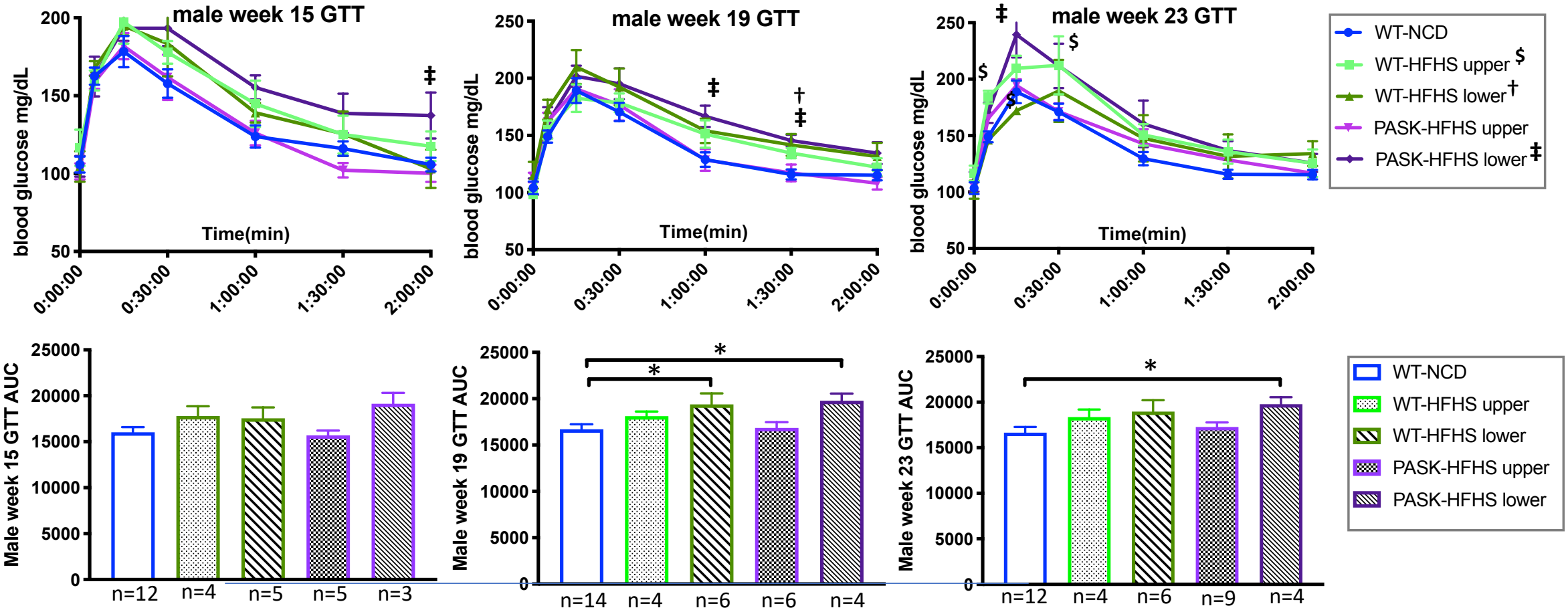




PASK$^{-/-}$ Upper Cluster Mice Are Protected From Decreased Claudin-1 Expression



Upper Cluster Mice Are Protected From Glucose Intolerance



Conclusions

- Mice on a HFHS Diet Display a Forked Shift in the Microbiome at Week 22, that Results in Two Discrete Clusters of Mice
- The Lower Clusters Displays Increases in *Bacteriodetes, Firmicutes, Actinobacteria, Proteobacteria*, etc. and Displays Increased Weight Gain and Glucose Intolerance
- WT Mice Were More Resistant to Weight Gain on the HFHS Diet, but $PASK^{-/-}$ Mice Displayed Resistance to Liver Triglyceride Accumulation and Decreases in Claudin-1 Expression (Leaky Gut)
- $PASK^{-/-}$ mice are protected from Liver Triglyceride Accumulation, Decreases in Claudin-1 Expression, and Glucose Intolerance, but this can be Overwritten by the Microbiome in the Lower Cluster

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