Metabolic impacts of ketogenic diet on PPP1R3B-mediated liver disease

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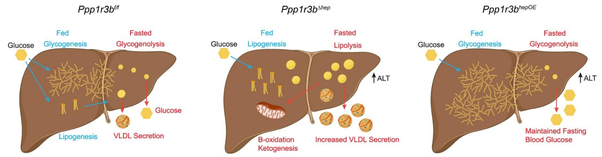
PPP1R3B is associated with multiple cardiometabolic traits

Summary of GWAS findings for *PPP1R3B* locus

SNP	Trait	Minor allele effect
rs4841132	fasting glucose	increases
rs4841132	fasting insulin	increases
rs9987289	fasting lactate	increases
rs9987289	total cholesterol	decreases
rs9987289	HDL-C	decreases
rs9987289	LDL-C	decreases
rs4240624	steatosis (CT)	protective
rs4240624	cALT	increases

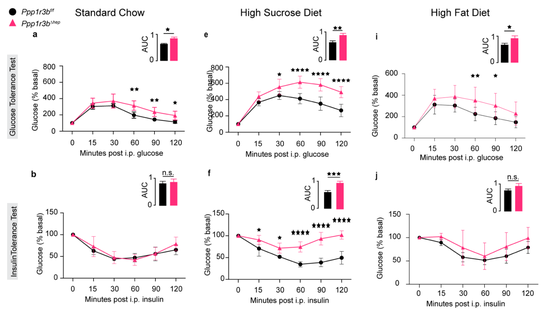
Ppp1r3b is a metabolic switch directing hepatic glucose storage as glycogen



Ppp1r3b^KO mice:
- ↓ glucose tolerance
- ↑ hepatic TG accumulation

→ T2D Liver Damage ←

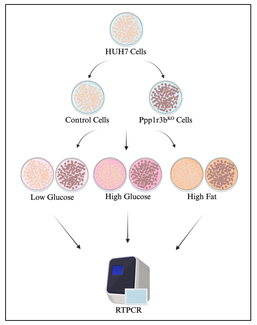
Ppp1r3b^OE mice:
- ↑ fasting glucose
- ↑ liver glycogen

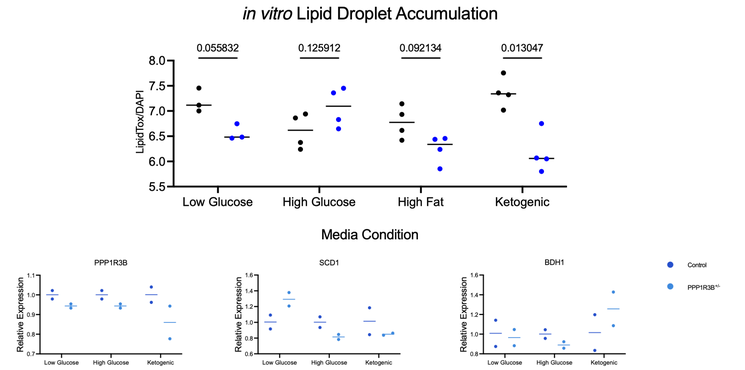


a-j: Metabolic impacts of varying dietary conditions on glucose and insulin response between Ppp1r3b WT and KO

Question: can a ketogenic diet improve glucose and insulin sensitivity and improve metabolic health for dysregulated *Ppp1r3b* expression?

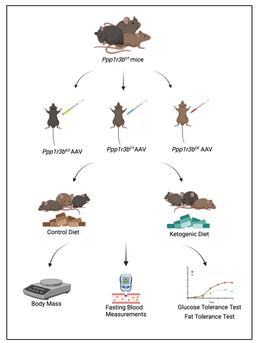
in vitro Ketogenic Conditions in Huh7 Cells



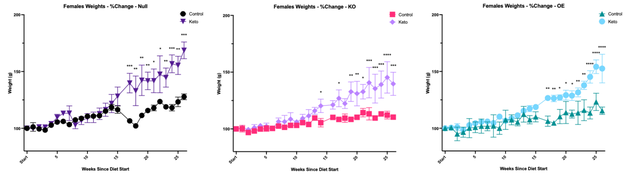


Top-Left: Experimental Design. **Right**: Effects of different media conditions on lipid droplet accumulation in Huh7 cells with siRNA knockdown of PPP1R3B. **Bottom**: mRNA levels of genes in Huh7 cells with CRISPR targeted PPP1R3B deletion (heterozygous).

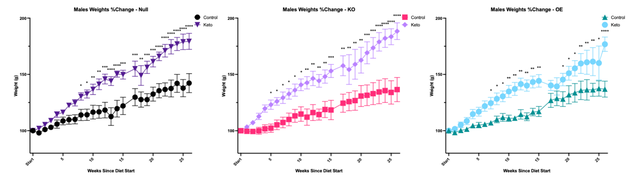
in vivo Keto Diet in Mice Reveals Sex-Specific Responses



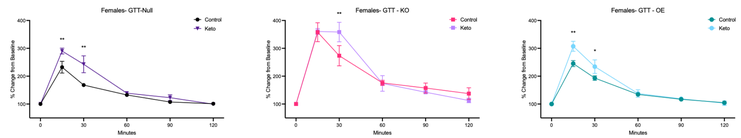
Female



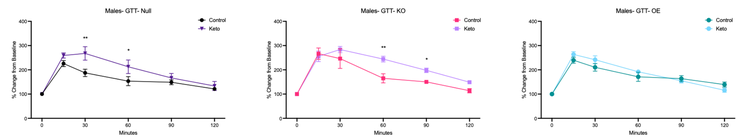
Male



Female



Male



Top-Left: Experimental Design. **Right**: Change in body weight over diet course. **Bottom**: Glucose tolerance test results after 8 weeks of diet.

Future Studies- *in vitro*

- *Use CRISPR to develop homozygous PPP1R3B deletion in human iPSCs*
- *Differentiate cells to hepatocyte-like cells*
- *Optimize in vitro system to test gene-diet interactions and the effects on glucose metabolism and lipid accumulation*
- *Develop liver organoid system for additional studies on metabolic disease pathogenesis*
- *Test possible personal nutrition interventions for metabolic disease*

Future Studies- *in vivo*

- *Measure plasma lipids and liver enzymes*
- *DEXA scans to understand body composition*
- *Promethion metabolic chambers to assess changes in energy utilization and activity*
- *Evaluate liver histology for glycogen and lipid content*
- *Investigate insulin signaling responses*
- *Continue to investigate sex-specific differences in gene-nutrient metabolism phenotypes*
  - *Estrogen and Testosterone levels*

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