Genetic screen to identify novel regulators of lipid metabolism and storage in zebrafish

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Abstract

Adipose tissue (AT) morphology and distribution contributes to the etiology of a wide range of human diseases and metabolic dysfunction including obesity, insulin resistance, and cardiovascular disease. However, the intestinal absorption and transportation of dietary fats, their storage in AT, as well as their subsequent metabolism in other tissues are incompletely understood.

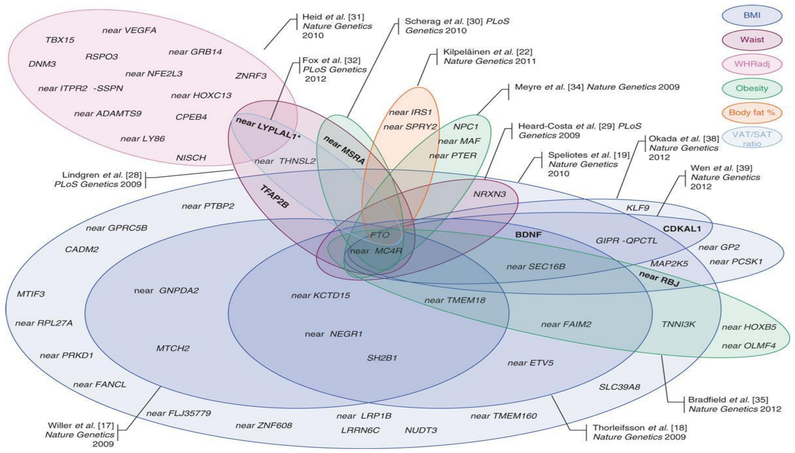
Zebrafish is an exceptional model for vertebrate lipid physiology and *in vivo* imaging. Optical transparency in larval stages allows for investigation of AT distribution and dynamics at an organismal and cellular level using fluorescent vital lipophilic dyes. Conservation between human and zebrafish includes not only anatomic AT development in diverse subcutaneous and visceral locations but also neutral lipid storage in digestive organs including liver and intestine.

Here, we have utilized our methods for in vivo imaging and measurement of zebrafish AT in a genetic screen to identify genes required for AT morphogenesis and lipid metabolism. We obtained ENU mutant alleles from the Zebrafish Mutation Project in genes predicted to have roles in lipid metabolism and AT development. Heterozygous mutant adults were incrossed and progeny screened at approximately 1 month post-fertilization. AT, depots and fish measurements were quantified utilizing fluorescent lipophilic dyes to examine the distribution and morphology of AT as well as body size.

Preliminary results include identification of a novel requirement for Stearoyl-CoA Desaturase in somatic growth and AT development. Scd is involved in synthesizing monounsaturated fatty acid (MUFA) and is upregulated in obesity as well as inducing insulin resistance in humans and mice. Zebrafish homozygous for a mutation in Scd display stunted body morphology coupled with increased AT area and adipocyte hypotrophy.

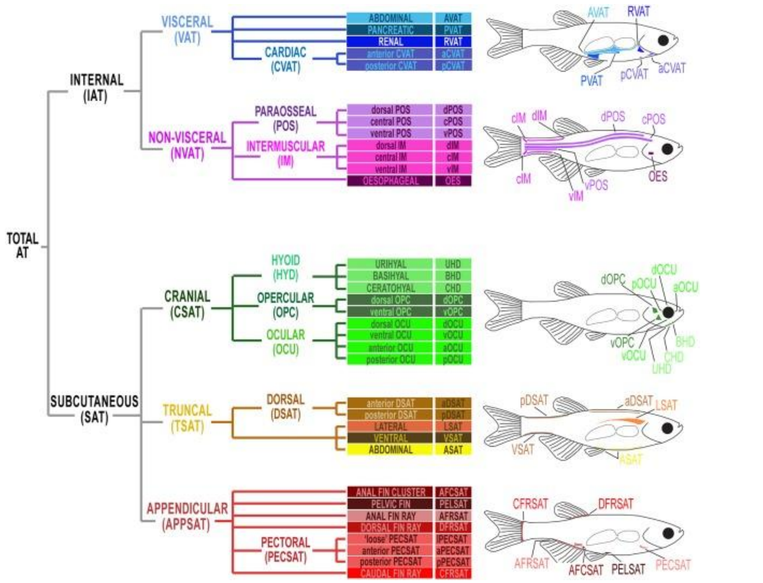
The goal of this work is to identify novel genetic factors regulating lipid storage and AT development and function, which could lead to new treatments for human disease such as dyslipidemia, CVD, Type II Diabetes and associated metabolic disorders.

Obesity-susceptibility loci discovered through human genome-wide association studies for body mass index (blue), waist circumference and waist-to-hip ratio (pink) and extreme and early onset of obesity (green)



Adapted from Lu & Loos, 2013

Zebrafish develop 34 regionally distinct adipose tissues



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Project outline and Zebrafish Mutation Project (ZMP) alleles in Rawls Lab

Identify candidate genes implicated in human adiposity traits

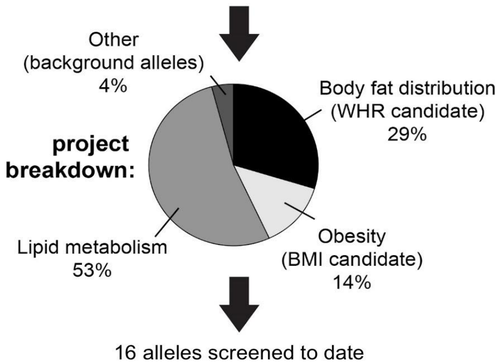
Obtain mutant alleles from ZMP

Nile red labeling of triacylglycerides

Adipose tissue quantification

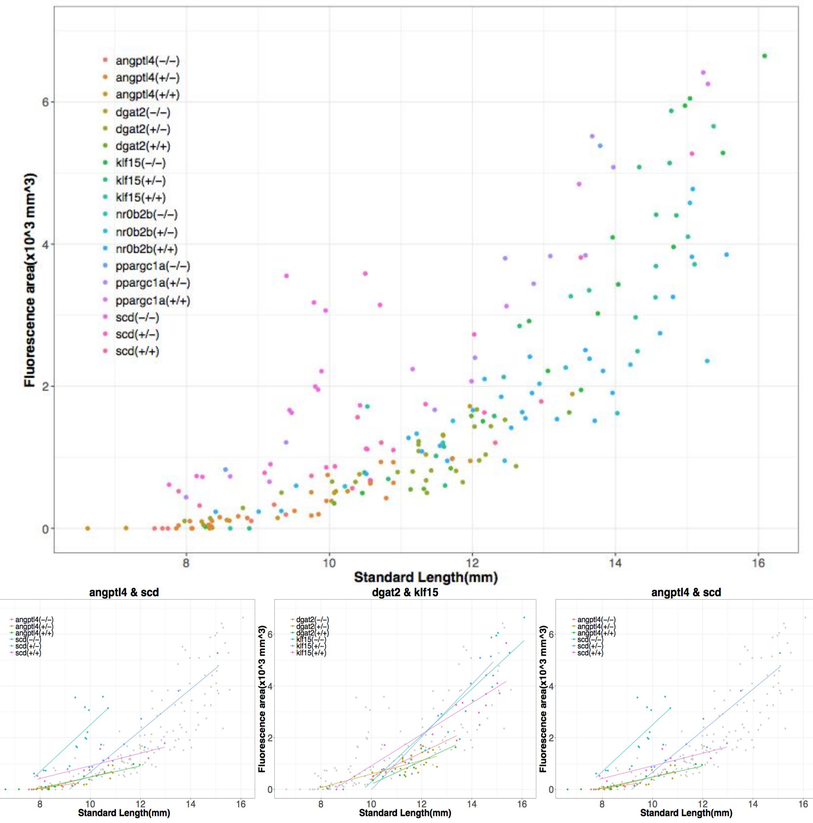
Identify mutants with adipose tissue phenotypes

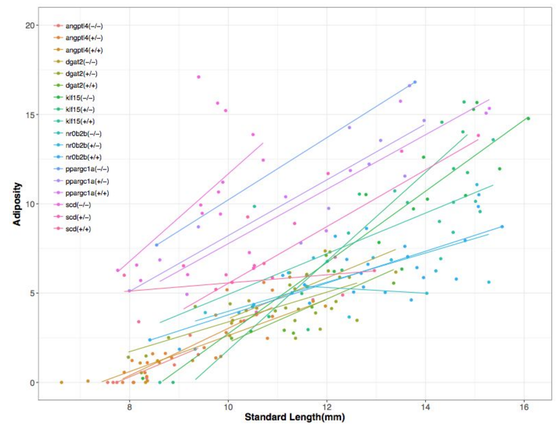
87 alleles received/established in Rawls lab



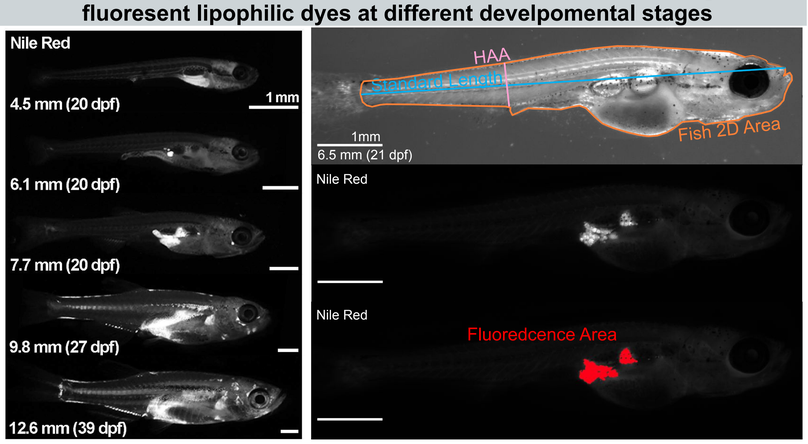
16 alleles screened to date

Zebrafish mutant adipose tissue morphology quantification

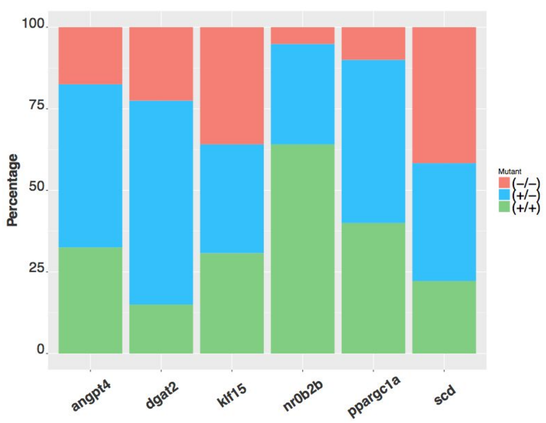




Zebrafish adipose tissues can be visualized and measured using vital fluoresent lipophilic dyes at different develpomental stages



Nr0b2b and ppargc1a Zebrafish Mutants have increased mortality



Zebrafish homozygous for a mutant allele in Stearoyl CoA Desaturase (*scd*) have increased adiposity and stunted morphology