

Pilot project update : 3/12/2015

Includes non peer review and preliminary results

Genetic Investigations into Adiponectin as a Biologic Mediator for Cardio- metabolic Health in African Americans

Co-Investigators:

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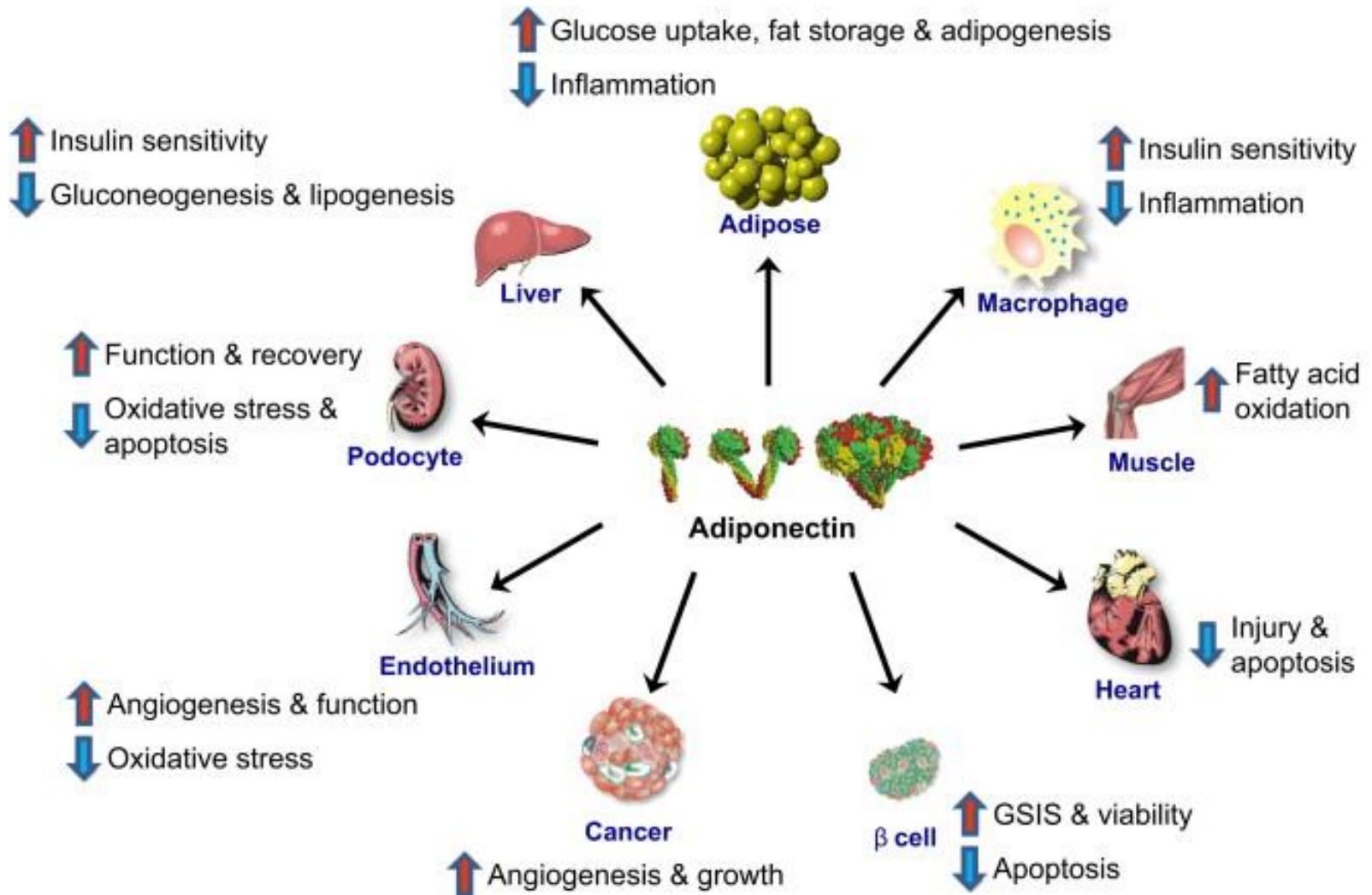
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Research

Center For public health genomics, Wake Forest School of Medicine, Winston Salem,
NC. Pilot project: 125-120340-00000-830021-PILOT. 05/01/2014-04/30/2015

Adiponectin

Physiological and Cellular Response



Specific Aims

Specific Aim 1.

- Quantification of adiponectin protein in fasting plasma samples of non diabetic African-American (AA) subjects which have undergone comprehensive metabolic characterization.
 - The primary goal of this aim is to generate adiponectin protein level data from serum of a suitably powered cohort of African Americans.
 - We will measure total adiponectin in all subjects and HMW adiponectin in a subset of subjects

Specific Aim 2.

- Association analysis of genetic variants with adiponectin levels and their relationship to cardio-metabolic health.
 - Analysis will be conducted using adiponectin transcript (from DK090111, PI: Swapan K DAS) and protein levels (Aim1 PILOT) with genetic variation from the Illumina Omni5+ array (from DK090111) to identify polymorphisms that regulate alterations in the transcript (eSNPs) and protein (pSNPs) level . eSNPs and pSNPs identified will be subsequently evaluated for their contribution to cardiometabolic health.

Specific Aim 3.

- Identify transcripts that are co-regulated with adiponectin gene expression in adipose tissue and adiponectin protein level from plasma in African Americans (AAs).
 - Using a systems biology approach, we will integrate adipose tissue global transcriptome profiling data, adiponectin genotype data, and plasma adiponectin protein levels in AAs to identify
 - 1) Adipose transcripts that are co-expressed and co-regulated with adiponectin transcript level,
 - 2) Adipose tissue transcripts that are correlated with plasma adiponectin level, and
 - 3) adipose tissue transcripts whose expression are associated with polymorphisms in the adiponectin gene.

Study Characteristics

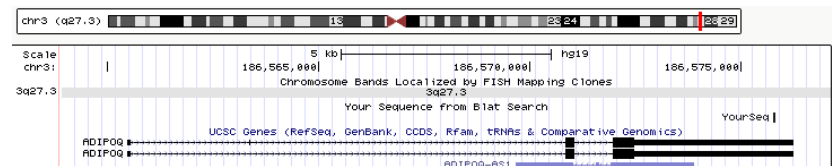
Physiological

Trait	Mean ± Std Dev
n	261
Gender (% Female)	53.60%
Age (years)	40.6 ± 11.4
Glucose Homeostasis	
S ₁ [(μg/l) ⁻¹ .min ⁻¹]**	4.1 ± 3.5
AIKg [(μg/l).min ⁻¹]**	765.7 ± 636.3
Fasting Glucose (mg/dl)	91.4 ± 9.2
Obesity	
BMI (kg/m ²)	28.9 ± 5.6

**from FSIVGT

Genetic

- Genotyping:
Illumina Omni5+Exomev1.1 (~4.5 million markers): **COMPLETED**
- Gene Expression:
HumanHT-12-v4 (>47,000 probes):
COMPLETED
 - Adipose (256 subjects)
 - Muscle (255 subjects)



- Adiponectin Protein Levels :
Total and HMW (subset): **COMPLETED**
 - ELISA performed in the Hypertension Core Lab
 - HMW in 36 subjects (lean/obese)

Adiponectin's Relationship to Cardio-Metabolic Health

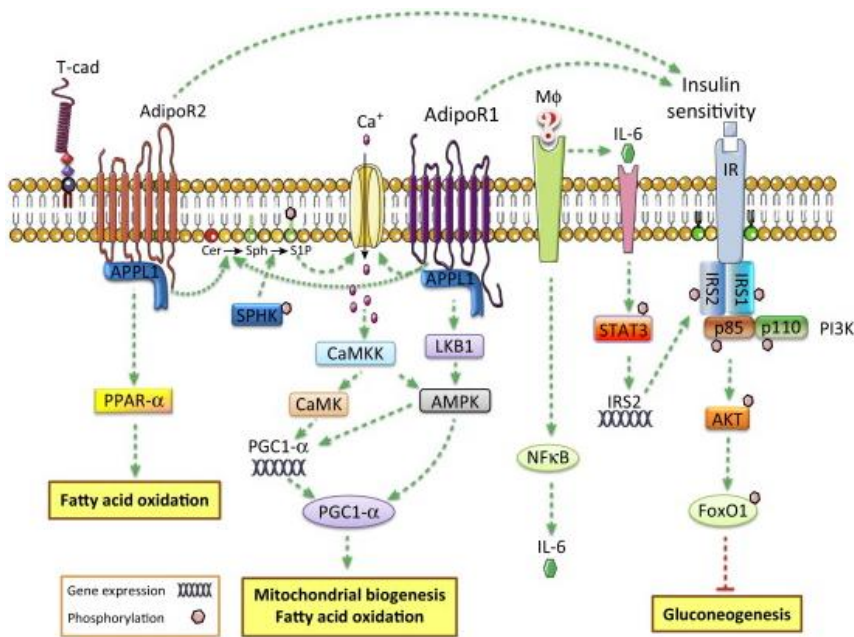
Phenotypic Correlations

Trait	Plasma Adiponectin		ADIPOQ Transcript	
	Spearman Correlation	P-Value	Spearman Correlation	P-Value
Plasma Adiponectin			0.28	1.51E-05
<i>ADIPOQ</i> Transcript	0.28	1.51E-05		
S ₁	0.22	8.89E-04	0.18	6.07E-03
BMI	-0.25	9.31E-05	-0.37	1.24E-09

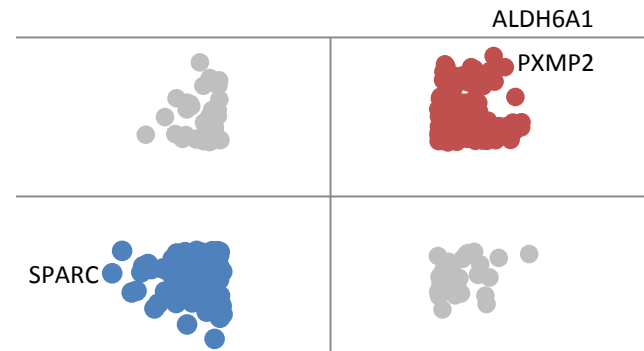
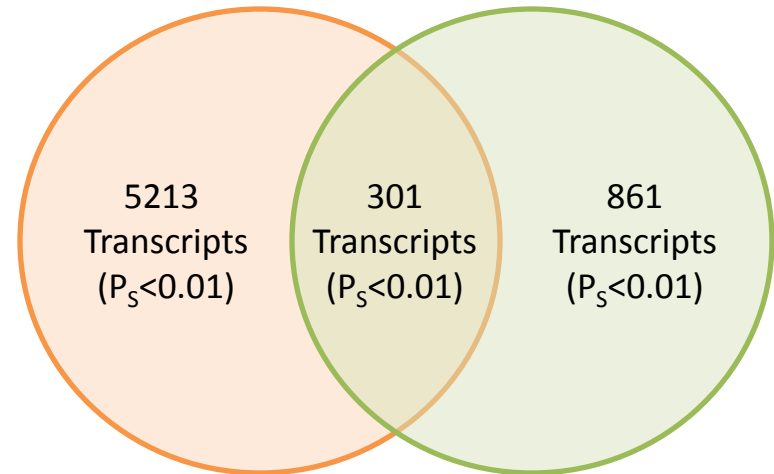
Adiponectin Protein Levels

Correlation among Adipose (Muscle) Transcripts

Known Biology



Novel Biology

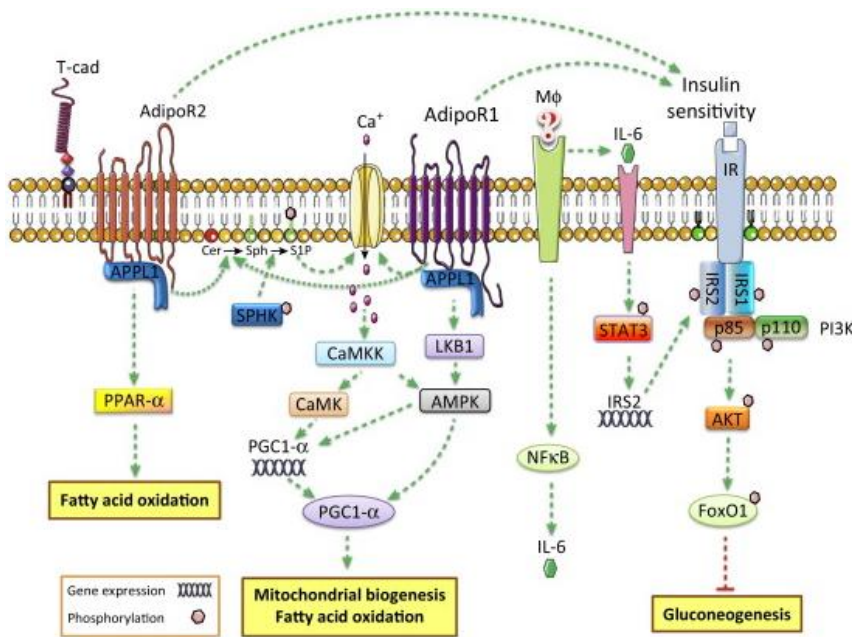


Gene	Genomic Location	Spearman Correlation	Spearman P-value
ADIPOQ	3q27.3a	0.29	6.07E-06
IRS2	13q34a	0.21	0.001442
IRS1	2q36.3b	0.18	0.006475
PPARA	22q13.31d	0.23	0.000426

Adiponectin Gene Expression

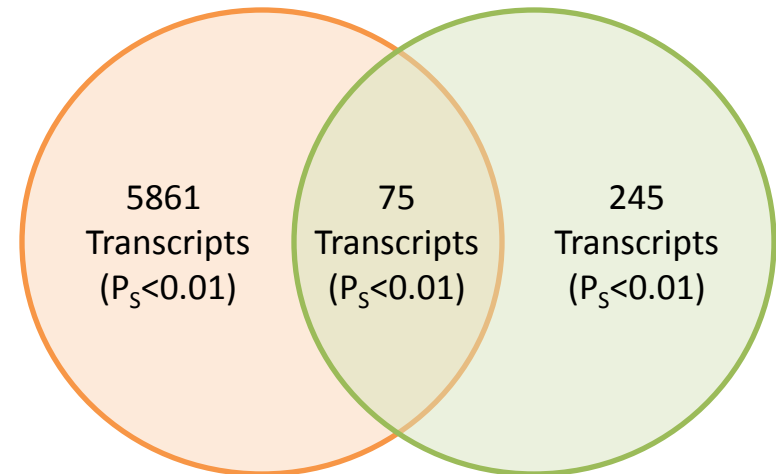
Correlation among Adipose (Muscle) Transcripts

Known Biology



Gene	Genomic Location	Spearman Correlation	Spearman P-value
ADIPOR2	12p13.33b	0.25	6.08E-05
IRS1	2q36.3b	0.27	1.58E-05
IRS2	13q34a	0.25	5.58E-05
PPARA	22q13.31d	0.24	1.19E-04
ADIPOR1	1q32.1d	0.23	3.55E-04

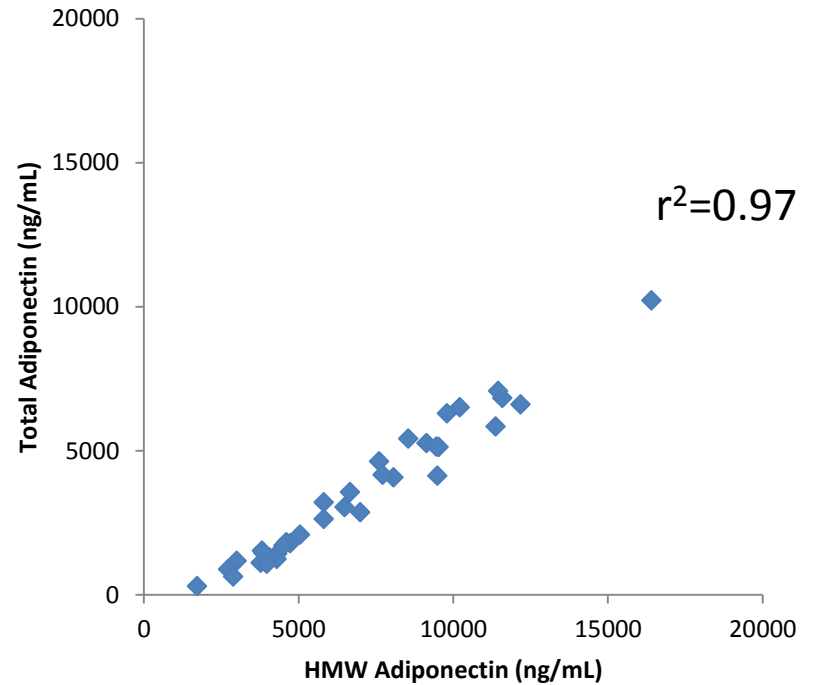
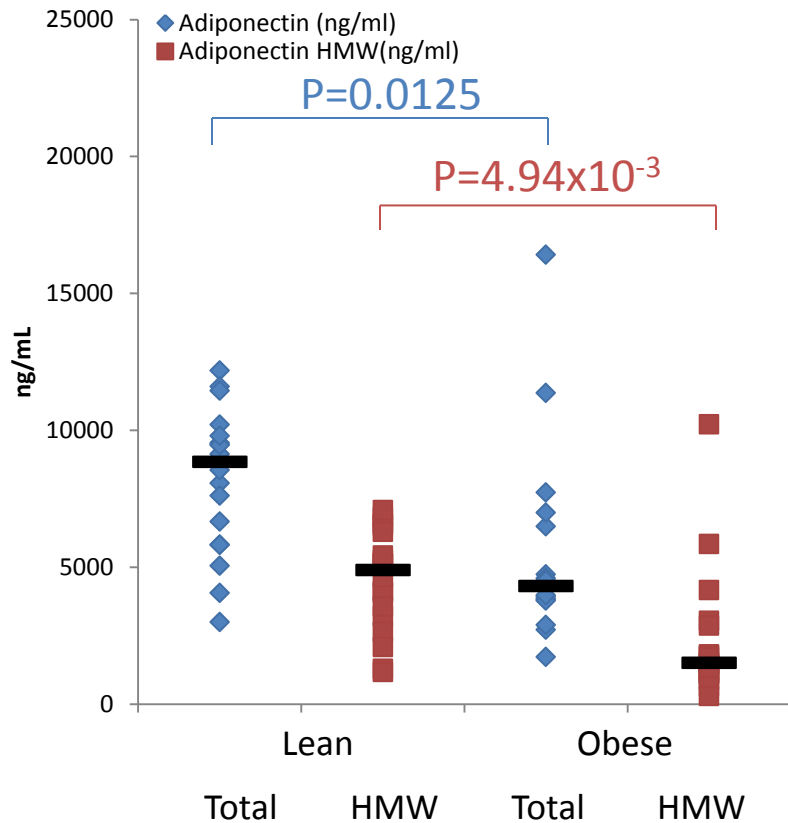
Novel Biology



Symbol	Cytoband	Spearman Correlation
FGFRL1 (2)	4p16.3c	0.57
CS (2)	12q13.2c	0.57
DLST	14q24.3b	0.54
C21orf33	21q22.3d	0.52
ECH1	19q13.2a	0.50
MGC70857	8q24.3h	0.50
PEX19	1q23.2d	0.50
PHYH	10p13d	0.50
ACY1	3p21.1e	0.49
ALDH1L1	3q21.2c	0.49

Secondary Analyses

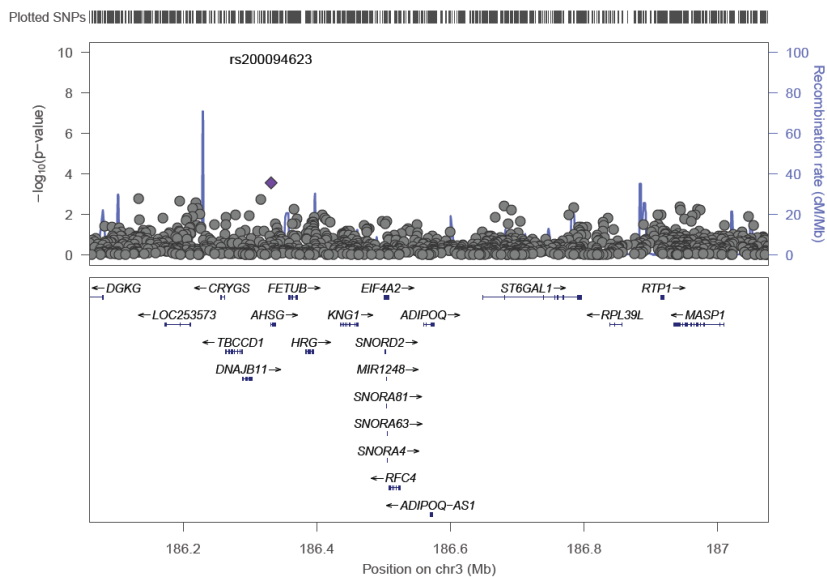
High Molecular Weight (HMW) Adiponectin



Secondary Analyses

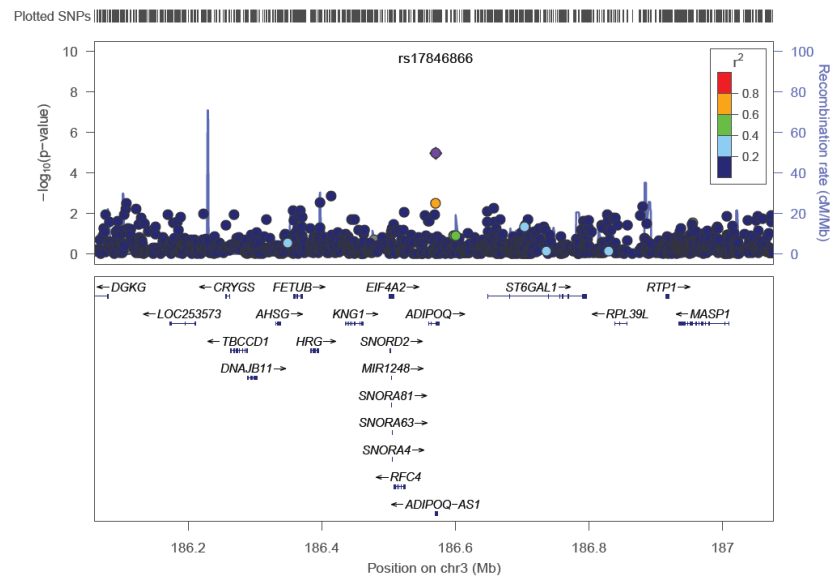
Genome-Wide Association Study: cis (+/-500kb) and trans

Protein Levels(pQTL)



SNP	Beta	P-value	Gene
rs10962016	12606.91	8.15E-15	TTC39B/SNAPC3
rs17557337	18519.1	5.19E-14	GPR158
rs113783014	12847.98	3.37E-13	ANKRD17
rs78192375	12626.72	1.12E-12	ODZ4
rs62570967	10908.86	1.21E-12	TTC39B/SNAPC3
rs79694101	13001.28	2.13E-11	
rs62573015	8859.542	2.2E-11	TTC39B/SNAPC3
rs76271166	11705.64	4.81E-11	B4GALT4/ARHGAP31
rs61528724	11624.02	5.96E-11	
rs17094193	12739.06	9.77E-11	TMEM117

Transcript (eQTL)

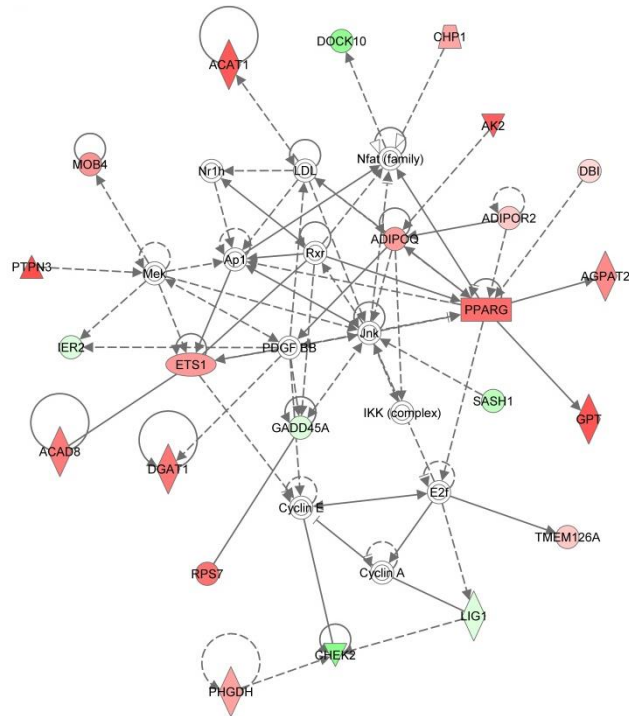


SNP	Beta	P-value	FDR	Reference
rs17846866	-0.56433	0.0000106	0.01364	
rs17366568	-0.34373	0.0031302	0.655873	Heid et al
rs6773957	-0.02511	0.433889	0.990304	Ling et al

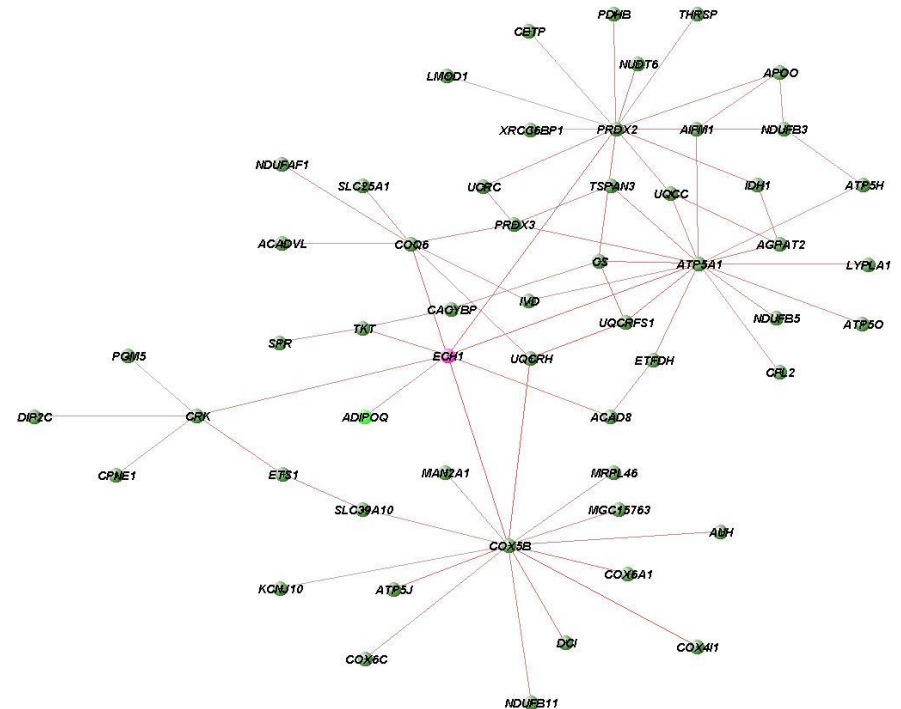
Secondary Analyses

interaction and co-expression network Analyses

Literature-based interaction



Observation-based transcript co-expression network



Project Benefits

Nicholette Allred | WFSM | TBrS

- Preliminary/Complimentary data for a resubmission of a grant application entitled, “*Genetic and Biological Approaches for Understanding the Role of Human Adiponectin*”
 - *Goal:* Explore the biological basis of rare genetic mutations and their impact on cardiometabolic health.

Swapam Das | WFSM | DK090111

- Extension and future funding of the parent grant, “*Mapping Diabetes Susceptibility by Expression Traits in African Americans*”
 - *Goal:* Identify novel variants associated with intermediate phenotypes of insulin sensitivity and gene expression

Mildred A. Pointer | NC Central | 5P20MD000175-12

- Extended research for a subproject entitled “*Genetic investigations into adiponectin as a biologic mediator and a therapeutic target for cardio-metabolic health disparities*”
 - *Goal:* Expansion of our understanding of adiponectin biology and development of key resources for enabling future investigations into adiponectin-modifying treatments