# Sex-Specific Genetic Regulation of Adipose Mitochondria and Their Relationship to Metabolic Syndrome

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## ABSTRACT

**Background and Objectives:** Mitochondria plays a major role in the pathophysiology of complex metabolic traits such as obesity, insulin resistance and fatty liver disease. However, the exact causal relationship between mitochondrial function and these traits is not completely understood. Similarly, sex differences in susceptibility to metabolic phenotypes have been amply described in mice, humans and other species, with females generally exhibiting a beneficial metabolic profile. Yet, the vast majority of previous studies examined sex differences in phenotypes or gene expression in isolation, generating trait or tissue specific results without putting them in context of genetic variation.

**Methods:** To understand the nature of the sex differences and causal relationships, we examined genetic factors contributing to mitochondrial function using a mouse reference population that were extensively phenotyped called hybrid mouse diversity panel.

**Results:** We identified a genetic locus on mouse chromosome 17 that controls mitochondria levels and function in adipose tissue in a sex- and tissue-specific manner. It regulates the expression of at least 89 mitochondrial genes, many of them related to oxidative phosphorylation, as well as mitochondrial DNA levels, in female but not male mice. Overexpression studies indicate that the effects of the locus are mediated by the Ndufv2 gene that encodes a subunit of the mitochondrial complex-I. The gene is activated by gonadal hormones and is regulated in cis only in females.

**Conclusion:** We report that adipose mitochondria are regulated by both genetic variation and sex hormones and that high levels are an important determinant of metabolic syndrome traits.

## BACKGROUND

Sex/Gender

HMDP – 100 strains

Females are Resistant

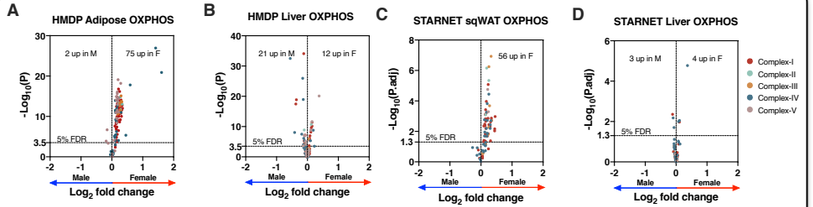
**Phenotypes**

- Obesity: FEMALE < MALE
- Insulin Resistance: FEMALE < MALE
- Liver Steatosis: FEMALE < MALE

MitoCarta2.0: 911 genes in HMDP

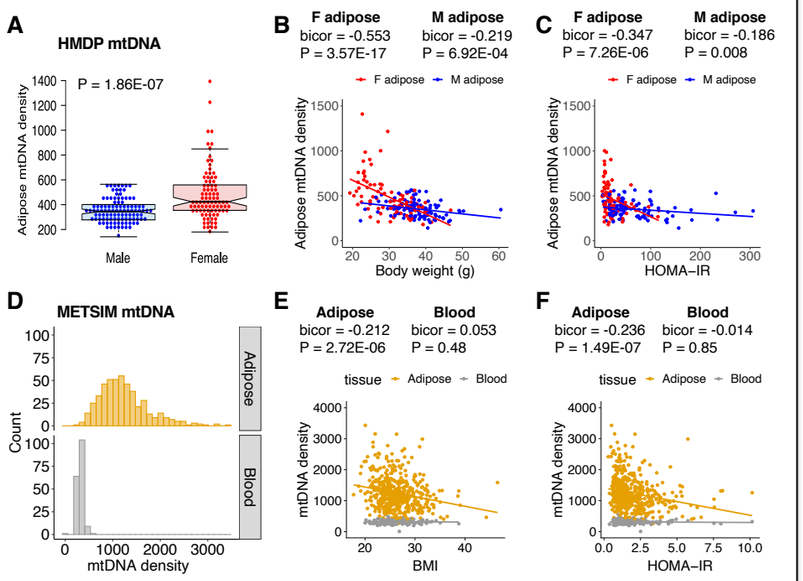
## RESULTS

**Figure 1.** Sex- and tissue- specific profiles of OXPHOS genes in both mice and humans.




OXPHOS genes: *Female HMDP (75/91 genes up); Female STARNET (56/80 genes up); no enrichments in liver.*

**Figure 2.** Adipose mitochondria levels strongly predict metabolic traits in both mice and humans.




mtDNA content: *Female HMDP (~30% high); Negatively metabolic-related trait correlations in both mice (HMDP) and humans (METSIM)*

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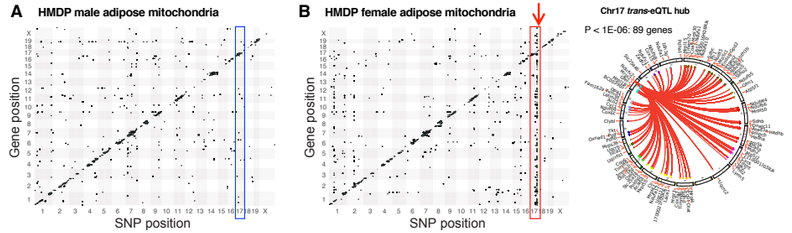
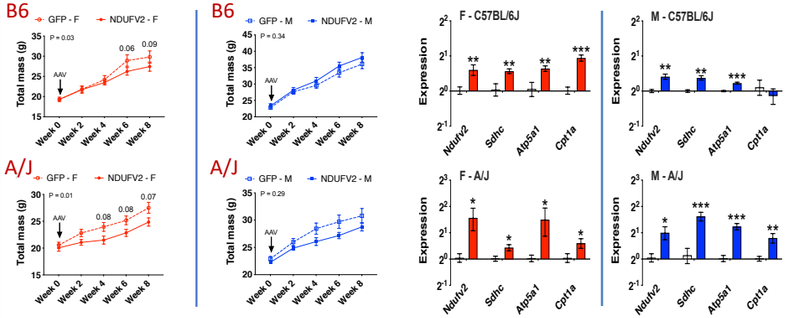
## RESULTS

**Figure 3.** Sex-specific genetic architecture of adipose mitochondrial gene expression.




OXPHOS genes: *Female HMDP (unique trans-eQTL hotspot) that controls ~89 genes (P < 1e-06).*

**Figure 4.** Animal overexpression studies to validate the role of adipose NDUFV2 in obesity.




NDUFV2 overexpression: *Reduces obesity (females of both strains) and controls OXPHOS genes.*

## CONCLUSIONS

- OXPHOS genes: both tissue/sex-specific upregulation in both mice and humans.
- mtDNA content: high in female adipose.
- Functional role in metabolic traits in females.
- *Trans*-eQTL hub: unique to female adipose.
- *Trans*-eSNP affects OXPHOS genes.
- NDUFV2 is a potential candidate in influencing obesity in females.
- Supercomplex analyses -> I/III and I/III/IV.