PATERNAL MITOCHONDRIA ARE IMPORTANT FOR OFFSPRING METABOLIC HEALTH

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INTRODUCTION – Epigenetic inheritance describes non-genetic transmission of acquired complex phenotypes from parents to offspring. As such, epigenetic inheritance can contribute to our understanding of the exponential rise in the incidence of diabetes and obesity worldwide. While maternal effects have been documented in humans and animal models, paternal effects are still debated. Known as the powerhouse of the cell, mitochondria carry out a wide range of actions regulating key cellular and organismal functions, such as apoptosis, calcium homeostasis and heat production. Mutations affecting mitochondrial structure and function lead to a plethora of life threatening phenotypes.

METHODS – We interrogated the IMPC resource of gene/phenotype associations in the mouse to understand whether parental mutations in genes important for mitochondrial function have intergenerational consequences. In particular, we compared phenotypic terms of metabolic health (glucose and lipid metabolism, body weight and composition, liver function and indirect calorimetry) in two populations of C57BL6 animals sired from either mutant (WT^{het}) or C57BL6 control (Baseline) parents. We further validated the results in an environmental model of mitochondrial dysfunction (the diet-induced obesity model) and cross-referenced them to a large human birth cohort.

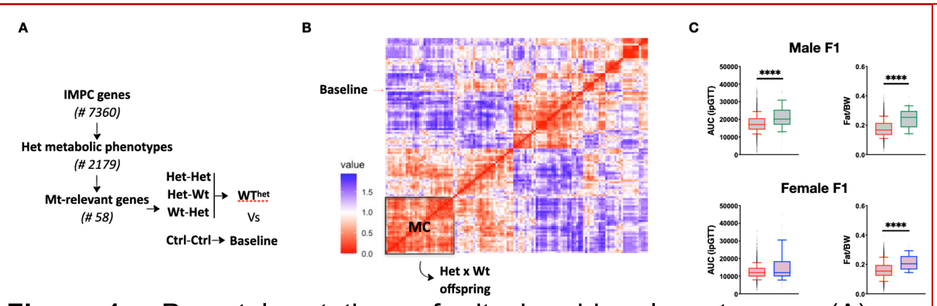


Figure 1 – Parental mutations of mitochondria-relevant genes (A) are analysed for intergenerational effects. Wt offspring of mutant fathers (MC – B) show impaired glucose tolerance and increased adiposity (C).

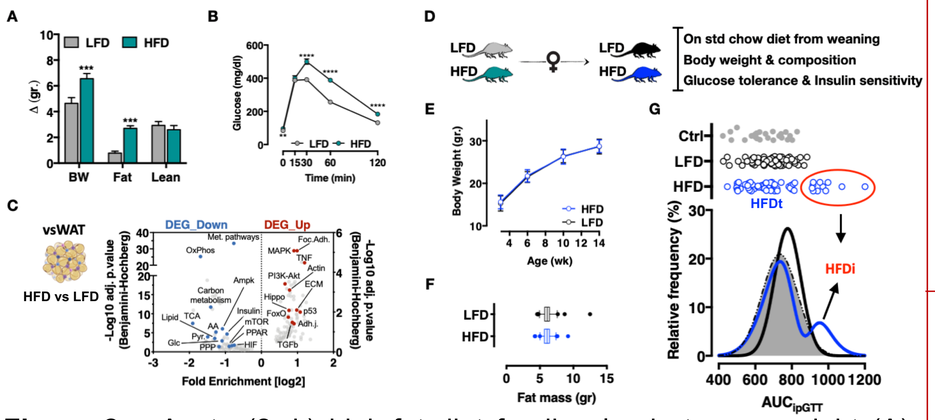
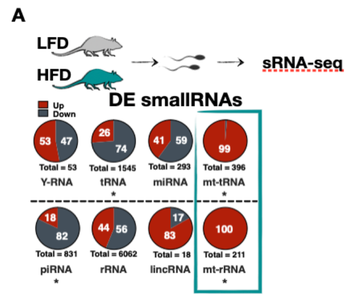
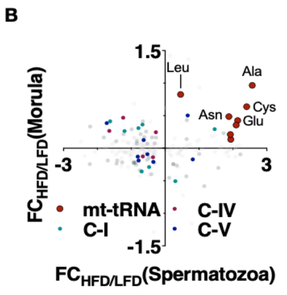
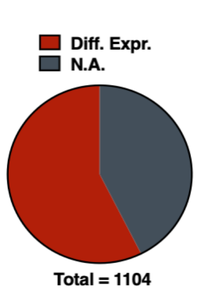
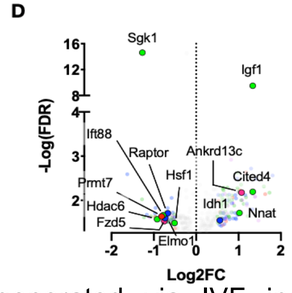


Figure 2 – Acute (2wk) high-fat diet feeding leads to overweight (A), glucose intolerance (B) and impaired adipose tissue metabolism (C) in male mice. Unexposed offspring of HFD-fed males and unexposed females (D) show a 30% penetrant glucose intolerance (HFDi – G) despite no change in body weight (E) and adiposity (F).









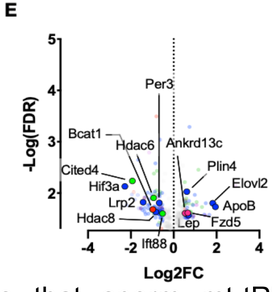
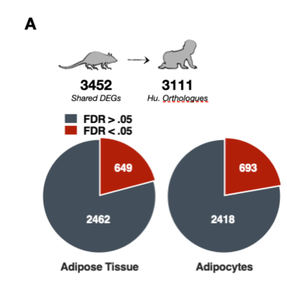
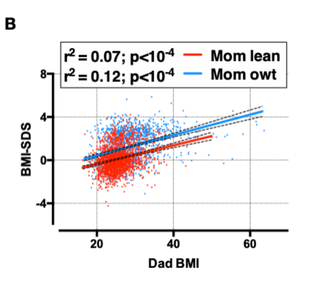


Figure 3 –. Acute HFD feeding alters the composition of the sperm smallRNA pool with specific upregulation of mito derived tRNAs (A). RNA-seq of embryo generated via IVF indicates that sperm mt-tRNAs are inherited at fertilization (B). 60% of mt-tRNAs predicted targets are differentially expressed (C) in F1 adult muscle and vsWAT (HFDi vs HFDt D-E).





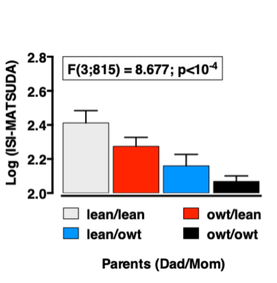


Figure 4 – 30% of the differentially expressed genes in F1 muscle and vsWAT (HFDi vs HFDt) are associated to childhood obesity in humans (A). Paternal overweight at conception affects offspring body weight (B) and insulin sensitivity (C) independently from maternal BMI.

CONCLUSIONS

- Genetic and environmental perturbations of paternal mitochondria affect metabolic health in unexposed offspring
- Sperm-borne smallRNAs transcribed from the mt genome are inherited at fertilization