Pathway analysis reveals genetic regulation of mitochondrial function and branched-chain amino acid catabolism in Type 2 Diabetes

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1. Background

In recent years, the number of genetic loci found to be associated with T2D has increased substantially, mostly through large-scale genome-wide association studies (GWAS). Recent work has, however, highlighted an underappreciated contribution of rare variants and variants in areas of low linkage disequilibrium (LD) to complex disease heritability[1,2], both of which are difficult to map using single-SNP tests of association. High-resolution genetic maps offer increased power to detect associations in areas of low LD and were recently used to map and replicate 111 novel loci associated with T2D[3]. Co-location of eQTL (genetic 'expression quantitative trait loci' which associate with gene expression levels) with disease loci (genetic loci that associate with risk of T2D), based on population-specific LD, was used to identify genes regulated by disease-associated variants (*cis*-genes). A co-localization approach overcomes difficulties in replicating lead SNPs between studies, making it an effective tool to identify likely *cis*-genes and the corresponding biological pathways implicated in heritable risk of disease. In this work, a total of 255 nominally significant disease loci were co-located with adipose eQTL and *cis*-genes were studied at the individual and pathway level. Specifically, we aimed to address the hypothesis that changes in mitochondrial function are a heritable, causal risk factor for T2D, by searching for *cis*-genes involved in mitochondrial function.

2. Methods

Disease loci and eQTL location estimates were generated using high-resolution genetic maps[3] and filtered using physical co-location of 100kb. *Cis*-genes were defined as nuclear-encoded mitochondrial genes according the mitoCarta2.0 database[4] and functionally annotated using publicly available databases. Enrichment of mitochondrial pathways was investigated using a permutation approach with pre-defined mitochondrial gene sets from the MSigDB database. Independent T2D case-control gene expression datasets were identified from GEO and meta-analysed using a random-effects linear regression.

3. Results

237 out of 255 nominally significant disease loci co-locate with adipose eQTL for a total of 1110 *cis*-genes, of which 80 are nuclear-encoded mitochondrial genes (NEMGs). These 80 NEMGs are involved in mitochondrial functions including organization, dynamics, translation, transcription, OXPHOS, the TCA cycle, apoptosis, purine, pyrimidine, propanoate, butanoate, amino acid, carbohydrate metabolism, lipid metabolism, protein transport and ion transport. *cis*-NEMGs include *CPT2*, the fatty acid carnitine transferase, three biotin-dependent carboxylases

MCCC1, *PCCA* and *ACACA*, in addition to the gene responsible for adding biotin to these carboxylases (*HLCS*) and the critical regulator of mitochondrial fission, *MARCH5*. The total cis-genes are enriched for branched chain amino acid (BCAA) catabolism (n=6) and ABC lipid transporters, suggesting a genetic mechanism driving perturbed amino acid and fatty acid catabolism in T2D. Independent evidence confirms that the total cis-genes (n=1110) and cis-NEMGs (n=80) are enriched for differential expression in T2D cases compared to healthy controls. This exploratory study highlights the use of genetic maps in identifying *cis*-genes and therefore causal mechanisms underlying T2D heritability.

4. Conclusions

This exploratory study highlights the use of genetic maps in identifying cis-genes and implicates a heritable basis to mitochondrial dysfunction in the development of T2D.

References

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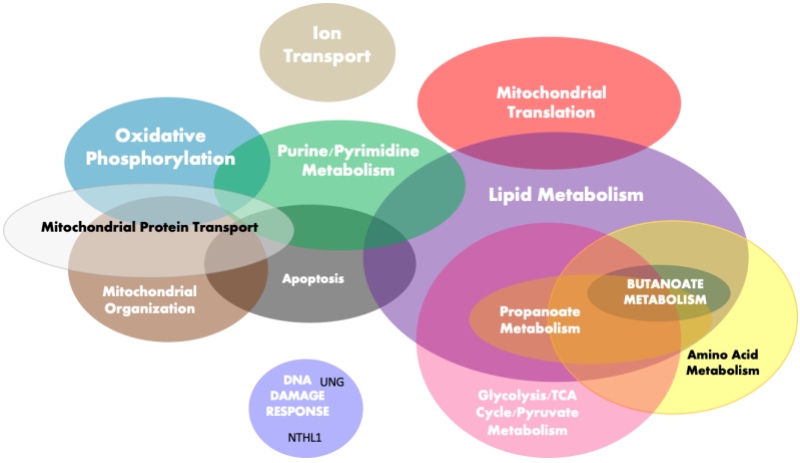

Figure 1 *The total 80 cis-NEMGs are involved in multiple mitochondrial pathways represented in the above diagram, scaled to the number of genes assigned to each pathway.*