# Genetic fine-mapping and targeted sequencing to investigate allelic heterogeneity and molecular function at genomic disease susceptibility loci for Type 2 Diabetes

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## 1. Background

Empirical genomic studies and long-established genetic theory show that complex traits - including many common diseases - are likely to be polygenic with numerous non-coding variants conferring risk of disease via the regulation of gene expression[1] and post-translational modification[2]. Using high-resolution genetic maps[3], we have identified 173 Type 2 Diabetes (T2D) precise disease susceptibility location estimates[4] and using gene expression quantitative trait loci (eQTL) analyses for subcutaneous adipose tissue, have shown strong evidence that approximately two thirds of these closely collocate (± 50Kb) of eQTL location estimates that regulate the expression neighbouring *cis*-genes (within ±1.5Mb of the disease locus; see *Figure 1*)[4]. Our follow up analyses show that ~80 of the 111 T2D disease loci are also eQTLs that regulate the expression of nuclear encoded mitochondrial cis-genes with the eQTLs showing a high degree of co-location with in silico functional annotation. In this talk I will discuss our current understanding of the genetic and allelic architecture of T2D and illustrate this with results from genomic analyses and follow-up fine-mapping studies conducted by our research groups. In particular, we are investigating two interesting novel loci for evidence of complex association with T2D and mitochondrial function. The first locus, a 79kb stretch in intron 3 of *FGF14*, was observed to harbour eQTL for genes including *PCCA*, for which the encoded carboxylase catalyses a terminal step in both branched chain amino acid (BCAA) catabolism and odd-chain fatty acid oxidation; two pathways relevant to T2D aetiology. The second is a predicted eQTL for the fatty acid dehydrogenase *ACAD11*.

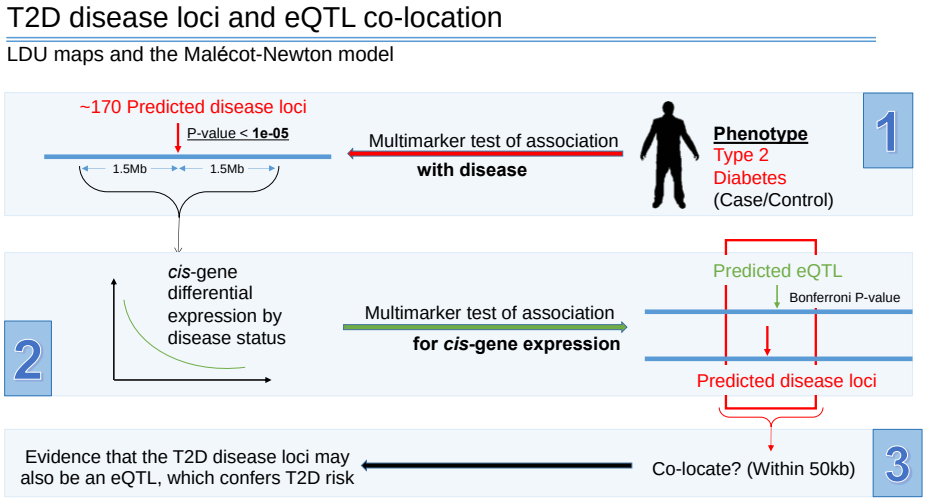


***Figure 1. Summary of Analysis Pipeline:*** *Genome wide association study using high-resolution maps for*

*European and African American samples identified 173 Type 2 Diabetes (T2D) location estimates (1). Additional expression quantitative trait locus (eQTL) analyses tested collocation (±50kb) of disease and eQTL location estimates (2) providing preliminary evidence that the disease location estimates regulate the expression of neighbouring genes and confer risk of T2D disease via cis-eQTLs (3).*

## 2. Pilot study Methods

Using targeted next-generation sequencing data for independent samples of European ancestry, 84 cases (family-history of T2D) and 91 controls (no family-history) to investigate: a) the complex genetic mechanisms that drive the association at these two novel loci; b) the enrichment of intermediate and rare frequency variants and allelic heterogeneity[5] and c) candidate functional elements for functional studies.

## 3. Results

Both loci show locus-wide enrichment of rarer variants (MAF<0.016) at annotated regulatory elements in cases and ACAD11 also showing evidence of coding variant enrichment.

## 4. Conclusions

We detect enrichment of variants in T2D cases within enhancers at two novel T2D loci. Several candidate elements are being investigated in ongoing functional studies, along with analysis of a much larger case-control sequencing dataset to replicate allele frequency differences. Similar methodology will be employed to fine-map other novel loci, thus facilitating the discovery of novel pathological mechanisms. Finally, going forward, we contend that hypothesis driven genomic analyses are the best way to ensure molecular functional insights for future genetic studies of Type 2 Diabetes.

## References


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