Genetic Studies of Syndromes of Severe Insulin Resistance and Type 2 Diabetes: a candidate gene approach

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Declaration

I hereby declare that my dissertation contains material that has not been submitted for a degree or diploma or any other qualification at any other university. This thesis describes my own work and does not include the work that has been done in collaboration, except when specifically indicated in the text.

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Dedication

Though I should dedicate this thesis to my younger self whose love of learning and naïve ambition has seen me through to a graduate degree, I would also like to mention my grandparents - two of whom, James Johnson and Joan Fawcett, are no longer with us. Despite their keen intelligence they were denied the educational opportunities that many of my generation now take for granted. May we never cease to value and improve the comprehensive education system.

Abstract

Insulin resistance plays a significant role in the pathogenesis of type 2 diabetes (T2D), a severe metabolic disease and major public health concern. Discovery of genes underlying insulin resistant syndromes can provide insights into pathophysiology and identify novel pathways for drug discovery. Moreover, these genes may also impact common T2D risk. The aim of this work was to investigate genetic variants for effects on insulin resistance, T2D and related continuous traits. Candidate genes studied included lipin family genes (Ch 3), components of the mTOR pathway (Ch 4), *PARL* (Ch 5) and genes involved in pancreatic β-cell function (Ch6), including *WFS1* (Ch 6 and 7).

The lipin 1 gene is responsible for two mouse models of lipodystrophy and insulin resistance and has been suggested to influence human insulin sensitivity and adiposity. I sequenced human *LPIN1*, *2* and *3* in insulin resistant patients to identify potential pathogenic mutations and tested for association of common variation in *LPIN1* with metabolic traits underlying T2D. These studies demonstrated that variants in the lipin family are unlikely to be common causes of severe insulin resistance, and that *LPIN1* common variants do not importantly contribute to risk of T2D.

Sequencing genes in the mTOR pathway revealed a number of rare variants in insulin resistant patients. Given that these genes are key players in the insulin signalling pathway some of these variants may be contributing to insulin resistance in patients. More detailed genetic and functional studies are needed to confirm this.

In the *PARL* gene the polymorphism Leu262Val had previously been reported to associate with fasting insulin levels. Despite a larger sample size (N=3666) I could not replicate this result in UK populations (P=0.79).

I contributed to a large candidate gene association study that investigated 1536 SNPs in 84 genes involved in pancreatic β-cell function for association with T2D. This study identified common variants in *WFS1*, a gene responsible for an autosomal recessive form of diabetes, impacting T2D risk. These results were confirmed in additional populations and updated meta-analysis (OR=0.89, *P*-value= 4.9×10^{-11}). In addition, I initiated re-sequencing and genotyping efforts to refine the association signal and investigated whether rare variants in *WFS1* also impact T2D risk. Further work is still required to identify the causal variant, and there was no evidence for association between rare variants and disease risk.

Recently, genome-wide association studies (GWAS), agnostic in terms of prior biological knowledge, have identified a number of genes underlying T2D and related traits. My work, which identified a novel T2D susceptibility gene not detected in initial GWAS results, *WFS1*, suggests that candidate gene studies can sometimes complement genome-wide approaches.

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Figures and Tables