Project Details	
Project Code	MRCPHS26Ex Dempster
Title	Epigenetic Signatures in Rare Genetic Disorders of Insulin Secretion: Developing Diagnostic Classifiers
Research Theme	PHS
Project Type	Dry lab
Summary	During this PhD, you will use innovative bioinformatic techniques to investigate how epigenetic processes contribute to rare genetic disorders that affect insulin secretion. Critically, you will use these disease-specific epigenetic patterns to develop classifiers termed "episignatures" to assist with the interpretation of novel genetic variants and as a diagnosis tool. This means that people with these rare genetic disorders can receive the right treatment and support sooner, potentially improving their quality of life.
Description	Mendelian disorders, while individually rare, are collectively common affecting around 3.5% of the population. New sequencing technologies have revolutionised medical genetics and enabled the identification of rare deleterious variants as the cause of many different disorders. However, determining the exact genetic cause can still be challenging when dealing with variants with uncertain clinical significance and when the clinical presentation is complex with overlapping symptoms, complicating the clinical diagnosis. Recently there has been increasing evidence that epigenetic modifications can assist in the interpretation of genetic variation. Epigenetic modifications are biochemical modifications to DNA or DNA/protein complexes, which control gene expression independently of DNA sequence variation. Epigenetic processes such as DNA methylation are highly dynamic during development. Alterations in a developmental trajectory due to a change in the underlying genetic sequencing can therefore have profound effects on the epigenome. Thus, an altered DNA methylation signature can be propagated and maintained across multiple cell lineages resulting in a stable epigenetic signature of a monogenic disease. The clinical laboratories in Exeter are a national and international referral centre for genetic testing for insulin secretion disorders; the Beta-cell Research Bank at Exeter provides a unique resource of >25,000 patient samples with DNA sequencing data available for thousands of these samples. Patients with congenital hyper- and hypoglycaemia represent the extreme ends of the spectrum in terms of insulin secretion. Studying the underlying genetic aetiology of disease in these individuals provides a unique opportunity to improve understanding of pancreas development and function. Great progress has been made in understanding the genetic basis of disease in patients with neonatal diabetes with 23 disease-causing genes reported. Screening of these genes identifies a pathogenic mutation in >82% of individuals. For patients with hyperinsulinaemic hypoglycaemia the underlying genetic aetiology is only found in 50% of cases. Current efforts have focused on using genome sequencing to search for the 'missing' mutations in insulin secretion disorders. The success of this approach is however reliant on 'missing' causative mutations being present in the DNA sequence, however epigenetic changes, which

	control gene expression independently of DNA sequence variation, cannot be detected by this approach. The importance of epigenetics in controlling insulin secretion is well-established. DNA methylation defects at the imprinted loci on chromosome 6q24 are reported in 70% of patients with transient neonatal diabetes whilst patients with Beckwith-Wiedemann syndrome, which features hyperinsulinism, have epigenetic abnormalities on chromosome 11p15.1. Hyperinsulinism is often a feature of the genetic syndrome Kabuki which has an established “episignature” but what is not clear is why only a subset of patients present with insulin secretion abnormalities. Characterising the role of DNA methylation in insulin secretion disorders will provide further insight into the regulation of the genetic pathways controlling insulin secretion which will be crucial for informing studies investigating models of beta-cell regeneration which are being developed to treat patients with more common forms of insulin dysregulation such as type 1 diabetes. We are currently profiling DNA methylation in the cohort using the Illumina DNA methylation array to create an epigenetic data resource for monogenic insulin secretion disorders. This PhD project aims to bring together expertise in monogenic disease and epigenetics, and the largest international cohort of patients with neonatal diabetes (n= >4000) and hyperinsulinism (n= >5000) to help the student achieve the following aims: 1, To perform a thorough review of the literature regarding epigenetics and insulin secretion disorders and the development and application of episignatures. 2, To use an integrated genomics/methylomic approach to investigate the role of DNA methylation in the aetiology of insulin secretion monogenic disorders. 3, To develop and test different methods to determine the optimal epigenetic classifier method. 4, To develop disease-specific episignatures that will aid variant interpretation and potentially provide patients with a genetic diagnosis that could have treatment and disease management implications.
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