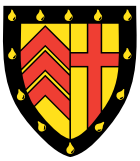
UNIVERSITY OF CAMBRIDGE

Primary sclerosing cholangitis: from genetic risk to disease biology

Elizabeth Claire Goode



Clare College

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Declaration

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface and specified in the text. It is not substantially the same as any that I have submitted, or am concurrently submitting, for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my dissertation has already been submitted, or is being concurrently submitted, for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. This dissertation does not exceed the prescribed limit of 60 000 words.

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Abstract

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One in 10,000 people in the Western world lives with Primary Sclerosing Cholangitis (PSC), an immune-mediated, inflammatory disease of the bile ducts that is highly co-morbid with inflammatory bowel disease (IBD). PSC confers risk of serious disease sequelae including hepatobiliary malignancy and progression to end-stage liver failure, for which the only treatment option is liver transplantation. The absence of effective medical therapies for PSC reflects our current limited understanding of the disease's aetiology and pathogenesis.

Our DNA, laid down at conception, gives us an unrivalled opportunity to understand the underlying causal biology of disease. This is because the genetic variants associated with disease susceptibility perturb genes and biological pathways that contribute to disease causality. Twenty-two regions of the genome, outside of the HLA, have been associated with PSC risk. These loci offer the potential for huge insight into the causal biology of PSC, if only we can robustly identify the true causal variants driving these loci and the genes they perturb. However, this is complicated by several scientific challenges. Firstly, the majority of disease-associated risk loci occur within non-coding regions of the genome. Secondly, patterns of correlation between variants within a risk locus means that the true causal variant driving the signal could be any of those highly correlated with the variant with the smallest p-value.

In this thesis, I present analyses aimed at identifying the true genes and causal variants underlying each of the twenty-two PSC risk loci. Many non-coding risk variants associated with complex disease exert a quantitative affect upon gene expression i.e. are expression quantitative trait loci (eQTLs). Colocalisation assesses the evidence that a single shared causal variant is responsible for driving PSC risk and gene expression via an eQTL. In order to assign dysregulated genes to PSC risk loci, I perform colocalisation with eQTLs mapped in multiple cell-types and tissues mechanistically relevant to PSC. Because PSC is rare, eQTLs have not previously been mapped in all cell-types most relevant to this disease. In addition, I therefore map eQTLs in six peripheral blood T-cell subsets (including the rare CCR9+ gut-homing T-cells) from ∼80 patients with PSC and IBD. With colocalisation, I assign causal genes to five PSC risk loci, and assign other epigenetic regulatory features

including methylation or histone modification, to six risk loci. Statistical fine-mapping of each risk locus in both the GWAS and eQTL data enables me to resolve three PSC risk loci to a single causal variant and nine loci to 95% credible sets containing ten or fewer variants.

The results presented in this thesis identify three genes (*PRKD2, ETS2* and *UBASH3A*), causal in the pathogenesis of PSC, which are currently the target of existing or experimental therapeutic agents. Firstly, reduced expression of *PRKD2* causes excessive cell-autonomous T-follicular helper cell development and B-cell activation, and is associated with increased risk of PSC. Several studies are investigating the therapeutic effects of increasing the kinase activity of PRKD2. *ETS2* is involved in the induction of pro-inflammatory cytokine release from macrophages and IL-2 regulation in Th to Th0 transition. ETS2 inhibitors are currently the subject of early therapeutic trials. Finally, *UBASH3A* attenuates the NF-$\varkappa$B/I-KKβ pathway, an inflammatory pathway that is already targeted by proteasome inhibitors and acetylsalicylic acid, both of which could be potentially therapeutic in PSC.

PSC is a debilitating disease with serious disease sequelae, for which new therapeutic options are urgently needed. In this thesis, I elucidate multiple genes with a causal role in PSC pathogenesis, several of which are potential candidates for future therapeutic target.

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