Lay Summary
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UK IBD Genetics Consortium study of anti-TNF pharmacogenomics and IBD genetics in the UK South Asian population.

The last 5 years has seen great progress towards identifying the genetic variants which predispose to Crohn's disease and ulcerative colitis. With the support of Crohn's and Colitis Uk, the UK IBD Genetics Consortium (UKIBDGC) has been at the forefront of this exciting scientific field. The progress made is beginning to provide important clues about the *causes* of these conditions – recognised as the key to the development of better treatments and preventative strategies long-term.

To build on the group's recent achievements, and translate these discoveries into new therapies and improved use of existing therapies for IBD, further genetic investigations are required. We in the UKIBDGC are particularly mindful of the need to broaden the range of our studies and include goals with the potential for early clinical impact. This proposal represents the first critical step – to assemble the clinical resources required to undertake these studies.

Our key goal is to collect 5000 DNA samples UK-wide from patients with IBD who have not previously participated in our studies. This new collection will focus on:

1. UK South Asians with IBD (a group excluded from genetic studies to date)
2. Selected sub-groups of patients with Crohn's disease who have been treated with the powerful, expensive and potentially toxic anti-TNF antibody therapies infliximab and adalimumab.

Studying a large group of UK South Asians with IBD will allow very valuable comparisons with 'European origin' IBD. This will provide critical insights into two key aspects of Crohn's and colitis. Firstly, how the same clinical picture of IBD might arise through different pathways. This has the potential to provide insights into causal mechanisms, perhaps including environmental triggers, in both populations. Secondly, where regions of the genome are shown to confer increased risk of IBD in both groups, this could greatly increase our ability to pinpoint the causal genetic variants in both populations, due to their known differences in genetic structure. Such trans-ethnic studies are seen as key next steps in complex disease genetics.

Anti-TNF therapies have revolutionised the management of severe Crohn's disease. However, these powerful medications are not successful in all patients and can result in severe side effects in some. For the anti-TNF antibody study, our goal is to define genetic markers which predict response to or toxicity from these key therapies in Crohn's disease.

This proposal builds on the successes of UKIBDGC and also links the genetic research to the newly created IBD anti-TNF registry. Nation-wide coverage can be achieved through the use of the Clinical Research Network (CRN) and access to the CRN portfolio that Crohn's and Colitis UK support would bring. Thus relatively modest financial support from Crohn's and Colitis UK to purchase the DNA extraction saliva kits we can achieve the much larger research objectives of a pharmacogenomics study related to anti-TNF treatment, the additional breadth of including a South Asian population, and increased ability to identify causal genetic variants within many of the ~100 areas of the genome already known to influence IBD.