Deconstructing disease pathology

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Having entered the field of inflammatory bowel disease biology somewhat by chance, Dr Isabelle Cleynen discusses her collaborative efforts to unravel the risk factors contributing to this debilitating disease.

Why have you chosen to focus your research on inflammatory bowel disease (IBD)? How well is this condition currently understood?

It was by chance that I ended up in the KU Leuven IBD research group when I was looking for a new position as a postdoctoral fellow. I had previously been working in oncology, but the enthusiasm exhibited by my future supervisor convinced me to make the transition. I have not regretted it as the study of IBD pathogenesis is a fast moving field and, more importantly, IBD represents a serious health problem that significantly impacts the lives of patients. It is highly rewarding to contribute to understanding this disease and developing therapies.

Currently, the precise pathogenesis and risk factors for IBD are unknown. We do know that it is a multifactorial disease involving both genetic and environmental factors, and in the last five-10 years, significant progress has been made toward understanding its genetic basis. Thanks to international efforts, over 150 different regions of the human genome have been implicated, but these only explain about 10-20 per cent of the total genetic risk. Moreover, the non-genetic risk factors have proven to be very difficult to study.

In what ways do genome-wide association studies (GWAS) help you to explore the genetic basis of IBD?

One of the great advantages of GWAS is that they allow you to search the entire human genome for regions involved in complex diseases in a systematic and assumption-free manner. Historically, one could only study a small section of the genome based on the belief that a specific region was important, an approach that was only seldom successful. We compare it with looking for your dropped keys at night – it is more difficult when there is only one lamp post, especially if the lamp post is not where the keys were dropped; but if you have lamp posts scattered around, you increase your chances of finding your keys.

Can you outline the work you have done in collaboration with the International IBD Genetics Consortium (IIBDGC)?

We have contributed genetic and clinical data from patients and healthy controls to aid in their investigations. During my time at the Wellcome Trust Sanger Institute in Cambridge, UK, I worked on a project attempting to link genetic variants with clinically observed IBD subphenotypes. Within the framework of the IIBDGC, we have assembled the largest deeply characterised cohort to date. The results of this study are currently being finalised.

To what extent does the wider expertise of the Leuven IBD research group facilitate the success of your work?

The Leuven IBD research group works on different aspects of IBD, including clinical studies, genetics, immunology and transcriptomics. We have experts in each of these fields working together and this is key to the success of our research. Each of these aspects are often studied separately, but it is important to bring them all together, and having wide expertise within the group makes this achievable. Furthermore, our link to a hospital and involvement of clinicians ensures direct access to patient material. This enables us to perform translational research and to stay at the forefront of the field.

As a female academic, have you had to overcome any obstacles to be successful?

The main obstacle thus far has been becoming a mother for the first time. I always felt I first wanted to achieve in my scientific career, and motherhood had to come after that; I was afraid I would miss out on important opportunities and would not remain on top of the research. Having gone through the experience just a few months ago, I did sometimes feel I was missing out. However, my colleagues were very understanding, both during my pregnancy and maternity leave, taking over some tasks and keeping me up to date on research. The real challenge will come now that I have restarted work and will need to combine family, home and work.
INFLAMMATORY BOWEL DISEASE (IBD) describes a group of conditions characterised by chronic inflammation of the gastrointestinal tract, including ulcerative colitis and Crohn’s disease. Inflammation can be debilitating; symptoms include severe abdominal pain, diarrhoea, weight loss, joint pain and loss of appetite. IBD presently affects over 2.5 million people of European ancestry and its prevalence is growing in other populations. It is known to be the result of both genetic and environmental factors, but interactions between the two are complex and the precise mechanisms remain unknown. As a result, treatments merely alleviate symptoms and are frequently associated with negative side-effects.

Recent advances in the understanding of human genetics, alongside improved sequencing technology, have revealed several genetic loci associated with IBD. However, to fully harness the power of this information, scientists must integrate this knowledge with experimental biology. Doing precisely that, Dr Isabelle Cleynen supervises a team within the Translational Research Center for Gastrointestinal Disorders (TARGID) at KU Leuven. Her work is integrating genetics, genomics and molecular biology to better understand the function of IBD-associated genetic variants, identifying causal genes and translating this knowledge into new treatments for IBD.

MISSING HERITABILITY

Genome-wide association studies (GWAS) are frequently used in complex disease genetics. This technique involves the rapid scanning of markers across the genomes of many people to find variations associated with a particular disease. GWAS have been applied to several complex conditions in recent years and, as a result, have successfully identified over 150 IBD-associated loci. Although this has provided an important insight into the pathogenesis of the disease, it can only account for a small proportion of total heritability. Furthermore, even if an individual carries certain risk alleles, it does not necessarily mean they will develop the disease.

GWAS have their limitations; they study common genetic variation and can therefore miss rare differences that are implicated in disease. Further genetic and functional studies are required, explains Cleynen: “While the discovery of so many genetic associations has provided a great insight, we now face the challenge of translating that information into an understanding of the underlying biology of the disease, and then back to the patients”. Future IBD genetics research, and indeed all complex disease genetics, requires not only the discovery of additional associated genes, but also the successful integration of genetics and experimental biology.

THE INTERNATIONAL IBD GENETICS CONSORTIUM

The University Hospital Leuven houses the most important IBD centre in Belgium – and a global leader in this field. For over 15 years, working under the umbrella of the International IBD Genetics Consortium (IIBDGC), the clinic has been collecting DNA and serum from patients, family members and healthy controls, and has made a major contribution to efforts identifying genes associated with IBD. The Leuven IBD group plays a prominent role within the IIBDGC, participating in the Consortium’s next-generation genetic studies by sharing clinical data, genotype data and DNA samples, and developing methodologies to understand their functional relevance.

These findings could lead to molecular classification of IBD subtypes – paving the way for personalised treatment of the disease

Under the framework of the IIBDGC, Cleynen was one of the lead analysts on a project aiming to determine the genetic basis for clinically distinct IBD subtypes such as Crohn’s disease and ulcerative colitis IBD – each of which has its own pattern of disease behaviour and outcome. A number of studies have endeavoured to connect Crohn’s disease-associated genetic variants with particular clinical presentations, or subphenotypes. However, significant associations have only rarely been found and most have not been replicated.

To address these limitations, the Consortium assembled the largest cohort to date: clinical
INTELLIGENCE

TRANSLATIONAL RESEARCH IN GASTROINTESTINAL DISORDERS

OBJECTIVES

• To study the genetic background of inflammatory bowel disease by identifying the genetic variants that make someone susceptible to disease
• To establish the biological mechanism(s) through which the associated variants act
• To translate variants into a better categorisation of patients with respect to disease progression and treatment strategies

KEY COLLABORATORS

Dr Severine Vermeire, KU Leuven, Belgium
• Dr Jeffrey Barrett, Wellcome Trust Sanger Institute, UK • Dr Alessio Fasano, MassGeneral Hospital for Children, USA

Members of the Belgian IBD genetics consortium (ULg-CHU de Liège, KUL-UZ Leuven, UGENT-UZ Gent, ULB-Hôpital Erasme)

Members of the International IBD genetics consortium (www.ibdgenetics.org)

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European Crohn’s and Colitis Organisation (ECCO)

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ISABELLE CLEYNEN is a postdoctoral research fellow in the Translational Research Center for Gastrointestinal Disorders (TARGID) at KU Leuven, Belgium. After being awarded her PhD in Molecular Oncology from KU Leuven, Cleynen shifted her focus to the investigation of inflammatory bowel disease and spent a year at the Wellcome Trust Sanger Institute in Cambridge, UK. Cleynen has had her research published in 28 peer-reviewed international journals, written one book chapter, and is a member of the Y-ECCO committee, working to support the career development of young clinicians and research scientists.

ZONULIN – PATHWAY TO A NOVEL DRUG

1) Characterise the relationship between zonulin levels and intestinal permeability
2) Analyse zonulin expression in a large IBD cohort
3) Define the temporal relationship between zonulin upregulation and inflammation
4) Define the spatial relationship between the locations of impaired permeability and disease
5) Investigate the reversibility of zonulin-induced impaired permeability and possible therapeutic possibilities for an antagonist

The moment a patient presents in the hospital and is diagnosed with IBD, the disease has already developed. When we observe increased permeability, it is not clear if it was the cause of the disease, or a consequence of the inflammation,” Cleynen explains.

A NOVEL INHIBITOR

While this archetypal ‘chicken or egg’ scenario remains unanswered, preventing or reversing the permeability would undoubtedly be of benefit. The main focus of Cleynen’s work in this area is on zonulin, a positive regulator of intestinal permeability that also has a genetic association with IBD.

Cleynen believes that carriers of the zonulin risk variant have an increased risk of developing IBD, due to its permeating effect on the intestinal barrier. Based on this hypothesis, she is studying how zonulin expression correlates with intestinal permeability to gain insight into its role and provide new therapeutic perspectives.

If impaired permeability is in fact an early stage in IBD pathogenesis, treating IBD patients with a zonulin antagonist could prevent recurrence of the disease or, if diagnosed early enough, even prevent its full development. “A zonulin antagonist has already successfully been tested in human clinical trials in coeliac disease patients. If zonulin serum levels correlate with intestinal permeability, a positive serology for zonulin could be used as a predictor to identify those patients that could benefit from antagonistic treatment,” elaborates Cleynen.

Cleynen’s work has generated an entirely new level of understanding of IBD pathogenesis, and she has made great strides towards more effective treatment options for the disease. In the future, she hopes to extend the insights she has gained and methodologies she has learnt from IBD to other complex immune disorders, such as primary sclerosing cholangitis and psoriasis.

and demographic information was collected from over 26,000 Crohn’s disease and 21,000 ulcerative colitis cases, with genotypes across almost 200,000 genetic variants. Using both established and novel statistical methods, the team performed genotype-phenotype analyses that revealed a new region specifically implicated in age at onset, as well as associations between two specific genetic loci and several Crohn’s disease phenotypes. They then combined all the different genetic risk factors into a risk score for each patient. The team used the score to demonstrate that colonic Crohn’s disease – a subtype phenotypically similar to ulcerative colitis – represents a genetic intermediate between ideal Crohn’s disease and ulcerative colitis.

These results indicate that genetics do significantly influence the clinical heterogeneity of IBD and strongly suggest that ulcerative colitis and Crohn’s disease should be considered as part of a continuum. This understanding could lead to improved molecular classification of specific IBD conditions – paving the way for more personalised treatment of the disease.

BIOLOGICAL EXPLORATION

Aside from her purely genetic research, Cleynen is also working on the functional aspects of IBD-associated genetic variants. Understanding the underlying biological mechanisms is important, not only to improve understanding of the disease, but also to directly enhance patient care.

Although IBD pathogenesis is scarcely understood, a growing body of evidence heavily implicates dysfunction of the intestinal epithelium barrier – the largest and most important interface of the intestines with the external environment. Under normal circumstances, it is selectively permeable, allowing the absorption of nutrients and water whilst excluding toxins and antigens; however, in the diseased state, permeability is increased.

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