The Genetics Behind Chronic Inflammatory Bowel Disease

Chronic inflammatory bowel disease is on the rise in industrialized countries and it poses a diagnostic and therapeutic challenge to physicians. Researchers from the Institute for Clinical Molecular Biology in Kiel, Germany, believe that learning more about the genetic basis through next-generation sequencing might lead to more specific approaches.

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Chronic inflammatory bowel disease (IBD) – especially Crohn’s disease and ulcerative colitis – are affecting an increasing number of people in industrialized countries. This may be due to the immune system not being sufficiently activated during childhood. Even hygiene has its downside.

Professor Andre Franke, PhD, is a geneticist at the Institute for Clinical Molecular Biology (IKMB). Earlier this year, he and his team of researchers were able to show how a lack of contact with ubiquitous microorganisms during early childhood increased the likelihood of developing chronic inflammatory diseases in later life – be they of the intestine, skin, lung, or joints. When insufficiently challenged, the immune system seems to get bored and initiate inflammatory reactions.

Therefore, IBD may be considered a paradigm of a disease resulting from civilization, as Stefan Schreiber, MD, Director of the IKMB, puts it. Patients affected by IBD must not only deal with bloody diarrhea of differing intensity, but also with life-threatening complications like fistulae, rupture, or cancer of the colon. Their quality of life is severely impaired; their life expectancy shortened.

Despite advances in IBD therapy over recent years, more specific and individualized therapies are needed. Beyond that, an altogether different approach is required, as Schreiber – who is also Director of the Clinic for Internal Medicine at the University Hospital of Schleswig-Holstein (UKSH) and Dean of the Medical Faculty at the Christian Albrechts University in Kiel – explains: “Today, we are treating illnesses like Crohn’s disease at a stage were macroscopic damage to the intestinum has already taken place. Controlling the disease at this stage is no longer possible. We need to advance the diagnosis to earlier stages of the disease process, before the immune system has run amok.” Schreiber expects that a more comprehensive risk assessment, including information on gene mutations, will help to detect diseases at a much earlier stage.
Stefan Schreiber, MD, Director of the IKMB, aims to detect IBD at a much earlier stage than it is now, by using information on gene mutations.
earlier stage when true healing is still possible.

**At the Forefront**

Physicians, geneticists, biologists, and bio-information specialists work together at the IKMB, studying the complex interaction of genes, epigenetics, and environmental factors in the pathogenesis of IBD. The IKMB and the Clinic for Internal Medicine are world-renowned centers of excellence for the diagnosis and treatment of IBD. They have made great contributions to the understanding of the underlying processes of IBD. By bringing together high-level patient care and basic research, they are also providing an opportunity for the transfer of research results to the clinic.

**Impact of Mutations**

As with many diseases, IBD cannot simply be blamed on one mutant gene. There is more to the puzzle. Genetic research has shown that several genes are involved. Besides, even though the phenotype of affected patients in Asia and Europe is the same, the genetics are not. To determine the clinical relevance of each mutation found, the mutant genes must be matched up to a representative pool of genetic information from the population. To find and understand disease-associated alterations in DNA requires the comparison of huge amounts of data from genome sequencing and the need for algorithms to help annotate it.

**High-Throughput Sequencing: An Important Tool**

Today, a patient’s genome can be sequenced within six weeks, thanks to next-generation sequencing. As Franke explains, the first step is taking blood from the patient. Then lymphocytes are purified; their DNA is enriched and prepared for sequencing. Afterwards, the data is semi-automatically transferred to a server for analysis. Thanks to the targeted re-sequencing approach developed in Kiel, which selectively enriches coding regions of the genome – the so-called exome – the process can be sped up. Exome sequencing involves about one percent of the genome, and it is therefore not only faster, but also cheaper and more likely to make it into clinical practice. According to Schreiber, the possibilities for exploring the sequence of the human genome have expanded tremendously over recent years, much like they did for personal computers about 15 years ago. “Nobody could have imagined that we would be able to do such complex things on a computer as we can nowadays on an iPhone2,” Schreiber explains. “It is similar with genetics. The technical revolution in creating sequencing data has opened new doors. It is no longer the privilege of human geneticists to analyze genetic data and then announce the connection to symptomatic diseases in a black-and-white manner. Today, researchers and physicians from different fields DNA data is semi-automatically transferred to a server for analysis.

**From Bench to Bedside**

In Kiel, one successful example of the effect that high-throughput sequencing can have on treatment choices comes from a 3-year-old boy with transmural, discontinuous colonic inflammation resembling Crohn’s disease. The intestinal inflammation was resistant to both immunosuppressive treatment and modern treatment approaches using antibodies against the cytokine Tumor Necrosis Factor alpha. Even a protective ileostomy couldn’t stop the inflammation. It only reduced the severity of the colitis. It is known that, especially in young patients, the genetic impact on disease manifestation is very strong: the more severe the disease, the more likely a genetic contribution. “We performed whole exome capture and sequencing on the affected child and his parents,” Franke explained. The exome of child and parents was enriched and sequenced, with the base sequences read automatically. Thereafter, the sequences of all three were compared to the human reference genome and among each other. The final step of the annotation of variants was performed using an algorithm developed in Kiel (snpActs) and a commercially available algorithm (ANNOVAR). “For the identification of de novo mutations in the child, we used Varscan’s somatic mutation detection command together with our own in-house scripts,” says Franke.

With this procedure, the Kiel researchers identified a novel, hemizygous nonsense de novo mutation in an exon of a gene that had recently been shown to cause a Crohn’s disease-like illness1. For Franke, this demonstrates that exome sequencing allows an unbiased detection of the genetic alterations associated with rare clinical phenotypes and provides significant insights into the pathophysiological mechanisms of IBD.

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can explore the data and relate mutations to human phenotypes."

Managing the Flood of Data
Sequencing is no longer the challenge. "Today’s challenge lies in finding the few mutations within the set of the hundreds of thousands of letters of the genome that contribute to the clinical phenotype; especially, the high-penetration phenotypes of children affected by IBD, where genetics play a major part in the disease’s development," Franke states. Therefore, bio-information algorithms that automatically separate meaningful data from that which is unimportant are needed to improve clinical usability of high-throughput sequencing. "This is where we need an industry partner like Siemens, who has experience in dealing with huge volumes of data," says Franke. The intellectual contribution for developing these algorithms comes in part from a large technological platform, the pop-gen biobank. This was developed in Kiel within the Deutsche Forschungsgemeinschaft (German Research Foundation)-sponsored Excellence cluster, ‘Inflammation’. It allows the Kiel researchers to systematically compare the genetic make-up of large populations and to generate new insights into the relationship between variants and specific human phenotypes. This work builds the intellectual context in which data from high-throughput sequencing is interpreted. Until recently, this information was distributed by a number of sources, including the Internet, yet it wasn’t freely accessible. Now, it all flows into the system supporting the annotation algorithm. To fully understand how and where genetic information plays a role in diseases – and not just those like IBD – Franke believes that it will take another ten years.

Hopes for the Future
In the long run, identifying genetic make-up might lead to approaches like gene therapy or stem cell therapy – especially in those young patients with a really bad prognosis – "but," Schreiber cautions, "it is not just the genes. It’s the whole risk profile, including nutrition, body type, and exercise habits that will have to be included in patient management choices in the future. I see the physician of the future as a guide for the patient, helping him or her balance genetic risks against lifestyle choices."

Medical writer Wiebke Kathmann is a frequent contributor to medical magazines aimed at German-speaking physicians. She holds a Master's Degree in Biology and a PhD in theoretical medicine. She worked as an editor for many years, before becoming a freelancer in 1999. She is based in Munich and Karlsruhe, Germany.

Summary
Challenge:
• Increasing numbers of patients in industrialized countries suffer from chronic inflammatory bowel disease (IBD)
• Improving the specificity of diagnosis and therapy in IBD
• Identifying the genetic make-up of the individual IBD patient
• Mastering the huge amount of data derived from genome or exome sequencing

Solution:
• Next-generation sequencing as a means of saving money and time
• Biobanks providing the necessary data on the genome of healthy individuals
• Algorithms helping to distinguish functional from ineffective mutations: in other words, detecting clinically relevant mutations
• An interdisciplinary approach: integrating insights from molecular biological approaches with clinical experience

Result:
• Greater understanding of the individual risk profile of patients as the basis for individualized medicine
• Better understanding of the genetic basis of diseases like IBD, thanks to a targeted resequencing approach
• Improved clinical usability of high-throughput sequencing results

Further Information
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