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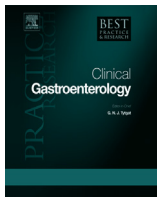

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How will insights from genetics translate to clinical practice in inflammatory bowel disease?

E.A.M. Festen, MD, PhD [a,b], R.K. Weersma, MD, PhD [a,*]

[a] University of Groningen, University Medical Centre Groningen, Department of Gastroenterology and Hepatology, Groningen, The Netherlands
[b] University of Groningen, University Medical Centre Groningen, Department of Genetics, The Netherlands

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A B S T R A C T

Inflammatory bowel disease, consisting of Crohn's disease and ulcerative colitis, is a chronic inflammatory disease of the gut, which arises through an excessive immune response to the normal gut flora in a genetically susceptible host. The disease affects predominantly young adults and due to its chronic and relapsing nature gives rise to a high disease burden both financially, physically and psychologically. Current therapy still cannot prevent the need for surgical intervention in more than half of IBD patients. Consequently, advances in IBD therapy are of high importance. Recently, several new forms of targeted therapy have been introduced, which should improve surgery-free prognosis of IBD patients. Recent identification of genetic risk variants for IBD has led to new insights into the biological mechanisms of the disease, which will, in the future, lead to new targeted therapy. In the meantime repositioning of drugs from biologically similar diseases towards IBD might lead to new IBD therapies.

Introduction

Ever since the first human genome was sequenced in 2003 the clinical world has been waiting for translation of this genetic knowledge into therapies for disease or personalized care for individual patients [1,2]. This article is mainly focused on the implications of genetics for Inflammatory Bowel

* Corresponding author. Tel.: +31 503610426; fax: +31 503619306.
E-mail address: R.K.Weersma@umcg.nl (R.K. Weersma).

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Disease (IBD), consisting of Crohn's disease (CD) and ulcerative colitis (UC), both chronic inflammatory diseases of the gastrointestinal tract. In the last few years the knowledge on the genetic background of IBD has been growing fast: 163 genetic risk loci have been identified for IBD, making it the most successfully studied complex disease [3]. The promise genetics hold for clinical practice is three-fold (Fig. 1). (1) Better understanding of disease mechanisms allowing for the development of targeted therapies; (2) prediction of disease in the general population allowing for preventative measures; and (3) adapting medical therapy to the genetic profile of the individual patient. The last two items together constitute the concept of 'personalized medicine'. Personalized medicine will help us determine which patients will benefit from specific therapies and which patients will not respond to therapy or even develop side effects. Since IBDs are chronic disorders with an unpredictable disease course that need intensive and expensive treatment, and have potentially severe disease outcomes, the potential of personalized medicine is especially promising for this group of diseases. It is important for clinicians to identify those patients with a potentially severe disease course, since they might benefit from early intervention and a more aggressive treatment. Alternatively, patients with a favourable prognosis can be spared the side effects of unnecessary treatment. This is an important issue since, in the treatment of IBD patients, the so-called 'top-down' approach, in which biological therapies are administered early in the disease course, is increasingly being adopted [4]. This in contrast to the 'step-up' approach, in which treatment is started with milder therapy and escalated if this therapy proves to be insufficient, which in patients with severe disease can lead to months of insufficient therapy. However, at the moment, the 'top-down' approach may well lead to the over-zealous treatment of many patients, whereas a better selection of patients, based on genetic biomarkers, could very well prevent this. From the clinical perspective, genetics have not yet had much additional value to current therapy of IBD. However several steps have already been made: (i) genetic knowledge can already contribute to new targeted therapies for IBD; (ii) research is being done into whether genetic risk models can predict IBD in the general population and (iii) genetic predictors for disease course and therapeutic response are being investigated. We will review the current knowledge on these aspects of genetics in relation to the clinical care of IBD patients.

Translating knowledge on genetic background of a disease to therapy

Potentially many of the currently known 163 IBD genetic risk variants can be targets for disease therapy. There are, however, several caveats. First of all some genetic risk variants are not clearly linked to a gene. Several hundreds of genes reside within the 163 IBD loci and for many of these loci the truly associated gene is not known yet [5]. For a genetic variant to be a suitable target for therapy it has to be clearly linked to a gene, preferably influencing the expression or function of the protein encoded by the

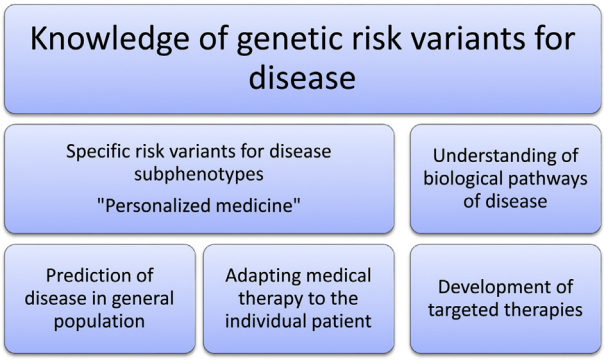

Fig. 1. The promise of genetic knowledge on complex disease for clinical practice falls into two main groups: genetic knowledge of association to (sub)phenotypes and biological understanding of disease pathways. The former, genetic knowledge, leads the way for 'personalized medicine': predicting disease in healthy individuals and adapting therapy to the individual patient. The latter, understanding of underlying biological pathways, allows for the development of targeted therapies.