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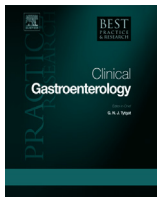

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Genetics of celiac disease

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A B S T R A C T

New insights into the underlying molecular pathophysiology of celiac disease (CeD) over the last few years have been guided by major advances in the fields of genetics and genomics. The development and use of the Immunochip genotyping platform paved the way for the discovery of 39 non-HLA loci associated to CeD, and for follow-up functional genomics studies that pinpointed new disease genes, biological pathways and regulatory elements. By combining information from genetics with gene expression data, it has become clear that CeD is a disease with a dysregulated immune response, which can probably occur in a variety of immune cells. This type of information is crucial for our understanding of the disease and for providing leads for developing alternative therapies to the current gluten-free diet. In this review, we place these genetic findings in a wider context and suggest how they can assist the clinical care of CeD patients.

Introduction

During the last few years, the field of human genetics has benefited from an enormous gain of knowledge, specially due to the development of new technologies and techniques, growing disease

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cohorts, and new methods of data analysis and data integration to uncover new disease genes, pathways and regulatory networks for complex diseases.

Nowadays it is possible to analyze almost every kind of biological sample. Apart from DNA for genotyping, samples can cover individual cell types, RNA for gene expression, and proteins and metabolites from serum or plasma. The information extracted from these biological systems yields important insights into the complex biology of disease.

This technological leap initially allowed for the interrogation of hundreds of thousands of single nucleotide polymorphisms (SNPs) across the human genome, a process called genome-wide association studies (GWAS). With genotype information from a random sample of the population and from a group of patients, case–control association studies are able to pinpoint the regions or genes potentially related to the pathophysiology of a disease, for example on celiac disease (CeD) [1,2]. Two GWAS studies in CeD on some 4,918 patients and 5,684 controls led to the discovery of 26 loci outside the well-known HLA association. By comparing GWAS results between different diseases, we can detect regions and genes common to multiple diseases. Such pleiotropic effects can discover common pathways involved in phenotypically different, but biologically related pathologies, as shown for a group of autoimmune diseases [3]. By 2010, GWAS had found 186 loci to be associated to ten different autoimmune diseases and many of these loci showed association to more than one disease.

The genetic analysis of CeD represents an outstanding example of this development, with an important number of loci discovered not only in Caucasian populations but also in other ethnicities. New disease pathways have been linked to these loci [4].

Immunochip in celiac disease

The release of the dedicated Immunochip platform in 2010 gave a huge boost to the process of discovering new genetic regions linked to autoimmunity. This customized array contains 196,524 SNPs that are located in the 186 regions of immunologic interest and includes evidence of association based on previous GWAS analyses in ten different autoimmune diseases [5]. The Immunochip has become a popular genotyping platform because of its customized coverage and cost-efficiency. Its special design means it is suitable for use in European populations, but it is less informative for other ethnic groups. The chip contains SNPs that were known in the public domain by February 2010 [6], which means it lacks an important number of rare variants that have been discovered since then. It has been assumed that these rare variants have a stronger effect on disease susceptibility, but they are also more difficult to find as this requires large-scale sequencing studies. Probably one of the major weaknesses of the Immunochip is that it does not cover the entire genome, it is now apparent that it eliminates potentially important regions for autoimmune diseases from analysis [5]. Nevertheless, the array has proven to be extremely efficient for deep replication of associations across a wide range of autoimmune diseases, as well as for the purpose of fine-mapping well-established and significant GWAS loci.

New findings from Immunochip

Using the Immunochip platform, in 2011 Trynka et al. [7] analyzed CeD cohorts from six different countries, encompassing 12,041 cases and 12,228 controls. They not only confirmed the loci discovered in previous analyses [1,2], but also identified new associations, bringing the number of known CeD loci, including the MHC-HLA region, to 40 (Fig. 1). These loci are represented by 57 independent SNP associations, of which 29 were localized to a single gene. With the use of proxies (i.e. closely correlated SNPs), three protein-altering SNPs were identified in the *MMEL1*, *SH2B3* and *IRAK1* genes, while other disease SNPs where localized in regulatory regions of the *RUNX3*, *RSG1*, *ETS1*, *TAGAP*, *ZFP36L1*, *IRF4*, *PTPRK* and *ICOSLG* genes. The remaining disease SNPs lie in intergenic regions [7]. The genes from these associated regions can be connected to multiple biological pathways like hematopoiesis, cell differentiation and selection, activation, co-stimulation and maturation of effector cells, or to regulation of the immune processes.

By linking genes and potential pathways it is possible to pinpoint genes that affect multiple independent autoimmune diseases (genes with pleiotropic effects), such as *CCR1*/*CCR2* (on chromosome 3p21.31) involved in cell differentiation, recruitment and signaling, or *FASLG* (on chromosome 1q24.3)