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Editorial

Polymorphisms: Genetic variations associated with irritable bowel syndrome

Irritable bowel syndrome (IBS) is currently the primary digestive reason why people seek medical help in western countries, with an estimated prevalence of 10-20 % among the adult population (1). IBS is characterized by abdominal pain or discomfort that subsides with defecation, in association with a change in stool number and/or consistency (2). Presently, IBS has no sensitive biologic markers, hence its diagnosis is still based upon clinical criteria and the exclusion of organic disease. This conditions a suboptimal therapeutic management and significantly impairs patient quality of life, which entails an increase in both direct and indirect costs for society that nearly reach 5 % of the national health care expenditure in many a western country (3). Despite a high prevalence, the pathophysiology of IBS and its development are not well established. Therefore, the study of the underlying etiopathogenic mechanisms and the development of both diagnostic and therapeutic specific tools are key to improve quality of life and reduce health care expenditure.

Because of the development of new technologies, highly relevant advances have occurred in recent years within the field of biomedicine. Specifically, genetic studies have revealed the presence of changes associated with selected conditions by using candidate gene -or whole genome- sequencing techniques. A most used strategy is the analysis of gene polymorphisms, genome variants resulting from mutations in some sequences (one or more bases) that are passed on to the offspring and exhibit a given frequency after multiple generations. Polymorphisms provide the basis for evolution, but not always become consolidated in the general population. Those that persist in subsequent generations may contribute advantages to individuals or be silent, but they also may be involved in the development of a disorder that may become expressed with either high probability (high-penetrance polymorphisms) or low probability (low-penetrance polymorphisms) in their carriers. As with other diseases, the prevalence of IBS in families for generations suggests the presence of related genetic factors, even though no gene or gene group responsible for its development has been identified so far.

The search for IBS-related genetic changes has been influenced by the disorder's own clinical manifestations, as well as the biologic findings from experimental studies. Thus, to date, over 50 genes with a specific role in the motor, secretory, and intestinal barrier functions, in the immune function, and in psychiatric disorders have been evaluated (4,5). One the best researched areas in IBS is the immune function, given the differences identified in these patients versus the healthy population, the presence of low-grade mucosal microinflammation, and the latter's association with intestinal dysfunction in these patients (6,7). Furthermore, several immune mediators in the plasma have been posited as biomarkers for the diagnosis of IBS because of their differential expression from control subjects. However, such differences were not witnessed in other studies, and no molecule has been validated so far.

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In the present issue of *Revista Española de Enfermedades Digestivas* Schmulson et al. (8) discuss the first association study on the polymorphisms of immune mediators -interleukine (IL) 10 and tumor necrosis factor α (TNF-α)- to be performed in Mexico. Prior studies suggested cytokine signaling disbalance as an etiologic factor for the development of IBS (9,10). Secretion of the pro-inflammatory cytokine TNF-α is associated with a single-nucleotide polymorphism (SNP) in this gene's promoter area (-308 G/A), with allele A (A/A or G/A) determining an increase in TNF-α production (11). In turn, anti-inflammatory cytokine IL-10 production is associated with SNPs at positions (-1082 G/A) and (-819 C/T) (12), and genotype (A/A at -1082 and T/T at -819) determines a decrease in IL-10 production. The paper reported in this issue is based on a previous study by the same authors, where they identified decreased serum IL-10 and increased serum TNF-α levels in patients with IBD as compared to healthy controls from the Mexican population (13). Their results revealed no differences in the frequency of high-production genotypes for IL-10 or TNF-α, but did find a higher frequency of low-production genotypes for IL-10 in patients with IBS, diarrheic subtype (IBS-D). The results of the present study are comparable to those of a previous paper, which showed that high IL10 production (-1082 G/G) is less common in patients with IBS as compared to healthy controls (14); however, studies in various countries could not find these associations, hence these findings should be interpreted with caution. While the direct role of these cytokines in the etiopathogenesis of IBS is unknown, persistent low-grade inflammation may result from a decrease in the production of anti-inflammatory cytokines such as IL10, as well as an increase in the production of pro-inflammatory cytokines such as TNF-α (15) or IL1-β (16), or even from a disbalance between these cytokines, regulated at the post-transcriptional level.

Although large-scale, population-based studies are needed to validate these observations, the finding of a genotype associated with decreased IL-10 production in patients with IBS-D suggests a genetic predisposition to changes leading to a reduced anti-inflammatory component in this clinical subgroup. Studies in a higher number of subjects will also allow an assessment of potential associations between polymorphisms and other IBS-related factors, including psychological stress, sex, and the presence of common comorbidities such as chronic fatigue and selected psychiatric disorders. The fact that these studies entail a high cost should be underscored, hence studies performed in a number of subjects such as here (< 150) are significant, as they represent an initial approach required for subsequent large-scale investigations.

Despite advances in the last few years, the pathophysiology of IBS remains unknown. IBS phenotype possibly represents the greatest barrier to this understanding, as this is a heterogeneous, unstable disorder with a clearly multifactorial development. Consideration of environmental factors is also relevant, as these are determinants for the manifestation of IBS-related symptoms. The performance of genetic studies requires clinically characterized subjects allowing subsequent correlation analyses between biologic and clinical findings and environmental factors in order to identify IBS development-related factors. With the aid of within-reach technologies, and as a result of knowledge obtained in recent years, we have possibly come near to defining the etiopathogenic mechanisms underlying IBS, whether conditioned by individual genetic predisposition, exposure to selected external factors, or the confluence of both.

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