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A Preliminary View on Some Genetic Aspects of Irritable Bowel Syndrome with Regards to Neuropsychiatric Manifestations

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Abstract. *Since the newest functional gastrointestinal disorders diagnostic criteria (ROME IV), the formely functional bowel disorder – irritable bowel syndrome (IBS) – is currently known as a common chronic disorder of the brain – gut interaction. The main clinical symptomatology including abdominal pain, discomfort, and altered gastrointestinal motility, as well as the absence of any organic impairment or significant histological changes led to the confirmed hypothesis of multicomponent pathology and multifactorial etiogenesis. Thus, considering our previous experience in this area of research, this mini-review aimed to present a preliminary view of the possible genetic component underlying or predisposing to neurolopsychiatric and gastrointestinal impairments co-ocurring in IBS.*

Key words: irritable bowel syndrome, affective disorders, anxiety, depression, polymorphisms, genetic predisposition

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Irritable bowel syndrome – is it the brain or is it the gut?

The recent studies on the irritable bowel syndrome (IBS) physiopathology and etiology showed that despite the former diagnostic criteria guide (ROME III) described IBS as a functional gastrointestinal disorder, it is currently associated with the brain – gut bidirectional interaction impairment [1,2]. One of the issues addressing this change in classification consisted in the pathophysiological features of IBS that suggested a multicomponent process [3]. Moreover, the description of the multiple non-gastrointestinal co-ocurring impairments led to the assumption that the loss of gastrointestinal functionality could also be an effect additional to the formely reported causes [4].

Still, the clinical characterization of IBS remains valid comprising in the gastrointestinal component – mainly altered gastrointestinal motility and abdominal pain, but also taking into consideration the enteric nervous system (ENS) functionality, central nervous system (CNS) stimuli response modulation, and their interaction [5]. In this way, many of the clinical symptomatological traits lacking organic endorsement (detectable by clinical and paraclinical evaluation) gained possible physiological pathways description (bowel mucosa permeability modulation, hypersensitivity in pain perception, HPA-modulated non-neuropsychiatric response to stress stimuli, etc) [6]. In this context, our group's previous work extensively addressed the neuropsychiatric component of IBS as well as other non-gastrointestinal symptomatology that contributed to the general multicomponent pathological background hypothesis [7].

Despite the fact that many of the IBS-predisposing factors included environemental factors, such as life style, nutrition, physical activity, stress coping mechanisms [8], as well as other physiological mechanisms that could influence the frequency or severity of IBS symptomatology (i.e. menstrual cycle physiology in women, as described by Mulak and Taché [9]), it was recently suggested that the genetic landscape could also play an important role in IBS physiopathology and the frequency/severity modulation of the symptoms [10]. In this way, this mini-review aimed to briefly and preliminarly describe some possible features of the IBS genetic component.

Neuropsychiatric comorbidities in IBS – from start to what end?

Recent studies regarding the effects of the fastidious chronic gastrointestinal symptomatology in the biopsychosocial model showed that its burden as well as the lack of chronicization prevention and treatment could lead to overall quality of life loss, including impaired daily activity, and social interaction [10,11]. In this context, IBS was frequently associated with socio-affective disorders, such as anxiety, depression, and phobias, in an age and/or sex-dependent manner [5,12-14]. In this way, at least half of IBS patients exhibit depressive, anxious, or hypochondriac behaviours [15-17].

Moreover, several reports suggested that several affective disorders predisposing factors, such as acute and chronic stress, early maternal separation, childhood trauma, various traumatic events, and any other abuse history could act as potent modulators of the symptoms severity, disease manifestation, and quality of life in patients with IBS [18,19]. In this way, a possible physiological connection between IBS and socio-affective disorderd could be related to the stress perception and response-associated mechanisms: HPA axis modulated-stress response, visceral pain receptors neuromodulatory pathways, and neuropsychiatric modulation of stress stimuli perception/response [20].

Also, on the other side of the coin, there were many reports on the frequent occurrence of IBS-like symptomatology in neuropsychiatric disorders patients. However, due to stigmatization of psychiatric patients, some of the comorbid pathologies are often missed in evaluation. Moreover, due to the specificity of IBS diagnosis – mainly based on symptomatological evaluation, it was estimated that the prevalence of IBS symptomatology could be much more prevalent, as a certain degree of subjectivity in self-perception could be implicated, as well as sex differences [20]. Despite these aspects, the most prevalent IBS-associated symptomatology was showed to occur in depression and anxiety [21-23].

In other words, the wide range of neuropsychiatric symptoms co-occurring in IBS could suggest common pathophysiological pathways of action or bidirectional potentiation of gastrointestinal, non-gastrointestinal, and socio-affective symtompatology. In this context, Aziz et al. [24] and Cafer and Okan [14], respectively, showed that affective behaviour and sleep regulating brain areas changes were significantly associated with dysbiosis and IBS all of which could be relevant evidence for anxyiolitic and antidepressant treatments efficiency in IBS-associated symptoms alleviation, as shown by Cafer and Okan [14].

Possible genetic features correlating IBS and affective disorders

Thus, since many of the psychiatric disorders undergo complex etiologies comprising genetic and non-genetic risk factors and considering that the neuropsychiatric impairment is a major component of IBS, it could be relevant to study the possible associations between IBS and some genetic features.

For an instance, giving that autism spectrum disorder (ASD) has the most significant genetic component, as compared to other prevalent psychiatric disorders, high prevalence of GI disorders was reported in a severity-depending manner [25,26]. Thus, in the context of a possible cause-effect relationship between ASD and GI impairments a recent genomic study on a large ASD population managed to identify several possible genetic susceptibility loci for IBS, such as the NCAM1, CADM2, PHF2/FAM120A, DOCK9, CKAP2/TPTE2P3 and BAG6, associated with IBS, mood and anxiety disorders [27].

The slow advancing research in IBS genetic component is however due to the phenotypical variations of IBS. Since moleculary opposite constipation and diarrhea were both characterized as hallmarks in IBS gastrointestinal symptomatology (defining two of the most prevalent IBS subtypes), it could be rather difficult to identify the genetic basis of IBS predisposition or, eventually, development. For an instance, Saito et al. [28] suggested that even considering within the affective-modulated IBS (anxiety and non-anxiety), the genetic susceptibility could be different. Despite that, Pace et al. [29] thourougly discussed the genetic landscape of IBS within twin studies and familial inheritance studies. In this way, they reported that the estimated inheritance of IBS risk could be more than 50%, while up to the third generation relatives with IBS showed complex polygenic conditions with combinations of common variants or rare abnormalities of the single gene.

The most studied genetic variants of IBS predisposition belong to the genes of the serotonergic and adrenergic signalling pathways, inflammation, intestinal barrier, pain regulatory processes, as well as resistance/response pathways to microbial infection. Also, the newest member of the brain – gut axis, the microbiome, could interact in certain genetic landscapes to determine a facile predisposition to IBS [30].

Conclusions and future perspectives

Irritable bowel syndrome, a former functional gastrointestinal syndrome, but currently characterized and diagnosed as a brain – gut interaction impairment is a complex multifactorial disorder involving many physiopathological components, such as the gastrointestinal component, the neurological component, and the psychosocial component. As many correlations between the emergence of IBS symptomatology and

already well studied socio-affective disorders were previously described by our group (anxiety, depression, autism), this mini-review brought additional evidence to support the hypothesis of a genetic component of IBS with relation to the genetic landscape reported in psychiatric disorders patients. In this way, several gene variants also implicated in psychiatric disorders could be considered possible genetic predisposing factors in IBS. However, further studies are needed to describe and characterize the interactions between the gastrointestinal and non-gastrointestinal IBS-associated symptomatogy pathways and psychiatric-associated genetic variants. In this context, the fact that neuropsychiatric disorders and IBS could share some genetic traits could also suggest the neurological, rather than functional gastrointestinal, etiology of IBS and provide a promising context in the management of both IBS and psychiatric patients comorbidities.

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