



## *Blastocystis* subtypes and their association with Irritable Bowel Syndrome

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### ABSTRACT

*Blastocystis* spp. is a common intestinal protozoan that affects humans and animals. The role of this parasite as a pathogen is still controversial and it is suspected to be linked to Irritable Bowel Syndrome (IBS), a functional bowel disorder characterized by chronic or recurrent abdominal pain associated with altered intestinal habits. A broad search in electronic databases, libraries, portals of journals, etc. for reports on the association between the parasite and IBS without language restriction was performed. The selection was not restricted by date, but articles published in the last seven years were given preference. We investigated the evidence regarding *Blastocystis* and IBS coexistence as well as the implications of the parasite in pathogenesis and clinical manifestations. Only standardized parasitological tools, supplemented by epidemiological analysis, will be able to clarify whether parasite carriage could be connected to IBS and its status as a human pathogen. Although a variation in pathogenicity and virulence between subtypes has been confirmed, *Blastocystis* can only be considered an indicator of dysbiosis. Accurate diagnoses of this parasitic eukaryote, specifically at genotypic and phenotypic levels, as well as the complete analysis of the intestinal microbial communities, have to be included in the protocol of those patients with IBS.

### Introduction

*Blastocystis* spp. (previously called *B. hominis*) belongs to the phylum Stramenopila, a complex and heterogeneous evolutionary assemblage of heterotrophic and photosynthetic protozoa [1,2]. It is an intestinal parasite that largely affects humans (the only stramenopile settling in the lower digestive tract) and animals such as mammals, birds, reptiles, amphibians and insects [1,3]. *Blastocystis* is considered a ubiquitous parasite of worldwide distribution, being the most prevalent parasitic eukaryote colonizing the human gut and infecting approximately 1 billion individuals worldwide [3,4]. Its prevalence varies from country to country according to hygienic-sanitary conditions, exceeding 5% in industrialized countries and reaching 30–60% in poor countries [5,6]. The use of molecular techniques has provided additional information on the distribution of subtypes, their zoonotic potential and transmission routes [3].

*Blastocystis* presents multiple evolutionary stages (vacuolar, granular, multivacuolar, avacuolar, ameboid and cystic forms) having

different replication strategies, the most common being binary fission [1]. It is a strict anaerobe and exhibits a strong tropism to the intestine [7]. However, its life cycle and transmission are still under investigation. The thick-walled cyst, present in human stools, is believed to be responsible for external transmission via the fecal-oral route, person to person, animal-person, or indirectly, through the ingestion of contaminated water or food [8].

A great genetic variability has been described among isolates from humans and animals, with humans being able to host multiple zoonotic genotypes [7,9,10]. Seventeen subtypes (STs) (ST1–ST17) have been identified based on gene coding of partial small subunit ribosomal RNA of the parasite, and the first nine (ST1–ST9) have been found in humans [11–13], which differ genetically to such an extent that they could, in fact, be considered distinct species [14]. Of the 17 known subtypes, only the entire genome three subtypes ST7, ST4 and ST1 isolates have been sequenced, with a great diversity between them in terms of genome sizes, guanine-cytosine (GC) content, intron numbers, and gene content. Sequencing and annotation of other ST genomes are under

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development and are bound to be useful for a better understanding of the genetic diversity, pathogenesis, metabolic potential and genome evolution of the parasite [15,16,17]. The vast genetic heterogeneity that exists among *Blastocystis* isolates, wherein the key to potential differences in the clinical outcome of parasite carriage may lie [18].

As aforementioned, *Blastocystis* has a zoonotic potential, since there is a preferential distribution of STs among animals that appear to constitute the main reservoir for environmental dissemination and human contamination [1,19]. However, whether *Blastocystis* is an intestinal commensal or a true pathogen remains controversial. Current evidence suggests that it is a pathogenic or opportunistic parasite, associated with a wide range of gastrointestinal and extraintestinal disorders including Irritable Bowel Syndrome (IBS) [2,3]. Scanlan et al. [4] proposed that this parasite should not only be considered a pathogen but also a possible commensal (different STs are found in asymptomatic hosts), or as a biomarker of intestinal functionality as it may be associated with specific intestinal microbial communities.

IBS is a common gastrointestinal condition characterized by chronic or recurrent abdominal pain associated with altered bowel habits. A person's quality of life, as well as health resources, is severely affected by this chronic disease. IBS is considered a functional disorder and is diagnosed using symptom-based criteria [20], in the absence of detectable organic causes, known as Rome IV criteria [21–24]. IBS has a worldwide prevalence of 11.2%, affecting all ages, although younger individuals are more likely to be affected than individuals above the age of 50, and with a female predominant sex ratio of 2:1 according to the World Gastroenterology Organization [24–26]. The Rome IV criteria provide a subclassification of IBS based on the patient's stool characteristics: IBS, with predominant constipation, with predominant diarrhea, with mixed bowel habits and an unclassified subtype [21–24]. The pathogenesis of IBS is not fully understood and has multiple etiologies. Some models consider IBS a product of the cumulative interaction between psychological, physiological, behavioral and environmental factors. The traditional approach has focused on the alterations of motility and visceral hypersensitivity. More recent studies have considered the influence of serotonin, fructose, microinflammation, parasites, alteration of gut microbiota and bacterial overgrowth. Yet, food awareness and genetic predisposition must be taken in account as well [24,27–32].

Post-Infectious Irritable Bowel Syndrome (PI-IBS) is defined as an onset of acute IBS after an individual has experienced a gastrointestinal infection with two or more of the following characteristics: fever, vomiting, diarrhea or a stool diagnosis positive for an infectious agent [33]. Several factors are believed to be involved in the increased risk of developing IBS and PI-IBS, including agent factors such as the nature of the pathogen (bacterial, parasites, virus), host-related factors (genetics, age, sex), psychological state (depression, anxiety, etc.) and dietary factors. Other host diseases or disorders may also be considered predisposing factors of IBS (altered gut microbiota, increased intestinal permeability, food intolerance, altered sensory motor function, etc.) [7,31–34].

In this paper, we hypothesize the potential relation between *Blastocystis* and IBS, and its implications in the pathogenesis of the disease. In addition, whether the clinical outcome could be related to genetic differences of the parasite subtypes or to the host condition will be examined.

## Methods

A systematic review was conducted to identify the most relevant information about *Blastocystis* and IBS. The sources consulted were: databases of health sciences (Medline, Scopus, etc.), scientific electronic libraries (Scielo, Cochrane Plus, ScienceDirect), portals of electronic journals (PubMed) that contain texts with bibliographic references, abstracts or full text databases, academic search engines (Google Scholar), websites (CDC of the United States federal agency),

dictionaries and health science encyclopedias (MedlinePlus).

A broad-based search strategy was used, applying the thesaurus of the databases and a corresponding combination of search terms including specific parasite ("*Blastocystis*", "subtypes", "prevalence" and "pathology") and disease ("Irritable Bowel Syndrome" and "Post infectious Irritable Bowel Syndrome"). A review of the abstracts and full texts of more than 100 publications was conducted. No language restriction was set, but English and Spanish were given preference. The search was not restricted by date, but articles published in the last seven years (2010–2017) were prioritized. Manuscripts considered referential on the subject were included regardless of the date of publication.

## Evaluation of the hypothesis

### *Blastocystis* and IBS

*Blastocystis* is often detected in the stool samples of IBS patients [35–39] and has been related to the pathogenesis of IBS in numerous studies [1,9,26,40]. Infection could be asymptomatic or could be associated to symptoms such as diarrhea, abdominal pain, nausea, vomiting, anorexia, weight loss, lassitude, dizziness, flatulence, and bloating [2,37,41]. These symptoms are unspecific and compatible with IBS, suggesting that some patients harboring parasites could be misdiagnosed with IBS [37]. In addition, this parasite is also associated to skin disorders such as allergic cutaneous lesions (urticaria) and angioedema [42].

The first study considered relevant on the possible link between *Blastocystis* subtypes and IBS was carried out by Giacometti et al. [40]. The authors compared the prevalence of this parasite in IBS-affected individuals (Rome criteria) and in patients with gastrointestinal symptoms, finding that it was significantly more often present in IBS patients (Table 1). Other recent studies also advocated a higher prevalence of the protozoan among IBS patients compared to healthy individuals or patients with other gastrointestinal disorders, supporting a pathogenic role of this parasite in IBS [6,9,36,43–46]. Nourrisson et al. [6] found a higher prevalence of this protozoan in the IBS group (23.2%) than in the control group (16.1%), but only being statistically significant in men (36.8% IBS vs. 4.8% control) (Table 1); an intriguing result considering that women are twice as likely to suffer from IBS than men [28,47,48]. The results from the meta-analysis provided by these

**Table 1**  
Studies of *Blastocystis* spp. prevalence in IBS patients.

Country	Diagnostic Method	Prevalence (%)	
		IBS	Control
France [6]	PCR	F 23.2%	16.1%
		M 36.8%*	4.8%
Italy [40]	Trichrome stain	18.5%*	7.5%
Denmark [37]	Microscopy and culture	4.5%	22.1%
Turkey [43,50]	Lugol stain	38.0%*	11.6%
	Microscopy	5.8%	3.2%
Pakistan [9,44,45]	Microscopy	49.0%*	24.0%
	Culture	53.0%*	16.0%
	PCR	44.0%*	21.0%
	Microscopy	32.0%*	7.0%
	Culture	46.0%*	7.0%
	Microscopy	73.0%*	27.0%
Thailand [49]	Culture	60.0%*	24.0%
	Culture	13.6%	12.0%
India [46]	Culture	16.7%	10.0%
	Microscopy	32.0%	13.0%
	Trichrome stain	28.0%	8.0%
Mexico [36,38]	Culture	30.0%	3.0%
	PCR	33.3%*	15.0%
	PCR	31.0%*	13.0%
	Trichrome stain	15.7%	12.0%

\* Significant association with IBS. F: female; M: male.

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