The role of mycobiota-genotype association in inflammatory bowel diseases: a narrative review

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Abstract
Inflammatory bowel disease (IBD) is a chronic inflammatory disease affecting various parts of the gastrointestinal tract. A majority of the current evidence points out the involvement of intestinal dysbiosis in the IBD pathogenesis. Recently, the association of intestinal fungal composition with IBD susceptibility and severity has been reported. These studies suggested gene polymorphisms in the front line of host defense against intestinal microorganisms are considered to play a role in IBD pathogenesis. The studies have also detected increased susceptibility to fungal infections in patients carrying IBD-related mutations. Therefore, a literature search was conducted in related databases to review articles addressing the mycobiota-genotype association in IBD.

Keywords: Inflammatory bowel disease, IBD, Fungal microbiota, Intestinal mycobiota, Single nucleotide polymorphisms, SNPs

Inflammatory bowel disease pathogenesis
Inflammatory bowel disease (IBD) is a chronic relapsing disease affecting various parts of the gastrointestinal tract and encompasses two common disorders: Crohn’s disease (CD) and Ulcerative Colitis (UC). IBD is a worldwide issue, especially in urban and westernized countries among young individuals [1], assumed to result from an improper and continuous inflammatory response to commensal microbes in a genetically susceptible host [2]. So far, the pathogenesis of the disease is considered to be a combination of genetic predisposition and environmental factors. The majority of current evidence emphasizes the involvement of intestinal dysbiosis in IBD pathogenesis [3]. While intestinal epithelial cells (IECs) are constantly exposed to microbial components; they are regarded not only as a structural but also a functional barrier in the front line of host defense against intestinal microorganisms. The functional alteration of these cells is hypothesized to be associated with IBD [4]. Bacteria as the predominant organisms of the gastrointestinal tract gained the greatest attention in IBD microbial studies [5–7]. Nonetheless, the association of intestinal fungal composition with mucosal inflammation in both CD and UC has recently become into consideration [8–11]. Of note, increased IBD flares were associated with increased global fungal load accompanied by alteration of certain fungal species in the microbiota [12–14].

To date, numerous gene polymorphisms are found to be connected to IBD susceptibility [15] and severity; for instance, an increased colitis severity was driven by activation of Leucine-rich repeat kinase 2 (LRRK2), an important enzyme that regulates innate immunity through nuclear factor kappa B (NF-κB) signaling pathway [16]. Some articles studied the association of specific intestinal bacterial microbiota with gene polymorphisms [17, 18]. However, few have focused on the role of fungal subsets in the intestine. The purpose of this study was to discuss the association of fungal flora with IBD and...
review the articles connecting the gene polymorphisms with intestinal mycobionta in IBD cases.

**Anti-Saccharomyces cerevisiae antibody**

The first sparks of fungi role in IBD pathogenesis flared by detecting elevated levels of anti-Saccharomyces cerevisiae mannan antibodies (ASCA) in the sera of IBD-affected patients since the early 90s [19, 20]. A twin study in 2005 has detected ASCA in CD cases more frequently compared with healthy controls [21]. ASCA was also found commonly in CD patients with a positive family history of IBD [22] and even in unaffected relatives of CD patients [23]. ASCA was not only detected in answer to Saccharomyces antigens but also in response to Candida albicans or the presence of anti-β2 glycoprotein I antibodies in CD patients [24, 25]. Marrakchi et al. revealed a positive correlation of caspase recruitment domain-containing protein 15 (CARD15)/nucleotide-binding oligomerization domain-containing protein 2 (NOD2) gene mutation, an important intracellular pattern recognition receptor (PRR) that is expressed by dendritic cells (DCs), macrophages, and IECs [26], with ASCA expression in IBD-affected patients [27].

**IBD affecting intestinal mycobionta**

In addition to animal studies, some articles are conveying the alteration of intestinal mycobionte in human subjects with IBD. Ott et al. first described significantly higher fungal diversity in patients with CD in comparison with healthy controls, albeit no disease-specific fungal species were present in the CD and UC group [28]. Ever since, many studies have consistently shown an elevated abundance of Candida sp. in IBD fecal samples [29–31]. Lewis et al. have reported an increased amount of S. cerevisiae [29], whereas Hoarau et al. reported a reduction in intestinal S. cerevisiae abundance in IBD patients [31]. Another study in 2009 reported a significantly elevated C. albicans population obtained from fecal samples of CD patients (44%) and their healthy relatives (38%) compared to healthy controls [22]. Li et al. assessed 19 patients with active CD and 7 healthy individuals and discovered increased fecal fungal richness and diversity in C. albicans, Aspergillus clavatus, Cryptococcus neoformans, and a decrease in S. cerevisiae in CD patients. The diversity of the fecal fungal community was also positively correlated with serum C-reactive protein level and the CD activity index [13]. Another study in 2016, revealed a significant increase in global fungal load in both inflamed and non-inflamed mucosa compared with healthy subjects (HS). However, no significant differences in fungal diversity were observed between the groups [12].

Unlike most similar articles, Chehoud et al. demonstrated pediatric IBD to be associated with reduced fungal diversity in the host gut microbiota. Specific Candida taxa were also found to have increased abundance in the IBD samples [30]. An additional study with de-novo pediatric IBD cases revealed a shift from the Ascomycota-predominant mycobionta in HS to a different fungal spectrum with a predominance of Basidiomycetes in patients with de-novo IBD without the conflicting impact of antibiotics or immunosuppression [32]. Later, another study investigated the possible fungal dysbiosis index in IBD; the fecal fungal composition of 235 patients with IBD and 38 HS showed an increased Basidiomycota-to-Ascomycota ratio that was dramatically higher in patients with IBD flares compared to patients in remission and HS [8]. There was also a negative correlation between the abundance of S. cerevisiae and C. albicans in fecal samples of IBD subjects, suggesting a competitive environment between these two species in the gut [8, 33]. The study also described a complex fungal-bacterial interaction in the fecal composition of subjects [8].

As opposed to Sokol and Mukhopadhya et al., Qiu and colleagues did not detect any significant difference in the abundance of Ascomycota, Basidiomycota, and the ratio of Ascomycota-to-Basidiomycota between the HS and UC patients. However, there was a prominent variation in the abundance of Aspergilli between the groups [11]. A recent report studied the cultivable intestinal mycobionta presented in feces obtained from 34 pediatric CD patients, 27 pediatric UC patients, and 32 healthy children. The authors observed increased load of S. cerevisiae and Candida sp. in IBD patients, which was in line with previous studies. Likewise, Di Paola et al. concluded that the presence of S. cerevisiae was associated with a favorable intestinal environment for beneficial bacterial genera, such as Faecalibacterium; whereas the absence of normal fungal flora or presence of unusual fungal species were conjugated with the presence of potential pathogenic bacteria that might lead to IBD [34]. The latest article by Nelson et al. reported an increased abundance of Candida sp. and a decreased Basidiomycota-to-Ascomycota ratio, in contrast to the previous literature, in CD cases [35]. Of note, the discrepancies between these studies might stem from different fungal extraction methods. In this regard, we provided additional information for these studies, including the fungal extraction method and the sample source, in Table 1.

**Innate immunity against fungi**

Several genetic polymorphisms have been detected in IBD over the years [15, 36]. The connection between various genetic polymorphisms with bacterial species in IBD patients has been widely studied [37–39]. Increased susceptibility to systemic fungal complications, such as candidemia was linked to polymorphisms of Interleukin
| Number of patients | Sample/method | Result | References |
|--------------------|---------------|--------|------------|
| 57 IBD patients     | Intestinal mucosa 18S rDNA-based sequencing | Significant higher fungal diversity in patients with CD in comparison with HS. No disease-specific fungal species were found in the CD and UC group | Ott et al. [28] |
| 47 HS               |               |        |            |
| 41 CD families composed of: 129 patients and 113 healthy relatives | Mouth swabs and stool samples were processed using chromogenic medium. Mouth swabs were rubbed directly onto the medium. Stool samples were taken with an inoculation loop. Plates were incubated for 48 h at 37°C. The yeast species were differentiated using the specific color of the colonies. Presumptive identification of yeast species was confirmed by either Bichro-Latex-albicans for C. albicans, or the API 32C system for other species | Top most prevalent mycobiome in CD patients: C. albicans mouth [26 (34.7%)] stool [13 (22%)]; C. glabrata mouth [3 (4%)], stool [1 (1.7%)]; C. tropicalis mouth [1 (1.3%)], stool | Standaert-Vitse et al. [22] |
| 14 healthy controls families composed of 76 individuals |               |        |            |
| 19 patients with active CD | PCR targeting fecal fungal 18S rDNA gene | Decreased S. cerevisiae and overrepresented Aspergillus clavatus, C. albicans, and Cryptococcus neoformans proportions were present in CD patients | Li et al. [13] |
| 7 HS                |               |        |            |
| 90 children with CD | Sequence was acquired using the Illumina HiSeq method (Illumina) | Five yeasts including, S. cerevisiae, C. lusitaniae, Pichia jadinii (also known as C. utilis), C. albicans, and Kluyveromyces marxianus were positively associated with CD, particularly in the setting of greater bacterial dysbiosis | Lewis et al. [29] |
| 26 HS children      |               |        |            |
| 32 patients with IBD | PCR primers targeting fecal fungal the ITS rDNA gene | IBD samples had significantly lower fungal diversity. The most commonly observed fungi were C. Pichia jadinii, C. parapsilosis, was also more common in the pediatric IBD samples. Cladosporium cladosporioides, was more common in HS | Chehoud et al. [30] |
| 90 HS               |               |        |            |
| 9 multiplex families comprising 20 CD patients and their 28 cohabiting NCDR 4 unrelated healthy families 21 individuals with no history of CD (NCDU) living in the same geographic area | PCR primers targeting fecal fungal ITS1 rDNA gene | Increased richness in the NCDU group compared to the CD or NCDR group but no difference in the mycobiome richness of CD patients and their healthy relatives. S. cerevisiae tended to increase in healthy (NCDR) individuals. C. tropicalis was significantly abundant in CD compared to NCDR group | Hoarau et al. [31] |
| 23 CD patients (16 in flare, 7 in remission) | Colonic mucosa ITS2, 16S, and 18S rDNA sequencing | Global fungi load was significantly increased in both inflamed and non-inflamed mucosa compared to HS. However, no significant differences in fungal diversity between the studied groups were observed | Liguori et al. [12] |
| 10 HS               |               |        |            |
| 25 children with IBD | Colonic mucosa 18S rDNA sequencing | A shift from the Ascomycota-predominant microbiota in HS to a different fungal spectrum with Basidiomycetes predominance in patients with de-novo IBD | Mukhopadhyya et al. [32] |
| 12 HS               |               |        |            |
| 235 IBD patients    | PCR primers targeting fecal fungal ITS2 rDNA gene | S. cerevisiae reduction in patients with IBD (vs. healthy controls) and with flare (vs. remission). Higher Basidiomycota-to-Ascomycota abundance ratio in patients with IBD in flare (either UC or CD) but normal ratio in remission | Sokol et al. [8] |
| 38 HS               |               |        |            |


| Number of patients | Sample/method | Result                                                                 | References |
|--------------------|---------------|----------------------------------------------------------------------|------------|
| 14 UC patients 15 HS | PCR primers targeting fecal fungal ITS1 and ITS2 rDNA gene | Wickerhamomyces, an unidentified genus of Saccharomycetales, Aspergillus, Sterigmatomyces, and *Candida* sp. showed an increasing trend in UC patients compared with HS. There was a marked difference in *Aspergillus* abundance between the groups. The proportions of *Ascomycota* and *Basidiomycota* were not significantly different between the groups. | Qiu et al. [11] |
| 93 pediatric; 34 CD, 27 UC patients, 32 HS | PCR primers targeting fecal fungal ITS1-5.8S-ITS2 regions of rDNA gene | *S. cerevisiae* (n = 7 fecal samples) and other yeasts (*Candida* sp.; n = 5 samples) isolated from 19 CD patients. *S. cerevisiae* is associated with a favorable gut environment for beneficial bacterial genera. Whilst, the absence of yeasts or the presence of other yeast species is connected with potential pathogenic bacteria. | Di Paola et al. [34] |
| 34 CD patients 47 HS without GI disease | PCR primers targeting fecal fungal ITS1 rDNA gene | *Candida* sp. was most associated with CD and *Cryptococcus* sp. with non-CD. The *Basidiomycota/Ascomycota* abundance ratio was found to be significantly lower in CD patients. | Nelson et al. [35] |

CD, Crohn disease; IBD, Inflammatory bowel disease; UC, Ulcerative colitis; ITS 1,2, Internal transcribed spacer 1,2; HS, Healthy subjects; *C. albicans*, *Candida albicans*; *C. tropicalis*, *Candida tropicalis*; *C. glabrata*, *Candida glabrata*; sp., species; *C. Pichia jadinii*, *Candida Pichia jadinii*; *C. parapsilosis*, *Candida parapsilosis*; M. restricta, *Malassezia restricta*; M. sympodialis, *Malassezia sympodialis*; *S. cerevisiae*, *Saccharomyces cerevisiae*; NCDR, Non-CD relatives.
As Table 2 represents, here, we concentrated on articles reporting the mutations of innate immunity components and resulted in the gut mycobiome alteration. In a recent article, Limon et al. expressed that colonization of the colonic mucosa with *Malassezia restricta*, a commensal fungus typically found on the skin, might increase IBD severity in patients with *CARD9*<sup>S12N</sup> risk allele. They found out that the *CARD9*<sup>S12N</sup> variant induces a potent pro-inflammatory cytokine response against *M. restricta* in IBD [57]. By examining the SYK-CARD9 signaling axis and gut fungi, Malik et al. also demonstrated the decreased occurrence of *Ascomycota* along with elevation of *Saccharomyces* in *Card9*<sup>−/−</sup> mice. They implied that a normal inflammasome assembly in an unperturbed SYK-CARD9 signaling axis led to protection against colitis and colon cancer and also promoted T cell-mediated anti-tumorigenic responses; thereby indicating that a healthy gut mycobiota could prevent the development of IBD [58]. According to Lamas et al., the fungal microbiota of wild type and *Card9*<sup>−/−</sup> mice with induced-colitis mainly were members of the *Ascomycota*, *Basidiomycota*, and *Zygomycota* phyla. However, there were different measurements at the days 0, 7, and 12, and both groups reached a peak at day 7 that was higher in *Card9*<sup>−/−</sup> mice. On day 7, *Card9*<sup>−/−</sup> mice showed decreased fecal *Ascomycota*, increased fecal *Basidiomycota*, and *Zygomycota* communities [59].

**CX3CR1-T280M** (rs3732378) is a common polymorphism that has been previously detected in extra-intestinal inflammatory diseases [60, 61]. In 2018, Leonardi et al. described that CX3CR1<sup>+</sup> MNPs not only modifies adaptive immune responses to intestinal fungi and controls the mycobiota during experimental colitis in animal models (without changing bacterial communities), but is also connected with a decrease in antifungal antibody responses in CD patients. They concluded that intestinal mycobiota and CX3CR1-dependent immune responses might provoke extra-intestinal manifestations of inflammatory diseases [62]. Elevated antifungal antibodies detected in patients with alcoholic liver disease, Graves' disease, spondyloarthritis, and systemic lupus erythematosus corroborate this hypothesis [63]. Finally, the article provided evidence for CX3CR1<sup>+</sup> MNPs as a mediator between gut mycobiome and both local and systemic immunity [55].

A previous study was conducted by Sokol et al. to examine the correlation between host genotype and fungal microbiota in IBD patients. The ten most significant connections between IBD-associated fungi taxa and single-nucleotide polymorphisms (SNPs) were as follows: *Malassezia sympodialis* association with Dectin-1 (rs2078178, rs3901533), TLR1 (rs4833095, rs5743618), and Mincle (rs10841845); *S. cerevisiae* with *CARD9* (rs10781499) and TLR3 (rs3775291); *Ascomycota* with DC-SIGN (rs2287886) and TLR1 (rs5743611); and *Basidiomycota* with TLR1 (rs5743611). They also provided evidence supporting the negative correlation of *M. sympodialis* fecal
**Fig. 1** The cascade of innate immune response against intestinal fungi. Several fungal cell wall polysaccharides initiates immune responses, Dectin-1 binds β-glucans, dectin-2 binds α-mannans, and Mincle attaches the glycolipid trehalose-6,6-dimycolate (TDM), trehalose-6,6-dibehenate (TDB), and α-mannose residues. DC-SIGN binds N-linked mannans. Dectin-1, dectin-2, and mincle begin intracellular signaling through the SYK activation. RAF-1 as an SYK-independent activator of NF-κB pathway actuated by DC-SIGN and dectin-1. NF-κB pathway leads to TH1 and TH17 activations and subsequent cytokine production. CX3CR-1 is expressed by intestinal-resident mononuclear phagocytes (MNPs) and participate in fungal recognition.

**Table 2** Intestinal mycobiota-genotype association in IBD

| Animal/ human sample | Fungal extraction | Mycobiota-genotype | References |
|----------------------|-------------------|--------------------|------------|
| CD patients Mucosal-tissue | The ITS1 rDNA sequencing | *M. restricta* (CARD9 S12N alleles) | Limon et al. [57] |
| Card9<sup>−/−</sup> mice feces | 18S ITS rDNA sequencing | Decreased Ascomycota, elevation of Saccharomycetes (CARD9) | Malik et al. [58] |
| Card9<sup>−/−</sup> mice feces | ITS2 rDNA sequencing | Ascomycota, Basidiomycota, and Zygomycota (CARD9) | Lamas et al. [59] |
| CX3CR1<sup>−/−</sup> mice, CD patients | enzyme-linked immuno-sorbent assay (ELISA) | Decreased antibody production against Candida sp. (CX3CR-1) | Leonardi et al. [62] |
| IBD patients Fecal samples | ITS2 rDNA sequencing | Positive correlation: *M. sympodialis* (rs2078178, rs3901533), [TLR1 (rs4833095, rs5743618)], [Mincle (rs10841845)] *S. cerevisiae* (CARD9 (rs10781499), [TLR3 (rs3775291)]) Ascomycota (DC-SIGN (rs2287886), [TLR1 (rs5743611)]) Basidiomycota (TLR1 (rs5743611)) Negative correlation: *M. sympodialis* (Dectin-1 (rs2078178, ‘T’ allele 12)) *S. cerevisiae* (CARD9 (rs10781499, ‘A’ allele 21)) | Sokol et al. [8] |
| Clec4d<sup>−/−</sup> mice feces | 18S rDNA sequencing | *C. tropicalis* (CLEC4D) | Wang et al. [64] |
| Clec7<sup>−/−</sup> mice feces | ITS1-2 rDNA sequencing | Increased Candida and Trichosporon sp. Decreased nonpathogenic Saccharomyces sp. | Iliev et al. [66] |
| CD patients Fecal sample | ITS1 rDNA sequencing | No differences were evident with NOD2 variances | Nelson et al. [35] |

**Notes:**
- ITS 1,2: Internal transcribed spacer 1, 2; CARD9: CARD9, Caspase recruitment domain-containing protein 9; TLR3, Toll-like receptors 3; TLR1, Toll-like receptors 1; CLEC4D, C-Type Lectin domain containing 4D; CLEC7A, C-Type Lectin domain containing 7A; DC-SIGN, Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin receptor; MINCLE, Macrophage inducible Ca<sup>2+</sup>-dependent lectin receptor; NOD2, Oligomerization domain-containing protein 2; *M. restricta, M. sympodialis, M. sympodialis*, *S. cerevisiae, Saccharomyces cerevisiae; C. tropicalis, Candida tropicalis*, sp., species.
abundance with Dectin-1 SNP (rs2078178, ‘T’ allele 12) in medically refractory UC; M. sympodialis was also decreased during the IBD flares in patients. Moreover, the IBD-associated CARD9 variation (rs10781499, ‘A’ allele 21) was inversely correlated with the fecal abundance of S. cerevisiae. Lastly, they reported a decrease in fungal biodiversity only in UC and CD patients without ileal involvement [8].

Wang et al. described the role of Dectin-3 (a family member of CLR) in recognizing Candida. tropicalis in experimental-colitis pathogenesis for the first time. They observed that C. tropical increased the disease burden in Clec4d−/− mice during the induced colitis. Since the C-Type Lectin domain containing 4D (CLEC4D) is the encoding gene for Dectin-3, Clec4d−/− mice were more susceptible to induced colitis due to the activation of the NF-κB signaling pathway64.

The impact of NOD2 variants on the intestinal bacterial community in CD patients has previously been described [65]. Thus, Nelson et al. investigated the presence of NOD2 polymorphisms in CD patients and its relation with fecal fungal diversity but did not find any significant correlation between NOD2 variants and specific intestinal fungi community [35].

Dectin-1 is the most important fungal PRR expressed by innate immune cells, such as macrophages, dendritic cells, and neutrophils. C-Type Lectin domain containing 7A (CLEC7A) is the gene that encodes Dectin-1. Clec7−/− mice with induced colitis had increased proportions of opportunistic pathogenic fungi including Candida sp. and Trichosporon sp. along with a decreased frequency of nonpathogenic Saccharomyces. Ilijiv et al. identified a significant association between CLEC7A SNP (rs2078178) and patients suffering from medically refractory UC and delineated the role of Dectin-1 as a fungal receptor during severe forms of colitis [66]. Other gene polymorphisms were also described to influence Dectin-1-associated immunity in IBD [16, 67]. Among these genes, LRRK2 has also been described as the familial Parkinson’s disease genetic risk factor. Multiple variations in LRRK2 comprising N2081D, rs11175593 LRRK2/MUC19, and rs11564258 LRRK2/MUC19 were associated with IBD as well [68]. Takagawa et al. suggested an increase in severity of colitis, mediated by increased Dectin-1–induced immunity, in (rs11564258) LRRK2/MUC19 polymorphism carriers [16]. Noteworthy, this variance (rs11564258) had the second-highest odds ratio in IBD patients of the European population [69]. Further studies are required to identify the intestinal mycobiota in the patients carrying this mutation.

Conclusion
In summary, the role of intestinal fungal mycobiota in IBD pathogenesis and severity index have been quite underrated. This review emphasizes that a majority of IBD-affected patients had increased diversity and richness of intestinal mycobiome, higher abundance of C. albicans and Basidiozyma-to-Ascomycota ratio, and a decreased proportion of S. cerevisiae despite a few contradictory results in other studies.

It is widely known that innate immunity takes part in intestinal fungal recognition and mutations in innate immunity mediators are linked to IBD pathogenesis. Even so, few articles aimed to examine the connection between gene polymorphisms and intestinal fungal dysbiosis in IBD.

Although DSS-induced colitis is a well-established experimental murine model with much resemblance to human IBD [70], we were able to find only three non-murine studies containing mycobiota-genotype data related to IBD patients. Additional evidence is needed to determine whether different gene polymorphisms can alter intestinal mycobiome or whether this information would be of use in providing novel insight into IBD pathogenesis. Therefore, our purpose was to highlight the importance of the matter and draw attention to this underappreciated aspect of IBD-associated research.

Abbreviations
IBD: Inflammatory bowel disease; CD: Crohn’s disease; UC: Ulcerative Colitis; IECs: Intestinal epithelial cells; LRRK2: Leucine-rich repeat kinase 2; ASCA: Anti-Saccharomyces cerevisiae antibody; CARD15: Caspase recruitment domain-containing protein 15; NOD2: Nucleotide-binding oligomerization domain-containing protein 2; PRR: Pattern recognition receptor; DCs: Dendritic cells; IL-10: Interleukin 10; MNCs: Mononuclear phagocytes; SYK: Spleen tyrosine kinase; SNPs: Single-nucleotide polymorphisms; TLR3: Toll-like receptors 3; CLEC4D: C-Type Lectin domain containing 4D; CLEC7A: C-Type Lectin domain containing 7A; TH1: T helper 1; TH17: T helper 17; IL-1: Interleukin 1; IL-17: Interleukin 17.

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