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ORIGINAL RESEARCH

Correlation Of Fut2 And Fut3 Gene Polymorphisms With Inflammatory Bowel Disease In Guangxi Zhuang Population

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Objective: This study aimed to investigate the association between the polymorphisms of the FUT2 gene (rs1047781, rs601338) and the FUT3 gene (rs3745635, rs28362459) with susceptibility to inflammatory bowel disease (IBD) in the Zhuang population of Guangxi.

Methods: Intestinal mucosal tissues were collected from 113 Zhuang patients (41 with Crohn's disease [CD] and 72 with ulcerative colitis [UC]) and 120 han patients (42 with CD and 78 with UC), all of whom were unrelated and diagnosed with IBD, as well as from 106 Zhuang and 119 han unrelated healthy controls, from January 2021 to December 2023. DNA was extracted from intestinal mucosal samples in each group. FUT2 gene polymorphisms (rs1047781, rs601338) and FUT3 gene polymorphisms (rs3745635, rs28362459) were amplified using polymerase chain reaction (PCR). PCR product fragments were analyzed by DNA sequencing, and sequence analysis was conducted using the GenBank database.

Results: The genotype and allele frequencies of the FUT2 rs1047781 polymorphism in the Zhuang UC patient group were significantly different from those in the control group ($P < 0.05$). Similarly, significant differences were observed in the genotype and allele frequencies of the FUT3 rs3745635 polymorphism in the Zhuang UC and CD patient groups compared to controls ($P < 0.05$). No statistically significant differences were found in the genotype and allele frequencies of FUT2 rs1047781 between the Zhuang CD patients and controls ($P > 0.05$). Additionally, no significant differences were observed in the genotype and allele frequencies of FUT2 rs601338 and FUT3 rs28362459 polymorphisms between the Zhuang UC and CD patient groups and the controls ($P > 0.05$).

Conclusion: The FUT2 rs1047781 and FUT3 rs3745635 polymorphisms may be associated with IBD in the Guangxi Zhuang population, while FUT2 rs601338 and FUT3 rs28362459 polymorphisms may not show such an association.

Keywords: fucosyltransferase 2, fucosyltransferase 3, inflammatory bowel disease, IBD, ulcerative colitis, UC, Crohn'disease, CD

Introduction

Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD), is a chronic, non-specific inflammatory condition of unknown etiology. Although the incidence and prevalence of IBD are lower in Asian populations compared to Western countries, there has been a notable rise in cases in East Asia in recent years.[1,2] The pathogenesis of IBD is multifactorial, involving genetic, environmental, infectious, and immune factors, with genetic susceptibility playing a critical role in its development.[3]

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Fucosyltransferase (FUT) is a class of hexosyltransferases responsible for glycosylation, where sugars are covalently attached to proteins or lipids to form glycoconjugates. Glycosylation, a significant post-translational modification, influences protein stability, folding, transport, localization, secretion, and biological functions, including receptor activation and signal transduction.[4] Cellular fucosylation, specifically, is catalyzed by FUT enzymes. The FUT2 and FUT3 genes are involved in the synthesis of histo-blood group antigens (HBGA) by adding fucose residues to precursor substrates.[5] HBGA include ABH and Lewis antigens.[6] Dysbiosis of the gut microbiota is one of the contributing factors to IBD, and HBGA serve as binding sites and energy sources for certain intestinal microbes, such as Helicobacter pylori, norovirus, and rotavirus.[7–10] Thus, HBGA play a crucial role in the formation and function of the intestinal microbiota.[8,11,12] Studies indicate that the FUT2 gene polymorphism, which causes a non-secretor state, influences innate immune responses by altering gut microbiota composition.[13–15] In European populations, the FUT2 rs601338 (G428A) homozygous mutation leads to the non-secretor phenotype, while in the Chinese population, the FUT2 rs1047781 (A385T) homozygous mutation is prevalent.[16]

Research has shown significant differences in the distribution and phenotype of FUT2 and FUT3 genes across ethnicities and geographical regions in IBD populations.[6,17] McGovern et al[17] reported an association between the FUT2 rs601338 polymorphism and CD but not UC. FUT2 rs601338 and rs1047781 are common mutation sites in Caucasian and Chinese populations, respectively.[18,19] However, a study from Finland suggested that the FUT2 rs601338 wild-type (GG) variant increased the risk of UC.[20] In China, FUT2 rs1047781 and rs601338 have been identified as UC-associated mutation sites in the Uygur population, and the FUT2 rs601338 polymorphism is associated with UC susceptibility in the Han population.[21]

Research on FUT3 gene polymorphisms in IBD is limited. Studies have linked FUT3 polymorphisms rs28362459, rs3745635, and rs3894326 with susceptibility to UC and CD in the Han population of southern China.[5,6,22,23] Currently, there is no research on the association between FUT2 and FUT3 gene polymorphisms and IBD in the Guangxi Zhuang population. This study aims to investigate the correlation between FUT2 and FUT3 gene polymorphisms and IBD susceptibility in the Guangxi Zhuang population, and to explore the relationship between these polymorphisms and clinicopathological features of IBD.

Materials and Methods

Patients and Controls

The study group comprised 113 patients with IBD of Zhuang ethnicity [72 with ulcerative colitis (UC) and 41 with Crohn's disease (CD)] and 120 patients with IBD of Han ethnicity [78 with UC and 42 with CD] without genetic kinship, recruited from the Gastroenterology Department at the First Affiliated Hospital of Guangxi Medical University, between January 2021 and December 2023. All patients had a confirmed diagnosis of UC or CD, based on the standard clinical criteria established by the Chinese Society of Gastroenterology in the 2018 Beijing Consensus.[24] Patients with other forms of infectious colitis or autoimmune diseases were excluded.

The control group included 225 healthy individuals without genetic kinship, comprising 106 Zhuang and 119 han subjects, with no history of tumors, autoimmune diseases, or familial IBD. Demographic data was collected (Table 1). There were no significant age or sex differences between the study and control groups. The lesion location, stages and severity of IBD group were shown in Table 2. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of The First Affiliated Hospital of Guangxi Medical University [2024-E795-01]. A written informed consent was obtained from all participants.

DNA Extraction

Fresh intestinal mucosa specimens (30–50 mg) were collected, washed with saline, and cut into pieces. DNA was extracted using the Genomic DNA Extraction Kit (TIANGEN Biotechnology Co., Ltd., Beijing, China) following the manufacturer's instructions. DNA was dissolved in 100 μL TE buffer, and its concentration and purity were measured before storage at −20°C.

Table 1 Demographic Characteristics of Patients With IBD and Controls

Items	IBD		Controls		P value
	Zhuang	Han	Zhuang	Han	
N	113	120	106	119	
Gender [n(%)]					0.989
Male	61	64	57	66	
Female	52	56	49	53	
Age, years(mean ± SD)	48.4±12.3	46.4±11.0	49.3±12.4	49.4±13.3	0.314
Current smoking[n(%)]					0.708
Yes	12	15	10	11	
No	101	105	96	108	

Note: P value > 0.05: No significance.

Table 2 Lesion Location, Stages and Severity of IBD Group

Characteristics	Zhuang Patients with IBD		Han Patients with IBD	
	CD	UC	CD	UC
N	41	72	42	78
Lesion location [n(%)]				
Rectum	–	30	–	34
Left hemicolon	–	5	–	15
Right hemicolon	2	4	4	–
Extensive colon	–	33	–	29
Terminal ileum	32	–	36	–
Ileocolon	7	–	2	–
Stages[n(%)]				
Remission	4	22	12	18
Activity	37	50	30	60
Severity[n(%)]				
Mild and Intermediate	39	63	40	67
Severe	2	9	2	11

Polymerase Chain Reaction (PCR) and Sequencing

Primers for amplifying FUT2 gene (rs1047781, rs601338) and FUT3 gene (rs3745635, rs28362459) were designed based on the National Center for Biotechnology Information (NCBI) gene database, as shown in Table 3 (primers synthesized by TAKARA Biotechnology Co., Ltd., Dalian, China). PCR reactions for all gene polymorphisms were conducted in a thermocycler (Veriti, Applied Biosystems, Inc). Each reaction used a 50 μL volume, including 2 μL genomic DNA, 25 μL Premix Taq (Ex Version 2.0 plus dye), 1 μL of each primer (forward and reverse), and RNase-free water up to 50 μL.

The temperature conditions were as follows:

- **FUT2** (rs601338, rs1047781): 35 cycles of denaturation at 98°C for 10s, annealing at 54°C for 30s, extension at 72°C for 1 min, with a final extension at 72°C for 10 min.
- **FUT3** (rs3745635): 35 cycles of denaturation at 98°C for 10s, annealing at 55°C for 30s, extension at 72°C for 1 min, with a final extension at 72°C for 10 min.
- **FUT3** (rs28362459): 35 cycles of denaturation at 94°C for 30s, annealing at 60°C for 30s, extension at 72°C for 1 min, with a final extension at 72°C for 10 min.

Table 3 Amplification Primers of FUT2 and FUT3 Gene

SNP	Sequence of Primers(5'→3')	Fregments(bp)
rs 601338	F:5'-GCGAGTACGCCACACTGTA-3' R:5'-CCAGCAAACACCACATCAC-3'	562
rs 1047781	F:5'-GCGAGTACGCCACACTGTA-3' R:5'-CCAGCAAACACCACATCAC-3'	562
rs3745635	F:5'- AGAGGTTGAGCGGTGGGT-3' R:5'- GCTGATTTTTGCTGTGAGTC-3'	719
rs28362459	F:5'- CATCAATGACCCTCACTCC-3' R:5'- ATGTCCATAGCAGGATCAGG-3'	257

All PCR products were stored at 4°C and electrophoresed in a 2% agarose gel using 1× TBE buffer at 140V for 40–45 minutes, visualized with a Gel imaging system (Bio-Rad Gel Doc-2000, United States), and confirmed with reference DNA. PCR products of FUT2 (rs1047781, rs601338) and FUT3 (rs3745635, rs28362459) were sent to GenScript Biotechnology Co., Ltd. (Nanjing, China) for purification and sequencing. Genotypes were interpreted using Chromas software.

Statistical Analysis

Genotype frequencies were calculated by direct counting, and the Hardy-Weinberg equilibrium test was used to assess the distribution of mutation genotype frequencies. Fisher's exact test and chi-square test were applied to compare genotype and allele frequency distributions between patients and controls using SPSS 24.0 software (SPSS Inc., Chicago, IL, USA). A p-value of < 0.05 was considered statistically significant.

Results

The PCR products from all subjects were consistent with the expected fragment sizes. After amplification, the fragment lengths of FUT2 (rs1047781, rs601338) and FUT3 (rs3745635, rs28362459) genes were 562 bp, 562 bp, 719 bp, and 257 bp, respectively, confirming successful amplification (Figures 1–3). Sequencing results of FUT2 (rs1047781, rs601338) and FUT3 (rs3745635, rs28362459) genes are presented in Figures 4–7. Genotype and allele frequency distributions of these polymorphisms were tested for Hardy-Weinberg equilibrium; no statistically significant differences were observed between groups (all $p > 0.05$), indicating that the case and control groups reached genetic equilibrium and are representative of the population.

Significant differences in genotype and allele frequencies of FUT2 rs1047781 were found in the UC group compared with the control group in both Zhuang and Han populations ($p < 0.05$). No significant differences in genotype or allele frequencies of FUT2 rs1047781 were detected between the CD group and control groups in either Zhuang or Han

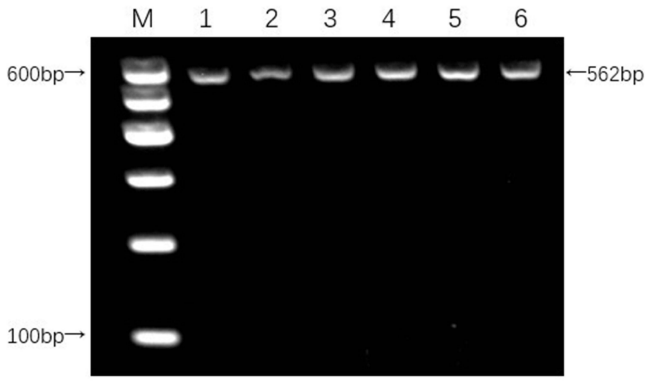

Figure 1 Polymerase chain reaction (PCR) product of FUT2 rs1047781 and rs601338, showing a single band at 562 bp. (M) Molecular weight marker.

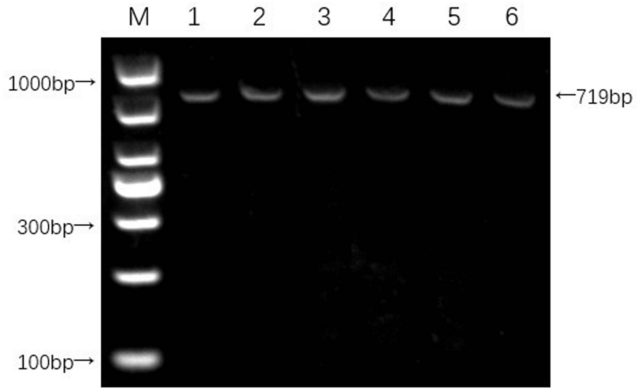

Figure 2 PCR product of FUT3 rs3745635, showing a single band at 719 bp. (M) Molecular weight marker.

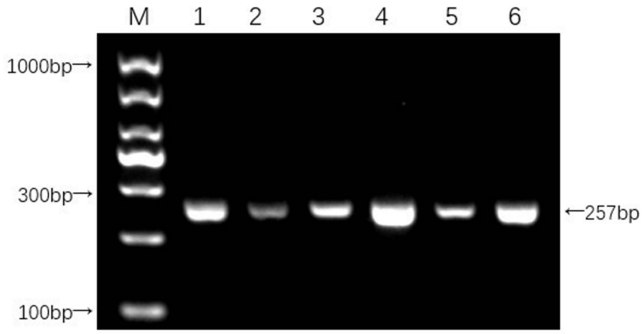

Figure 3 PCR product of FUT3 rs28362459, showing a single band at 257 bp. (M) Molecular weight marker.

populations ($p > 0.05$). Similarly, no significant differences were found in the genotype and allele frequencies of FUT2 rs601338 polymorphism between UC and CD groups and their respective controls in Zhuang and Han populations ($p > 0.05$). In contrast, significant differences in genotype and allele frequencies of FUT3 rs3745635 polymorphism were observed in the UC and CD groups of Zhuang patients compared with controls ($p < 0.05$), while no significant differences were detected in Han patients ($p > 0.05$). No significant differences were found in the genotype and allele frequencies of FUT3 rs28362459 polymorphism between UC and CD groups and controls in both Zhuang and Han populations ($p > 0.05$) (Tables 4 and 5). Furthermore, no significant differences in genotype and allele frequencies of FUT2 rs1047781 polymorphism were observed in UC patients with (El+E2) group compared to UC patients with E3 group in both Zhuang and Han populations ($p > 0.05$). Genotype and allele frequencies of FUT2 rs1047781 did not significantly correlate with disease severity in both Zhuang and Han UC patients (Table 6).

Discussion

The incidence and prevalence of IBD in Asia, particularly East Asia, have shown a continuous upward trend in recent years.[1,2] Although IBD is less common in China than in Europe and the United States, its incidence is gradually rising. China is now one of the Asian countries with a higher incidence of IBD.[25–27] The exact pathogenesis of IBD remains unclear, but it is generally thought to involve an interplay of genetic, immune, environmental, and microbial factors. These factors may act upon genetically susceptible individuals, leading to an abnormal immune response to gut microbiota and triggering intestinal inflammation, which results in tissue damage.[10] Genetic susceptibility plays a significant role in the development of IBD. Over the past two decades, genome-wide scanning has identified susceptibility loci on human chromosomes 1, 3, 4, 5, 6, 7, 10, 12, 14, 16, 19, and X, with nine specific loci associated with IBD, named IBD1-9.[28] Some susceptibility genes commonly found in Western patients with IBD, such as DLG5,

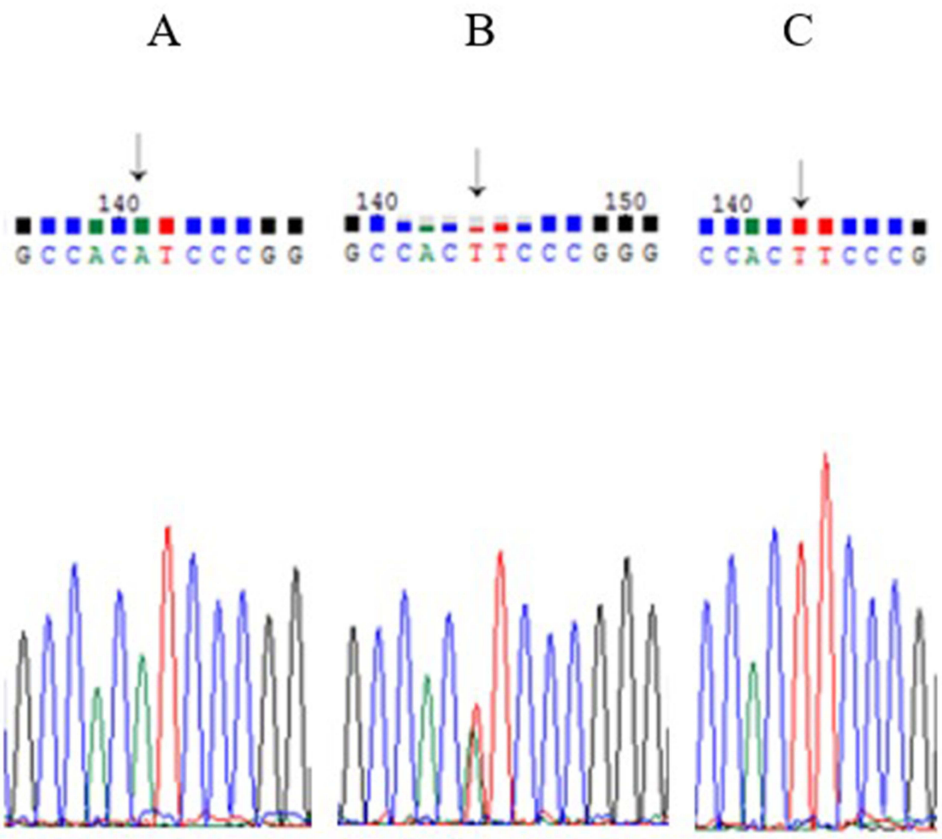

Figure 4 The sequencing results of FUT2 rs1047781. (**A**) The wild-type homozygotes; (**B**) The heterozygous mutant; (**C**) The homozygous mutant.

ATG16L1, and OCTN, show no polymorphisms or are not associated with IBD susceptibility in Asian populations, suggesting racial differences in IBD incidence and genetic predisposition.[29]

The role of gut microbiota imbalance in IBD pathogenesis has attracted increasing attention.[30,31] The human intestinal cavity hosts approximately 10^14 microorganisms, primarily classified into four major groups: Firmicutes, Actinobacteria, Bacteroidetes, and Proteobacteria.[32,33] A stable gut microbiota is crucial for maintaining health. Alterations in the number, structure, and diversity of gut microbiota impact IBD pathogenesis by affecting mucosal barrier function, metabolic processes, and immune responses.[34] The composition of gut microbiota is influenced not only by environmental and health factors but also, to some extent, by host genetics. The FUT2 and FUT3 genes, located on chromosomes 19q13 and 19p13, respectively, fall within the chromosomal region (IBD6) associated with IBD susceptibility. To date, 11 known fucosyltransferases (FUTs) are classified into four groups. The FUT2 gene is involved in α-1,2 fucoside bond synthesis, while FUT3 is associated with α-1,3/4 fucoside bond synthesis.[35]

Fucosyltransferases encoded by FUT2 and FUT3 co-regulate the expression of histo-blood group antigens (HBGA), including ABH and Lewis antigens.[5] The FUT2 gene encodes α-(1,2)-fucosyltransferase, which synthesizes the H antigen that can further form A or B antigens, constituting the ABH blood group antigen. Hence, ABH antigen expression is primarily regulated by the FUT2 gene.[36] Individuals expressing ABH antigen in saliva, secretions, and mucosal tissues are termed secretors; otherwise, they are non-secretors. This difference is due to polymorphisms in the FUT2 gene, with non-functional variants resulting in deficient enzyme activity.[37,38] Approximately 20% of the population lacks ABH antigen expression in body fluids.

Wacklin et al[39] investigated the intestinal microbiota composition of non-secretors and secretors, finding distinct differences between the two groups. Non-secretors exhibited a significantly lower diversity of intestinal flora. Specifically, bacteria genera such as Dorea formicigenerans, Blautia, and Ruminococcus gnavus, which have been associated with IBD in previous studies, were less prevalent in non-secretors. The absence of blood group antigens in

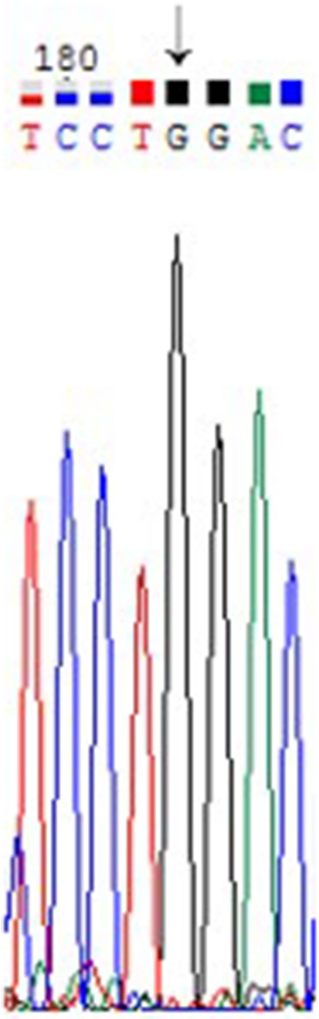

Figure 5 The sequencing results of FUT2 rs601338. The wild-type homozygote.

non-secretors affects the intestinal microbiota structure, potentially leading to inflammation. HBGA has been linked to various pathogenic infections, including Vibrio cholerae, Helicobacter pylori, and Norovirus.[7,40,41] HBGA functions not only as binding sites for microbes like H. pylori, Campylobacter jejuni, Norovirus, and rotavirus but also serves as a carbon source, providing energy for the metabolism of some intestinal microorganisms (eg, Bacteroides) and influencing microbiota structure.[5]

Studies show that non-secretor states caused by FUT2 mutations increase susceptibility to Haemophilus but reduce susceptibility to Norovirus.[41] Mucins (MUC), essential in the gut, undergo fucosylation, which promotes their maturation and enhances the mucosal barrier function.[42] Mucin also serves as a carrier for ABH and Lewis antigens.[43] Fucosylation, a critical glycosylation process, regulates mucosal infection resistance and inflammation. Fucosylation by FUT2 and FUT3 is vital for mucin maturation and integration.[43] Intestinal innate immune cells, especially ILC3, significantly increase epithelial fucosylation.[44] IL-22 from ILC3 binds to intestinal mucosal IL-22 receptors, activating the STAT3 signaling pathway and promoting defense gene expression, such as FUT2 and RegIIIγ, in the mucosa.[45] IL-22 upregulates FUT2 in the epithelium, contributing to the barrier's inhibitory effect on microbial translocation in chronic colitis.[46] Studies indicate that FUT2 deficiency in epithelial cells alters microbiota composition and function, increasing lysophosphatidylcholine (LPC), which promotes IBD progression.[8] Moreover, intestinal flora can induce FUT2 transcription via ERK and JNK pathways after binding to mucosal receptors, enhancing fucosylation of colon mucosal cell polysaccharides, which aids microbial colonization[47] (Figure 8).

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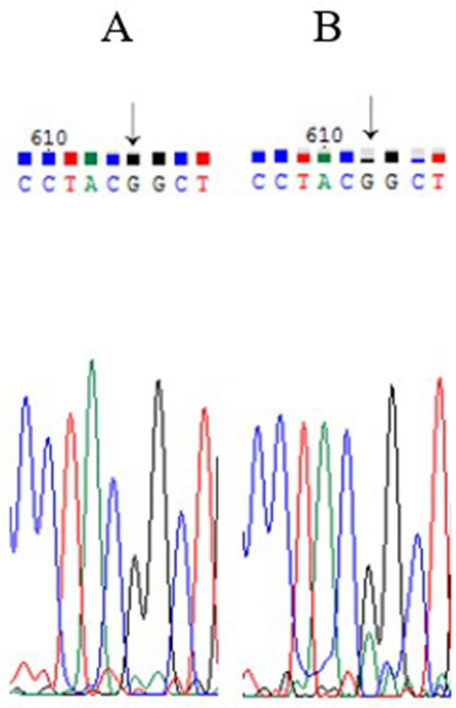

Figure 6 The sequencing results of FUT3 rs3745635. (**A**) The wild-type homozygotes; (**B**) The heterozygous mutant.

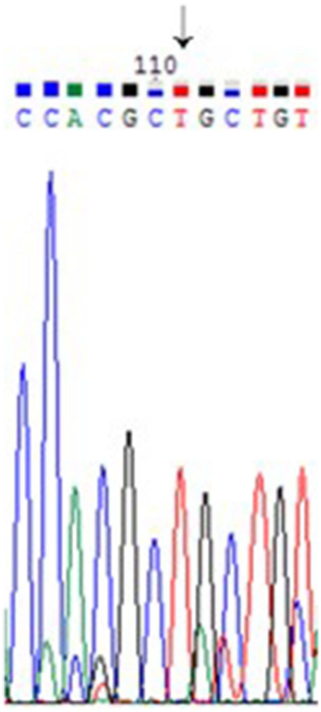

Figure 7 The sequencing results of FUT3 rs28362459. The wild-type homozygote.

Table 4 Genotype and Allele Frequency Distribution of the Four SNPs in Zhuang Population

	Genotype	Allele	Control	UC	CD
				P value	P value
rs1047781				[1]P=0.002	P=0.659
	A/A		40(37.7)	14(19.4)	13(31.7)
	A/T		48(45.3)	30(41.7)	22(53.7)
	T/T		18(17.0)	28(38.9)	6(14.6)
		T	84(39.6)	86(59.7)	34(41.5)
				[2]P<0.001	P=0.733
rs601338				[3]P=1.000	P=1.000
	G/G		106(100)	72(100)	41(100)
	A/G		0(0)	0(0)	0(0)
	A/A		0(0)	0(0)	0(0)
		A	0(0)	0(0)	0(0)
				[4]P=1.000	P=1.000
rs3745635				[5]P<0.001	P<0.001
	G/G		88(83.0)	72(100)	41(100)
	A/G		18(17.0)	0(0)	0(0)
	A/A		0(0)	0(0)	0(0)
		A	36(17.0)	0(0)	0(0)
				[6]P<0.001	P<0.001
rs28362459				[7]P=1.000	P=1.000
	T/T		106(100)	78(100)	41(100)
	T/G		0(0)	0(0)	0(0)
	G/G		0(0)	0(0)	0(0)
		G	0(0)	0(0)	0(0)
				[8]P=1.000	P=1.000

Notes: [1/3/5/7]Comparison of genotype frequency. [2/4/6/8]Comparison of allele frequency. UC: Ulcerative colitis; CD: Crohn's disease; A P value > 0.05: No significance.

Table 5 Genotype and Allele Frequency Distribution of the Four SNPs in Han Population

	Genotype	Allele	Control	UC	CD
				P value	P value
rs1047781				[a]P<0.001	P=0.297
	A/A		26 (21.8)	15 (19.2)	14 (33.3)
	A/T		77 (64.7)	34 (43.6)	22 (52.4)
	T/T		16 (13.4)	29 (37.2)	6 (14.3)
		T	109(45.8)	92(59.0)	34(40.5)
				[b]P=0.011	P=0.399
rs601338				[c]P=1.000	P=1.000
	G/G		119(100)	78(100)	42(100)
	A/G		0(0)	0(0)	0(0)
	A/A		0(0)	0(0)	0(0)
		A	0(0)	0(0)	0(0)
				[d]P=1.000	P=1.000

(*Continued*)

Table 5 (Continued).

	Genotype	Allele	Control	UC	CD
				P value	P value
rs3745635				[e]P=1.000	P=1.000
	G/G		119(100)	78(100)	42(100)
	A/G		0(0)	0(0)	0(0)
	A/A		0(0)	0(0)	0(0)
		A	0(0)	0(0)	0(0)
				[f]P=1.000	P=1.000
rs28362459				[g]P=1.000	P=1.000
	T/T		119(100)	78(100)	42(100)
	T/G		0(0)	0(0)	0(0)
	G/G		0(0)	0(0)	0(0)
		G	0(0)	0(0)	0(0)
				[h]P=1.000	P=1.000

Notes: [a/c/e/g]Comparison of genotype frequency. [b/d/f/h]Comparison of allele frequency. UC: Ulcerative colitis; CD: Crohn's disease; A P value > 0.05: No significance.

Table 6 Clinical Profile of UC of SNP rs1047781 Genotype

Characteristics	Genotype				P value	OR(95% CI)
Location	TT	AA+AT	Allele A	Allele T	0.209	0.65(0.33—1.28)
E1+E2	28 (40.5)	56 (59.5)	72 (42.9)	96 (57.1)		
E3	27 (43.5)	35 (56.5)	48 (49.5)	49 (50.5)		
Severity					0.431	1.51(0.54—4.17)
Mild and Intermediate	51 (39.2)	79 (60.8)	161 (61.9)	99 (38.1)		
Severe	6 (30.0)	14 (70.0)	17 (42.5)	23 (57.5)		

Notes: E1, rectum; E2, left hemicolon; E3, extensive colon. CI, confidence interval; OR,odds ratio.

FUT3 encodes α-(1, 3/1, 4) fucosyltransferase, which, alongside FUT2, determines Lewis antigen formation, an adhesion receptor for pathogens like Norovirus and H. pylori.[7] Bifidobacterium and Ruminococcus produce α-glycosidase, which degrades Lewis antigens into small molecules, such as galactose and fucose, providing metabolic energy for the microbiota.[8,9] Wacklin et al[8] reported higher microbiota diversity in hosts with normal Lewis antigen expression than in those with deficient expression, suggesting that microbiota composition closely correlates with Lewis antigen expression, with FUT3 polymorphisms potentially leading to dysbiosis.[6]

FUT2 encodes α-(1,2)-fucosyltransferase, synthesizing the H antigen, which, with α-(1, 3/1, 4)-fucosyltransferase from FUT3, forms Lewis b antigen. In FUT2 inactivation, the blood precursor forms Lewis a antigen instead of H antigen.[23] In the Chinese population, FUT3's most common mutation is rs28362459 (T59G), while dysfunctional mutations include rs3745635 (G508A), rs3894326 (T1067A), rs778986 (C314T), and rs8l2936 (T202C).[22,48] FUT3 mutations (eg, rs3745635, rs3894326) result in α-(1, 3/1, 4) fucosyltransferase losing activity, leading to Lewis antigen deficiency in the mucosa.[6] FUT3 (rs28362459) may alter the α-(1, 3/1, 4) fucosyltransferase's conformation, reducing Golgi apparatus transport, thereby lowering mucosal Lewis antigen levels.[6]

In summary, HBGA, regulated by FUT2 and FUT3, serves as microbial binding sites and a carbon source for microbial metabolism. Intestinal fucose provides a competitive edge for symbiotic bacteria in the gut. FUT2 and FUT3 polymorphisms affect the secretor state and Lewis antigen expression, influencing the microbiota composition and potentially linking to IBD.

Current studies report an association between FUT2 polymorphisms and Crohn's disease (CD) susceptibility in Caucasian and Japanese populations, though findings are inconsistent.[17,49] Some researchers in China have observed that mutations in FUT2 (rs281377 and rs601338) may be linked to ulcerative colitis (UC) susceptibility in the Xinjiang Han population, and

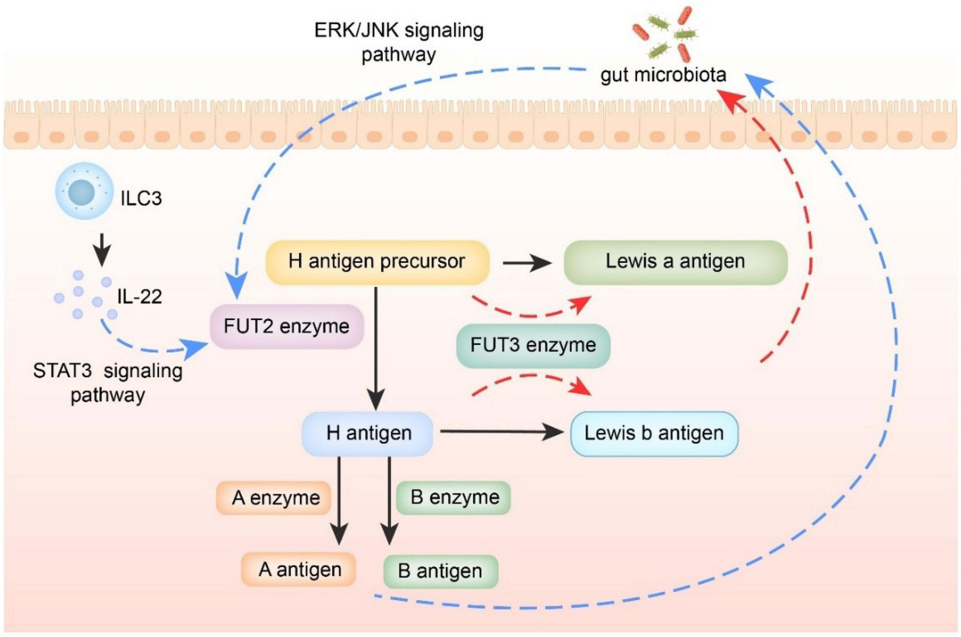

Figure 8 Fucosyltransferases encoded by FUT2 and FUT3 co-regulate the expression of HBGA. IL-22 upregulates FUT2 in the epithelium, contributing to the barrier's inhibitory effect on microbial translocation in chronic colitis. FUT2 and FUT3 polymorphisms affect the secretor state and Lewis antigen expression, influencing the microbiota composition and potentially linking to IBD.

FUT2 (rs1047781 and rs601338) mutations may be associated with UC susceptibility in the Uygur population.[21] McGovern et al[17] found that FUT2 rs601338 polymorphism was associated with CD susceptibility, but not with UC. Conversely, a study in a Finnish cohort suggested that the A allele of rs601338 had a protective effect against UC.[20]

Globally, research on the correlation between FUT3 polymorphisms and inflammatory bowel disease (IBD) remains limited. Dingyuan Hu et al[5,23] proposed that FUT3 polymorphism and its intestinal expression may be associated with UC susceptibility in Chinese patients. Mutations in two FUT3 SNPs (rs28362459 and rs3745635) may affect the lesion site in CD patients. Maodong Guo et al[6] reported that these SNPs were linked to certain clinicopathological features in UC and CD patients. Furthermore, Jiansheng Zheng et al[50] conducted a systematic review suggesting that FUT3 rs3745635 polymorphism may be associated with IBD susceptibility in the Chinese population, while rs3894326 and rs28362459 polymorphisms may not.

In this study, we found that the non-secretor state, caused by the FUT2 rs1047781 mutation, was associated with UC susceptibility in the Guangxi Zhuang population but was not related to CD susceptibility. These findings align with those of Aheman et al[21] in UC patients in the Uygur population in Xinjiang, China, and suggest that FUT2 rs1047781 mutation does not correlate with UC lesion location or severity. Due to the small sample size, analyses of UC severity and lesion location may lack sufficient power. Increasing the sample size would be needed to validate this result. Our study did not find an association between FUT2 rs601338 polymorphism and UC susceptibility in the Guangxi Zhuang population, which is consistent with the findings of McGovern et al[17] in the Caucasian population. Contrary to the results by Miyoshi J et al,[49] in our study, we found that FUT2 rs601338 did not associate with CD,which is consistent with the conclusion reached by Parmar AS et al[20] in the Finnish population. This underscores the influence of ethnic genetic backgrounds on the association between FUT2 polymorphisms and IBD susceptibility.

Additionally, we found that FUT3 rs3745635 is associated with both UC and CD susceptibility in the Guangxi Zhuang population, while FUT3 rs28362459 is not. This result aligns with the findings of Jiansheng Zheng et al.[50] We hypothesize that FUT2 and FUT3 gene mutations, which lead to the absence of ABH and Lewis antigen expression, could impact innate immune responses and the composition of intestinal flora to some extent. However, the precise mechanisms by which FUT2 and FUT3 influence IBD pathogenesis remain unclear. Future research should include larger follow-up studies and investigations into HBGA expression and gut microbial composition to clarify the roles of FUT2 and FUT3 in IBD.

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In summary, our study suggests that the FUT2 rs1047781 polymorphism is associated with UC susceptibility in the Guangxi Zhuang population, while FUT3 rs3745635 is linked to susceptibility to both UC and CD in this population. FUT2 rs601338 and FUT3 rs28362459 polymorphisms appear not to be associated with IBD in the Guangxi Zhuang population. These findings highlight the role of genetic predisposition in IBD development and underscore that susceptibility gene polymorphisms are closely related to ethnic genetic backgrounds. Functional studies about FUT2 and FUT3 should be included in the future study to confirm the biological impact of FUT2 and FUT3 polymorphisms. In terms of IBD treatment, investigating gut microbiota composition in individuals with these mutations, exploring therapeutic approaches targeting glycosylation pathways or microbiota modulation may help reduce colon inflammation and epithelial barrier damage, offering new therapeutic approaches for IBD. Future research should include larger, multi-center studies to validate these results and strengthen subgroup.

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Disclosure

The authors report no conflicts of interest in this work.

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