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ORIGINAL ARTICLE

Association of Serotonin Transporter Promoter Polymorphism (5-HTTLPR) with Microscopic Colitis and Ulcerative Colitis

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Abstract
Background Serotonin (5-HT) release and serotonin reuptake transporter (5-HTT) expression have been reported to be decreased in experimental colitis, in interleukin-10 knockout-associated colitis, and in patients with ulcerative colitis. Serotonin is known to play an important role in the pathogenesis of colitis, but individual genetic variants of 5-HTT gene in microscopic colitis and ulcerative colitis are not known.
Aim This study aimed to evaluate the association between the serotonin transporter gene promoter polymorphism (5-HTTLPR) and 5-HT concentration in microscopic colitis (MC) and ulcerative colitis (UC) patients.
Method This prospective case–control study included 41 patients with microscopic colitis (age 19–82 years, mean 35 ± 13.6), 75 patients with ulcerative colitis (age 16–65 years, mean 38.5 ± 11.6), and 100 controls (age 20–64 years, mean 38 ± 11). 5-HTTLPR gene polymorphism was studied by polymerase chain reaction-based assay. 5-HT levels were measured by ELISA.
Results The frequency of the 5-HTTLPR (SS) genotype was significantly lower in MC (12 %) patients compared to controls (30 %) ($p < 0.05$). When the L/L and L/S genotypes were combined into one group, the frequencies of the non-S genotype were significantly higher than those of S/S genotype between the MC patients and the controls ($p < 0.05$). 5-HT levels were significantly higher in UC and MC patients compared to healthy controls ($p < 0.01$).
Conclusions A significant association was observed between LL genotype of 5-HTTLPR polymorphism and microscopic colitis, suggesting that 5-HTTLPR is a potential candidate gene involved in the pathogenesis of microscopic colitis. Serotonin levels were significantly higher in microscopic colitis and ulcerative colitis patients compared to healthy controls.

Keywords Serotonin · Serotonin transporter promoter polymorphism · Ulcerative colitis · Microscopic colitis

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Introduction

Serotonin (5-hydroxtryptamine, 5-HT) is an important factor in gut function, playing key role in intestinal peristalsis, secretion, and sensory signaling in the brain-gut axis [1–4]. The 5-HT released from enteric neurons and enterochromaffin (EC) cells of the epithelium of the gut affect the intestinal wall by activating serotonergic receptors that are widely expressed within the intrinsic primary afferent neurons, on smooth muscle cells, enterocytes, and extrinsic afferent nerve fibers [1–5]. The action of enteric 5-HT is terminated by reuptake by 5-HT transporter [5-HTT or serotonin reuptake transporter (SERT)] [6].

The gene encoding serotonin reuptake transporter, *SLC6A4*, present on chromosome 17q11 within the

human genome, consists of 14 exons and encoding a 630-amino acid protein [7]. In the promoter region of the *SLC6A4* gene, 44-bp insertion/deletion polymorphism known as 5-HTTLPR (5-HTT-linked polymorphic region) has been described [7]. The homozygous for long or "L" allele of 5-HTTLPR found to uptake serotonin more than two times higher compared to cells with one or more short or "S" allele one or two copies of the short or "S" variant [8].

The action of 5-HT in the pathophysiology of ulcerative colitis (UC) and microscopic colitis (MC) remains unclear; however, studies showed change in serotonin levels and number of intestinal EC cell in patients with inflammatory bowel disease (IBD) [9–11], in experimental colitis [12–14]. Coates et al. [10] showed that SERT transcription decreased in the rectum of ulcerative colitis patients. However, serum 5-HT has not been evaluated in patients with MC and UC. There are scant published data on the role of 5-HT in UC and MC, although IBS-like conditions often coexist with UC and MC [15, 16].

Microscopic colitis (MC) is a group of chronic inflammatory bowel disorder which is characterized by chronic diarrhea and macroscopically normal-appearing colonic mucosa, but microscopic examination of mucosal biopsies shows histopathological changes [17]. Mostly patients have chronic diarrhea accompanied by weight loss and/or abdominal pain. Microscopic colitis classified into two diseases, lymphocytic colitis (LC) and collagenous colitis (CC). CC is characterized by a thick subepithelial collagen layer, whereas LC is characterized by a significant increase in intraepithelial lymphocytes without the thickened collagen layer [18]. In UC also, there is abdominal pain and diarrhea along with blood in stool off and on.

The etiology of microscopic colitis is still unknown. It has been suggested that an abnormal immune reaction to luminal antigens may be the underlying pathogenic mechanism [19]. Some environmental risk factors have been implicated as causative or triggering agents [20]. It has been shown that the consumption of selective 5-HT reuptake inhibitors (SSRI) is associated with microscopic colitis [21, 22]. There is a lack of study on the level of serotonin and 5-HTTLPR polymorphism in MC patients.

We could not come across any study which can demonstrate the relationship between the 5-HT levels and 5-HTTLPR polymorphism in microscopic colitis and ulcerative colitis. Therefore, the aim of this study was to investigate the association between the 5-HTT gene polymorphism in patients with microscopic colitis and ulcerative colitis, and to compare the level of 5-HT among those patients in Indian population.

Materials and Methods

Patients

In this prospective study, 300 patients with microscopic colitis and ulcerative colitis were requested to participate from October 2004 to November 2007. Of the 300 patients, 291 were enrolled for this study and 9 patients declined. Of the 291 patients who were enrolled (when they underwent different diagnostic tests), 175 patients were excluded. Of these 175 patients, 150 were of IBS, 20 Crohn's disease, and 5 functional dyspepsia.

A total of 41 microscopic colitis patients and 75 ulcerative colitis patients were finally enrolled from outpatient department of PGIMER, Chandigarh, India. This study also included 100 healthy controls, who had no prior history of any disease related to gastrointestinal (GI) tract. All patients and controls were from Chandigarh, Punjab, Haryana, Himachal Pradesh, the northern part of India. Patients diagnosed with microscopic colitis fulfilling strict clinical (the presence of watery diarrhea with normal or near normal endoscopic appearance) and pathological criteria were eligible to participate in the study [23]. Histological criteria included increased chronic inflammatory infiltrate (plasma cells, lymphocytes, and eosinophils) in the lamina propria, increased number of intraepithelial lymphocytes (IEL) (>7/100 epithelial cells), and damage of surface epithelium with flattening of epithelial cells and or epithelial loss and detachment. Collagenous colitis was diagnosed by the additional presence of diffusely distributed and thickened subepithelial collagen band with a thickness of $\geq$10 μm. A number of IEL >20 lymphocytes per 100 epithelial cells in the absence of a thickened subepithelial collagen layer were necessary to diagnose lymphocytic colitis [23]. The diagnosis of UC was based on standard clinical, radiographical, endoscopical, and histological criteria [24]. The study protocol was approved by the institute ethical committee, and blood samples were collected only after getting the informed consent from the subjects.

Blood Sample Collection

Six milliliters of fasting blood was drawn by venipuncture using ascetic condition. For serum determination of serotonin, 3 mL of blood was put into serum separation tubes (SST). The blood was centrifuged at 1500 RCF for 20 min at room temperature (22–25 °C). Serum was collected and immediately aliquoted in polypropylene tubes and frozen at −80 °C until assayed. The remaining 3 mL of blood was put into EDTA tube for DNA extraction.

Genotyping and Experimental Procedures

Genomic DNA was isolated from whole blood lymphocytes by the salting out procedure [25]. Genotyping of the 5-HTT gene polymorphism was performed using Eppendrof Thermal Cycler (Germany). The insertion/deletion polymorphism in 5-HTT gene was typed by polymerase chain reaction (PCR)-based method described previously [26]. The forward primer used was 5′ GGC GTT GCC GCT CTG AAT GC 3′, and reverse primer used was 5′ GAG GGA CTG AGC TGG ACA ACC AC 3′. Amplification was performed in a 25-μL reaction volume containing 100–200 ng of genomic DNA, 1× Taq DNA polymerase buffer (50 mM KCl, 10 mM Tris HCl pH 8.8, 1.5 mM $MgCl_2$), 0.2 mM deoxyadenosine triphosphate, 0.2 mM deoxycytidine triphosphate, 0.2 mM deoxythymidine triphosphate, 0.1 mM deoxyguanosine triphosphate, 0.1 mM 7-deaza-deoxyguanosine triphosphate, 10 pmol of each primer (forward and reverse primer), 5 % DMSO, 1.0 unit of *Taq* DNA polymerase (Sigma, India). Cycling condition included an initial denaturation at 94 °C for 4 min followed by 35 cycles of 95 °C for 30 s, 57 °C for 30 s, 72 °C for 60 s, and a final elongation step at 72 °C for 10 min. The amplified products were resolved by electrophoresis on 2.5 % agarose and visualized with ethidium bromide staining. The expected product sizes for the insertion (L) and deletion (S) alleles were 528 and 484 bp, respectively.

Enzyme-Linked Immunosorbent Assay (ELISA) for Serotonin

The level of serotonin in serum sample was determined using a commercially available enzyme immunoassay (ELISA; Serotonin-ELISA Kit) following the manufacturer's instructions (IBL, Immuno Biological Laboratories, Hamburg, Germany). The Serotonin-ELISA Kit has a detection limit of 1.5 ng mL^{-1}. On the day of assay, the samples were thawed and 20 μL was removed into glass test tube to which 100 μL of the diluted assay buffer was added. Then, 25 μL of kit acylation buffer was added into the same tube and vortex immediately. After incubation at 37 °C for 15 min, 2 mL of assay buffer was added to the tubes and the precipitated proteins were removed by centrifugation (10 min at 2,000 rpm). Fifty microliters of the supernatant was added to duplicate wells in the ELISA plate, which was then processed according to the directions of the manufacturer. Samples were read at 405 nm on an ELISA plate reader. The calibration curve was obtained by plotting the absorbance readings of the standards against the corresponding standard concentrations. The serum concentrations of 5-HT were read directly from the calibration curve.

Statistical Analysis

Statistical analysis was performed by means of two-sided Fisher's exact test, χ^2 tests, Student's *t* test, and one-way ANOVA, as appropriate. Departures from Hardy–Weinberg equilibrium were tested for using the goodness-of-fit χ^2 test. Differences in alleles and genotype frequencies between patients and controls were analyzed by using Fisher's exact test (two-sided). Insertion/deletion (L/S) and insertion/insertion (L/L) genotype frequencies were collapsed into one group to form 2 × 2 tables of deletion/deletion (S/S) and non-deletion/deletion (non-S) individual against disease status. Associations between UC and MC with 5-HTTLPR were measured by odds ratios (OR), corresponding 95 % confidence intervals (CI). Statistical analysis was performed using SPSS for Windows version 17.0 (SPSS Inc, Chicago, IL, USA). In all procedure, $p < 0.05$ was considered the level of significance.

Results

Characterization of Patients and Healthy Controls

A total of 41 MC and 75 UC patients who met the diagnostic criteria were enrolled for this study. The demographic data of patients and controls are shown in Table 1. Among 41 MC patients, 32 were diagnosed as LC and 9 patients as CC. In UC group, 40 patients were in active stage of the disease and 35 patients in remission stage. This study also included 100 apparently healthy subjects who were not the blood relative of the patients. The mean age of 37.5 and 36.5 years of UC and MC patients, respectively, were comparable with the mean age of 37.0 years of healthy controls. Sixty-four of 100 (64 %), 30 of 41 (75 %), and 40 of 75 (53 %) were males in controls, MC group, and UC group, respectively. The male patients

Table 1 Demographics data of microscopic colitis patients, ulcerative colitis patients, and healthy controls

Characteristics	Controls	Microscopic colitis	Ulcerative colitis
No. of subjects	100	41	75
Age—years (mean ± SD, range)	37.0 ± 11.2 (20–64)	36.6 ± 13.7 (19–82)	37.5 ± 11.5 (18–60)
Number of males (%)	64 (64 %)	32 (75 %)	40 (53 %)
Duration of disease (year, mean ± SD)	–	3.9 ± 4.1	3.5 ± 4.1
Diseases activity—active	–	–	40
Remission	–	–	35

SD standard deviation

Table 2 Distribution of serotonin transporter promoter polymorphism (*5-HTTLPR)* in the controls, microscopic colitis patients, and ulcerative colitis patients

Genotypic distributions	Controls $n = 100$ (%)	Microscopic colitis $n = 41$ (%)	Ulcerative colitis $n = 75$ (%)	Ulcerative colitis in active $n = 39$ (%)	Ulcerative colitis in remission $n = 35$ (%)
Wild-type L/L	17 (17 %)	12 (29 %)	18 (24 %)	7 (15.5 %)	11 (31.4 %)
Heterozygous L/S	53 (53 %)	24 (59 %)	40 (53 %)	20 (50 %)	20 (57 %)
Homozygous polymorphism S/S	30 (30 %)	5 (12 %)[ab]	17 (23 %)	13 (33.5 %)	4 (11.4 %)[cd]
Allele (no. and %)					
L allele	87 (43.5 %)	48 (59 %)[e]	76 (51 %)	34 (42.5 %)	42 (60 %)[f]
S allele	113 (56.5 %)	34 (41 %)	74 (49 %)	46 (57.5 %)	28 (40 %)

5-HTTLPR serotonin transporter gene-linked polymorphic region

[a] $\chi^2 = 6$, $df = 2$, $p < 0.05$ (controls vs. microscopic colitis patients)

[b] Odds ratio (95 % CI) for S/S versus non-S genotype; 0.324 (0.116–0.906), $p < 0.05$

[c] $\chi^2 = 6.235$, $df = 2$, $p < 0.05$ (controls vs. ulcerative colitis patients in remission)

[d] Odds ratio (95 % CI) for S/S versus non-S genotype; 0.30 (0.097–0.928), $p = 0.04$

[e] Allele distribution: Fisher's exact test, two-sided $p = 0.025$ (controls vs microscopic colitis patients)

[f] Allele distribution: Fisher's exact test, two-sided $p = 0.01$ (controls vs ulcerative colitis patients in remission)

predominate in MC groups. The male/female ratio was significantly higher in patients with MC than in patients with UC ($p < 0.05$). The duration of disease was 3.5 ± 4.1 and 3.9 ± 4.1 years in UC and MC patients, respectively.

Association Between MC and 5-HTTLPR Polymorphism

The genotypic distribution of the controls and MC patients was checked for deviation from Hardy–Weinberg equilibrium using the Chi-square test, and no deviation was observed for the 5-HTTLPR polymorphism. There was significant association found in the 5-HTTLPR genotype ($p < 0.05$) and allele frequency ($p < 0.05$) between the MC patients and controls (see Table 2). Consequently, it was found that the frequency of SS genotype was significantly lower in microscopic colitis patients (12 %) compared to controls (30 %).

The frequency of SS genotype was significantly lower than non-SS 5-HTTLPR genotype (LL and LS genotype combined) between the MC and the controls [odds ratio (95 % CI) for 5-HTTLPR (SS) vs. 5-HTTLPR (non-SS) = 0.3241 (0.1158–0.9067), $p = 0.0316$]. There were no differences of either the 5-HTTLPR (LL) (MC 29 %, controls 17 %) or 5-HTTLPR (LS) (MC 59 %, controls 53 %) genotypes between MC patients and controls.

Association Between UC and 5-HTTLPR Polymorphism

The genotypic distribution of the controls and UC patients was checked for deviation from Hardy–Weinberg equilibrium using the Chi-square test, and no deviation was observed for the 5-HTTLPR polymorphism. The genotype distribution and allele frequencies in the patients and controls are given in Table 2. 5-HTTLPR genotype and allele distributions did not differ significantly between UC patients and controls (two-sided Fisher's exact test: genotype, $p = 0.38$; allele distribution, $p = 0.19$). However, there was significant association found in the 5-HTTLPR genotype ($p = 0.025$) and allele frequency ($p = 0.042$) between the UC patients with remission (UC REM) and controls. The frequency of SS genotype was significantly lower in UC patients with remission (11.4 %) compared to controls (30 %).

The frequency of SS genotype was significantly lower than non-SS 5-HTTLPR genotype between the UC REM and the controls [odds ratio (95 % CI) for 5-HTTLPR (SS) vs. 5-HTTLPR (non-SS) = 0.30 (0.097–0.928), $p = 0.04$]. There were no differences of either the 5-HTTLPR (LL) (UC REM 31.4 %, controls 17 %) or 5-HTTLPR (LS) (UC REM 57 %, controls 53 %) genotypes between UC REM and controls.

5-HTTLPR Polymorphisms According to Sex

In the controls, the frequencies of the L/L, L/S, and S/S genotypes were 15.6, 54.7, and 29.7 %, respectively, in males and 16.6, 53, and 30.4 %, respectively, in females. In the MC group, the frequencies of the L/L, L/S, and S/S genotypes were 21.9, 59.4, and 18.7 %, respectively, in males and 33.3, 66.7, and 0 %, respectively, in females. In the UC group, the frequencies of the L/L, L/S, and S/S genotypes were 26, 53, and 21 %, respectively, in males and 22, 53.6, and 24.4 %, respectively, in females. The genotype frequencies did not differ between males and

Serotonin ng/ml	Controls	Microscopic colitis	Ulcerative colitis (total)	Ulcerative colitis- Active	Ulcerative colitis-Remission
Mean ± SD	135.4±65	190.7±107.7 *	178.7±97.2 *	189.9±110 *	167.1±82 #
no. of subjects	100	41	75	40	35

* p <0.01 vs controls
#p<0.05 vs controls

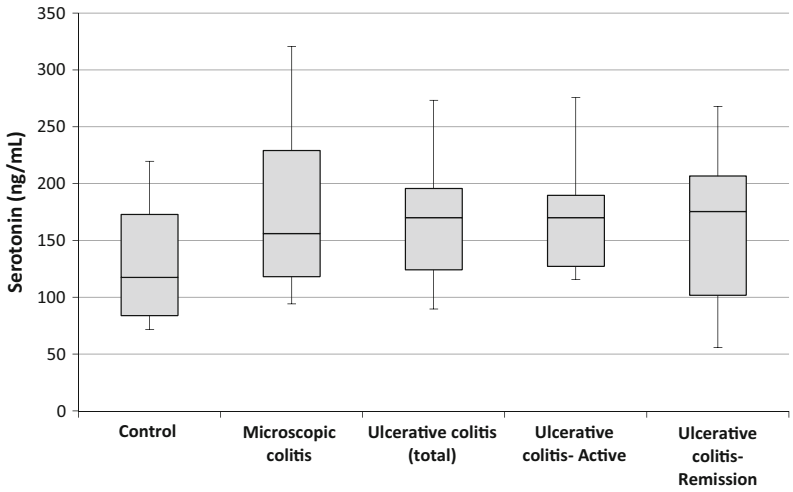

Fig. 1 Serotonin levels in ulcerative colitis patients, microscopic colitis patients, and healthy controls

females in either the controls or UC group and MC group ($p > 0.05$ for all groups).

Serotonin Concentrations Among Patients with Microscopic Colitis, Patients with Ulcerative Colitis, and Healthy Controls

The level of serotonin in serum was significantly higher in patients with MC and UC as compared to healthy controls (135.4 ± 65 vs. 190.7 ± 107.7 vs. 178.7 ± 97.2 ng/mL, respectively, $p < 0.01$) (Fig. 1). There was no significant difference in 5-HT level between active and remission stage of ulcerative colitis (189.9 ± 110 vs. 167.1 ± 82 ng/mL, respectively).

Relation Between Serotonin Levels with 5-HTTLPR Genotypes

Higher serotonin levels were observed with the presence of the SS genotype compared to LL genotype (Fig. 2). Mean 5-HT levels were highest in SS genotype and followed an order of SS > LS > LL, but this change was not statistically significant in any of the group of patients and controls. The microscopic colitis patients with LS and SS genotypes showed significantly higher 5-HT level compared to controls with LS and SS genotypes. When each genotype of controls was compared with UC phenotypes, there was a significant increase in 5-HT level of LS genotype of total UC and UC REM compared to LS genotype of controls ($p < 0.05$). SS genotype of UC active showed significantly increased 5-HT compared to the controls with SS genotype ($p < 0.05$).

Discussion

The present study evaluated the association of 5-HTTLPR polymorphism with microscopic colitis and ulcerative colitis patients in Indian population. This was the first study to examine the relation between microscopic colitis, ulcerative colitis, and serotonin transporter 5-HTTLPR polymorphism. Majority of serotonin (5-HT) is present in the GI tract, mainly in EC cells and neurons of myenteric plexus [4]. Serotonin present in the blood is derived from the GI tract. 5-HT activates the submucosal sensory branch of the enteric nervous system and controls gastrointestinal motility and chloride secretion via interneurons and motor neurons [27, 28]. In the present study, it was observed that the levels of 5-HT in serum were significantly higher in patients with MC and UC (active and remission stage) as compared to healthy controls. However, there was no significant difference in 5-HT level between active and remission stage of ulcerative colitis. This increase in 5-HT would have caused accelerated colonic motility and visceral hypersensitivity in patients with MC and UC. Accelerated colonic motility and visceral hypersensitivity can further cause diarrhea and abdominal pain that are common symptoms of these diseases. In support for this assumption are the findings that intestinal serotonin cells as well as plasma levels are affected in patients with ulcerative colitis and Crohn's disease [10, 29, 30].

Genotypes	Controls	Microscopic colitis	Ulcerative colitis (total)	Ulcerative colitis- Active	Ulcerative colitis- Remission
L/L	132.7±63.6	179.8 ±120	163.4±84	183.5±70	148±94
L/S	129.5±64.8	183±107 *	181±85 *	167±103	193±66 *
S/S	145.5±68.5	240.6±102 #	195.5±142	235±147 #	103±87

Serotonin concentrations are as ng/ml
* p<0.05 vs L/S control
# p<0.05 vs S/S control

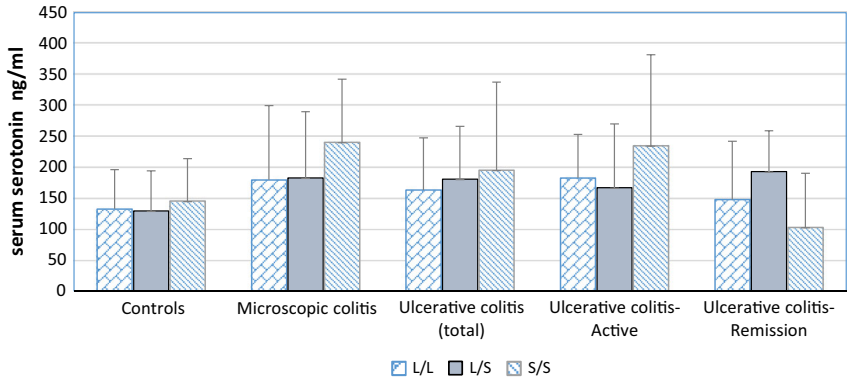

Fig. 2 Comparison of serotonin concentration with respect to 5-HTTLPR genotype in patients with microscopic colitis, patients with ulcerative colitis, and healthy controls

There are conflicting published data regarding the level of 5-HT in UC patients. Two studies reported that EC cells were significantly increased in patients with UC when compared to controls [29, 31]. El-Salhy et al. [29] showed an increased EC cells area in both UC and CD. Another study showed that catabolism of serotonin was increased in severely exacerbated UC, due to increase 5-HT [32]. In contrast to the present study, a decrease in 5-HT content has been reported in UC patients [9–11, 33]. In UC patients, a decrease in 5-HT tissue levels in inflamed and non-inflamed colonic mucosa was reported [11]. Coates et al. [10] showed reduced mucosal 5-HT, tryptophan hydroxylase mRNA, SERT mRNA expression, and SERT immunoreactivity in UC patients. Verity et al. [33], using a simple quantitative method, showed a decrease in number of EC and correlated this with low levels of mucosal 5-HT estimated biochemically. The conflicting results of 5-HT in ulcerative colitis could be due to site of its measurement. Most of the previous studies measured 5-HT in the mucosal tissue, and in our study, we measured 5-HT in the serum samples.

Only two case reports showed 5-HT in MC patients. Increase in serotonin marked cell with thick collagen deposition was found in 68 old women with collagenous colitis [34]. Another study showed elevated serotonin in collagenous colitis patients [35]. Recently, a study shows that serotonin and PYY cell densities were increased in colon of patients with LC [36]. These studies are consistent with our finding of increase serum 5-HT in MC patients.

Once serotonin is secreted from EC cells, SERT is activated to reuptake serotonin back into EC cells and attenuate the effect of serotonin in GI tract subsequently [8]. The present study showed significant association between 5-HTTLPR LL genotype and microscopic colitis. It was observed that the frequency of SS genotype was significantly lower in microscopic colitis patients compared to controls. Moreover, the frequency of SS genotype was significantly lower than non-SS 5-HTTLPR genotype (LL and LS combined genotype) between MC patients and controls. Previous studies have showed that SS and LS genotypes were associated with lower transcriptional activity, resulting in decreased serotonin transporter expression and density [8]. That means short allele have decreased clearance of 5-HT in the circulation and synapse. But this study showed that LL genotypes are associated with microscopic colitis and have increased the level of serum 5-HT. This signifies that LL genotype is not associated with serotonin transporter expression. Recent study showed that the transcriptional efficacy of the long (L) and short (S) alleles could be modulated by a single nucleotide polymorphism, rs25531, that is present near 5-HTTLPR [37, 38]. Hu et al. [38] reported that a SNP (rs25531, A/G) in the long form of 5-HTTLPR may have functional significance: The LA allele (more common) was associated with higher activity, whereas the LG allele (less common) has transcriptional activity no greater than the S. It could be possible that our MC patients with LL genotype may have

more LG alleles and have the decrease transcription of serotonin transporters.

This study could not find any association between 5-HTTLPR polymorphism and UC total (both active and remission). However, there was significant association found in the 5-HTTLPR genotype and allele frequency between UC patients with remission and controls. The frequency of SS genotype was significantly lower in UC patients with remission compared to controls. Similar to our results, Shiotani et al. [39] also observed that variants of 5-HTT genes were not significantly associated with UC.

When serum 5-HT level was compared with respect to serotonin genotypes, no significant difference was found between 5-HT levels and 5-HTTLPR genotypes. The level of 5-HT was non-significantly increased in SS genotype compared to LL genotype in controls. MC patients with LS and SS genotype showed significantly increased 5-HT compared to LS and SS genotype of controls, respectively. Active UC patients with SS genotype showed increase 5-HT compared to SS genotype of controls. In UC remission stage, patients with LS genotype showed increased 5-HT compared to LS genotype of controls. Although the frequency of SS genotypes was lower in MC and UC remission stage, but the serum 5-HT levels were significantly higher in these patients. The findings of increased levels of 5-HT in MC and UC contradict to our present finding on the 5-HTTLPR polymorphism, as it might have been expected that we should have detected an increased frequency of 5-HTTLPR SS genotype. This signifies that there may be some other factors or genotypes (other than SS) which increase the serum 5-HT level. Moreover, Hu et al. [38] reported that a SNP (rs25531, A/G) in the long form of 5-HTTLPR may have functional significance. It could be possible that in our study, patients at MC and UC remission stage may have LG genotype which has less transcriptional activity similar to SS genotype [38]. Therefore, the abnormal increase in serum 5-HT in patients at MC and UC remission stage may be related decreased SERT expression in the intestinal mucosa caused by 5-HTTLPR (SS) genotype-independent mechanism.

The present study could not find any association between 5-HTTLPR polymorphism in UC. Although in UC remission stage, patients with the SS genotypes were significantly lower than the controls. In conclusion, a significant association was observed between LL genotype 5-HTTLPR polymorphism and microscopic colitis along with increase serum 5-HT levels. These results support the need for further study to determine the SNP (rs25531, LA/LG) in the long form of 5-HTTLPR in microscopic colitis patients. Furthermore, since UC and MC are heterogeneous and multifactorial diseases, more comprehensive approach including multiple genes and gene–environment interaction should be considered.

Conflict of interest None.

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