Comparative Clinical Pathology (2023) 32:565–571
https://doi.org/10.1007/s00580-023-03465-2

ORIGINAL ARTICLE

lncRNA H-19 and miR-200a implication and frequency of lncRNA H-19 rs2170425 SNP in ulcerative colitis and Crohn's disease

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Received: 26 October 2022 / Accepted: 28 February 2023 / Published online: 11 March 2023

Abstract

Inflammation's impact on inflammatory bowel diseases is mostly due to altered non-coding RNA expression. This study aimed to explore the rs2107425 polymorphism in the long non-coding RNA gene H19 (lncRNA H-19) and emphasize the involvement of miR-200a and lncRNA H-19 expression in ulcerative colitis (UC) and Crohn's disease (CD). One hundred and ten participants, ranging in age from 22 to 58 years, participated in the current investigation study. Study participants were classified into forty healthy participants, thirty-four patients with UC, and thirty-six patients with CD. Participants with ulcerative colitis and Crohn's disease experienced a considerable elevation in C-reactive protein, total leucocyte count (TLC), platelets, and erythrocyte sedimentation rate (ESR), whereas a noticeable decrease in hemoglobin. Additionally, ulcerative colitis and Crohn's disease both have markedly increased expression of lncRNA H-19 and miR-200a. The frequency of the CT + TT genotype of the rs2170425 lncRNAH-19 SNP was linked to susceptibility to IBDs. lncRNA H-19 and miR-200a can be used as non-invasive diagnostic biomarkers for follow-up patients with ulcerative colitis and Crohn's disease.

Keywords Ulcerative colitis · Crohn's disease · rs2170425 · lncRNA H-19 · miR-200a

Introduction

Inflammatory bowel diseases (IBDs) are a category of bowel disorder that can impact a broad spectrum of organs throughout the digestive system (Gravina et al. 2018). The most common forms of IBDs that bring about the imbalance between an uncontrolled inflammatory response and the microbiota in the intestine are ulcerative colitis and Crohn's disease (Zhang et al. 2017; Ramos and Papadakis 2019).

Ulcerative colitis is a frequent emerging risk factor for inflammations that affects the colon and rectum mucosa. Inflammation affects continuous areas of the mucosa, and inflammation will be more pronounced in nearby areas of ulcerations (Jung 2012). The two key manifestations that have a diverse effect on the patient's performance in life are abdominal pain and diarrhea (Ahluwalia et al. 2018). Crohn's disease is an emergent chronic inflammatory disorder that affects any portion of the digestive tract from the mouth to the anus (Hussein et al. 2020).

Many kinds of clinical diseases are associated with various genetic backgrounds. As a result, the link between the pathophysiology of IBD and a genetic predisposition caused by the inheritance of particular contributing genetic variants offers new avenues for investigating and testing potential candidate biomarkers as diagnostic markers and has attracted more and more attention.

ncRNAs include miRNAs as well as lncRNAs, a type of ncRNA that has only recently been recognized for its importance. lncRNAs, on the other hand, are a new potentially important class of ncRNAs and implicated in the gene function regulation (Statello et al. 2021). A variety of ncRNAs have been shown to play a pivotal function in the onset, progression, and prognostic of a variety of disorders (Fan et al. 2020).

lncRNA H-19 is a telomeric long noncoding RNA identified at the telomeric region of chromosome 11p15.5 in the developing embryo. It is extensively expressed, but considerably down-regulated in neonates (Pope et al. 2017). In

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addition, lncRNA H-19 was linked to many cancers as an oncogene (Yang et al. 2021; Ghafouri-Fard et al. 2020). Moreover, lncRNA H-19 expression was up-regulated under hypoxic conditions, implying that H19 was implicated in hypoxia-induced cell damage (Yuan et al. 2020).

Regarding miRNA, it supports intestinal tissue barriers by forming tighter junctions and reducing permeability (Ye et al. 2011; Cichon et al. 2014). Thus, miRNA has the potential to be used as a therapeutic target for UC as well as to maintain the integrity of the intestinal barrier in IBD. Therefore, this study aimed to explore the frequency of lncRNA H-19 rs2107425 SNP and emphasize the diagnostic potential of miR-200a and LncRNA H-19 in IBDs.

Materials and subjects

This case–control study is a prospective basis of one hundred and ten study participants, ranging in age from 22 to 58 years, who were involved in the current study. Study participants were classified into forty healthy participants with no family history of IBDs, or any other diseases, thirty-four patients with UC, and thirty-six patients with CD. The diagnosis and discrimination between ulcerative colitis and Crohn's disease were accomplished according to clinical standards based on the Montreal classification. Age and sex-matched healthy volunteers with no history of IBD or any other inflammatory disease were likewise selected in the study. Study participants with any immune-related diseases or liver, kidney, thyroid, bone, and heart illnesses were excluded from enrolment. This cohort study's protocol and procedures were approved by the research Ethical Committee, Faculty of Medicine, Beni-Suef University and followed the Declaration of Helsinki's ethical criteria. Study participants also gave their informed consent to take part in this study.

Fasting venous blood samples were withdrawn and centrifuged in serum separator tubes for routine analysis. Sera were stored at −80 °C until use for genotyping and miR-200a, and lncRNA H-19 analysis.

Genotyping of lncRNA H-19 rs2107425 C/T

Qiagen's QIAamp kit (catalogue number#51306) was used to extract DNA from the mononuclear cell layer. A real-time polymerase chain reaction was performed to genotype samples using the TaqMan allelic discrimination assay (Applied Biosystems, USA). A pre-designed primer/probe pair (rs2107425) (Applied Biosystems, USA) was used for studying the genotypes. Both the quencher dye MGB and the reporter dyes FAM or VICV (Applied Biosystems, USA) were covalently bonded to the probe's 3′ and 5′ ends, respectively.

lncRNA H-19, and miR-200a expression assay

QIAzol lysis reagent was used to isolate total RNA. Total RNA was then purified from serum using the miRNeasy kit (Qiagen, USA). The miScript SYBR® Green PCR kit (Qiagen, USA) was used to amplify cDNA after reverse transcription of total RNA with the miScript II RT kit (Qiagen, USA). Equation $2^{-\Delta\Delta Ct}$ was used to calculate the relative expression of the miR-200a and lncRNA H-19 (Livak and Schmittgen 2001).

Statistical analysis

SPSS software statistical computer package version 22 was used to analyse the data (SPSS Inc, USA). For descriptive statistics, one way ANOVA was employed. The chi-square test was used to compare genotype frequencies for the rs210 7425 gene. ROC curve was used to identify the cut-off point at which miR-200a and lncRNA H-19 had the maximum sensitivity and specificity in discriminating between study participants. Statistical significance was considered as $P < 0.05$.

Results

The present cohort study was conducted on 110 participants aged 22 to 58 years. Study participants were classified into forty healthy participants with no family history of IBDs, or any other diseases, thirty-four patients with UC, and thirty-six patients with CD (Table 1).

Regarding age and sex, all participants with UC, and CD had no significant differences as compared to healthy individuals ($P > 0.05$). The UC and CD patients had more smokers than the healthy participants. The extent of UC cases; 15 (44.12%) left side, 14 (41.18%) had pancolitis, 3 (8.82) procolitis, and 2 (5.88%) had extensive colitis, respectively. With respect to location and size of CD disease, 10 (27.78%) L1 (ileum site), 12 (33.33%) L2 (colon site), and 14 (38.89%) L3 (ileum + colon), as shown in Table 1.

Regarding CBC profile, all UC, and CD participants had visibly remarkable higher levels of TLC, platelets, and ESR as compared to healthy participants ($P < 0.05$). However, hemoglobin levels differed significantly between both UC, CD patients, and healthy subjects, as shown in Table 2.

With respect to CRP and albumin levels, UC and CD participants had significantly higher CRP compared to healthy subjects. However, albumin levels declined significantly between UC and CD versus healthy controls, as shown in Table 2.

Table 1 Demographic data and clinical-pathological features of the studied groups

Variables	Healthy control participants	UC subjects	CD subjects
Age			
(mean ± SD)	27.00 ± 7.32	31.79 ± 11.19	29.59 ± 8.88
Gender			
Male (n,%)	25	20	21
Female (n, %)	15	14	15
Extent			
Extensive	NA	2	---
Left side	NA	15	---
Pancolitis	NA	14	----
Procolitis	NA	3	----
Site of the disease			
L1 (ileum)	NA	----	10
L2 (Colon)	NA	------	12
L3 (ileum+ colon)	NA	----	14
Smoking			
Yes	2	8	11
No	38	16	25
Therapy			
Yes		26	22
No		8	14
Duration			
< 1 year	NA	22	15
> 1 year	NA	12	21
Mayo Score (mean ± SEM)	NA	7.62 ± 0.63	----
CDAI (mean ± SEM)	NA	-----	295.62 ± 18.52

CDAI Crohn's disease activity index

To determine whether miR-200a and lncRNA H-19 were differentially expressed in the serum of UC, CD, and healthy participants, their expression was measured using RT-PCR. As shown in Table 3, miR-200a and lncRNA H-19 were expressed at higher levels in UC, and CD patients compared with the control samples. Moreover, the expression fold of miR-200a and lncRNA H-19 differed significantly between UC and CD participants.

In controls, the genotypically distributed polymorphisms of lncRNA H-19 rs21704525 were consistent with the Hardy–Weinberg equilibrium (Table 4). Interestingly, the CT + TT genotype of the rs2170425 LncRNAH-19 SNP was associated with UC and CD susceptibility in our study, as shown in Table 4.

A Pearson correlation analysis was performed to determine the relationships between lncRNA H-19 and miR-200a expression. According to correlation analysis, lncRNA H-19

Table 2 Biochemical characteristics of studied participants

Variables	Healthy control	UC	CD
Hb (g/dl)	12.35 ± 0.18^{b}	11.26 ± 0.34^{a}	11.92 ± 0.35^{ab}
TLC ($\times 10^3$/mm^3)	6.37 ± 0.39^{a}	8.01 ± 0.65^{ab}	8.55 ± 0.68^{b}
Platelets ($\times 10$/mm^3)	294.20 ± 10.86^{a}	322.15 ± 17.39^{ab}	348.47 ± 22.10^{b}
ESR (mm/h)	3.33 ± 0.21^{a}	32.24 ± 4.59^{b}	36.54 ± 3.78^{b}
CRP (µg/ml)	1.77 ± 0.14^{a}	17.65 ± 3.63^{b}	28.09 ± 7.02^{b}
Albumin (g/dl)	4.60 ± 0.05^{b}	3.68 ± 0.15^{a}	3.48 ± 0.11^{a}

Data were expressed as mean ± SEM; According to the Duncan multiple range test, the different letters indicate statistical significance different means

ESR Erythrocyte sedimentation rate, *CRP* C-reactive protein, *TLC* total leucocyte count, *Hb* hemoglobin

Table 3 Expression fold of H-19 and miR-200a of healthy controls, UC and CD patients (mean ± SEM)

Variables	Control	UC	CD
H-19	0.99 ± 0.01^{a}	3.50 ± 0.38^{c}	2.48 ± 0.29^{b}
miR-200a	1.00 ± 0.01^{a}	9.46 ± 0.54^{b}	11.16 ± 0.65^{c}

Data were expressed as mean ± SEM; According to the Duncan multiple range test, the different letters indicate statistical significance different means

Table 4 Genotype frequency of LncH19 rs2107425(C/T) gene single nucleotide polymorphism (SNP) between healthy control, UC and CD patients

Groups	Genotype frequency		
	CC	**CT**	**TT**
Healthy participants	29	9	2
UC subjects	17	12	5
CD Subjects	13	20	3
	$\chi^2 = 12.34$	$P = 0.015$	

had substantial positive relationship with miR-200a in UC and CD patients (Fig. 1a, b).

lncRNA H-19 was able to discriminate UC patients from healthy controls in ROC analysis, with AUC = 0.944, 94.12% sensitivity, 100% specificity, and $P < 0.001$ (Fig. 2a). Additionally, miR-200a was able to distinguish healthy controls from UC patients in ROC analysis, with $P < 0.001$, and 100% sensitivity (Fig. 2b).

Furthermore, ROC analysis demonstrated that serum lncRNA H-19 distinguished CD from healthy controls with AUC = 0.909, $P < 0.001$, 88.24% sensitivity, and 96.67% specificity (Fig. 3a). ROC analysis indicated the diagnostic efficacy of serum miR-200a and distinguished CD patients from healthy control with 100% sensitivity, and 100% specificity (Fig. 3b).

Additionally, with AUC = 0.66, lncRNA H-19 ROC curve was able to discriminate UC patients from CD patients with 79.41% sensitivity and $P = 0.023$ (Fig. 4a). miR-200a was able to distinguished CD from UC patients in ROC analysis, with $P = 0.028$, 58.82% sensitivity and 76.47% specificity (Fig. 4b).

Discussion

Ulcerative colitis and Crohn's disease are the two primary forms of IBD, which arise from various variables, such as genetic variations, leading to immunological and inflammatory responses (Ramos and Papadakis 2019). Recent studies showed the abilities of various non-coding RNA in regulation of physiological and pathological processes in the digestive system. Increased plasma levels of lncRNA and miRNA, for example, have been linked to an increased risk of cancer, inflammation, and neurological disorders (Fantini et al. 2021; Ratti et al. 2020; Zhang et al. 2021).

In this study, we revealed the association of lncRNA H-19 rs2107425 with ulcerative colitis and Crohn's disease susceptibility and pointed to the diagnostic significance of lncRNA H-19 and miR-200a in ulcerative colitis and Crohn's disease. As far as we know, no previous research has looked into the association of lncRNA H-19 rs2107425 with ulcerative colitis and Crohn's disease susceptibility.

In this study, lncRNA H-19 expression was demonstrated to be up-regulated in UC and CD patients significantly versus the healthy control group. Accordingly, previous studies reported that patients with UC exhibited a noticeable overexpression in lncRNA H-19 compared to healthy control and suggested a potential role of H19 in the development of UC (Chen et al. 2016). In addition, lncRNA H-19 expression dramatically up-regulated in a colitis model induced in mice (Geng et al. 2018), as well as, lncRNA H-19 is up-regulated in inflamed colonic tissues from IBD patients (Lin et al. 2020). Intestinal epithelial proliferation and mucosal healing need the inflammatory cytokine IL-22, which stimulates the production of lncRNA H-19 in intestinal epithelial cells (IECs) (Geng et al. 2018). Therefore, to enhance

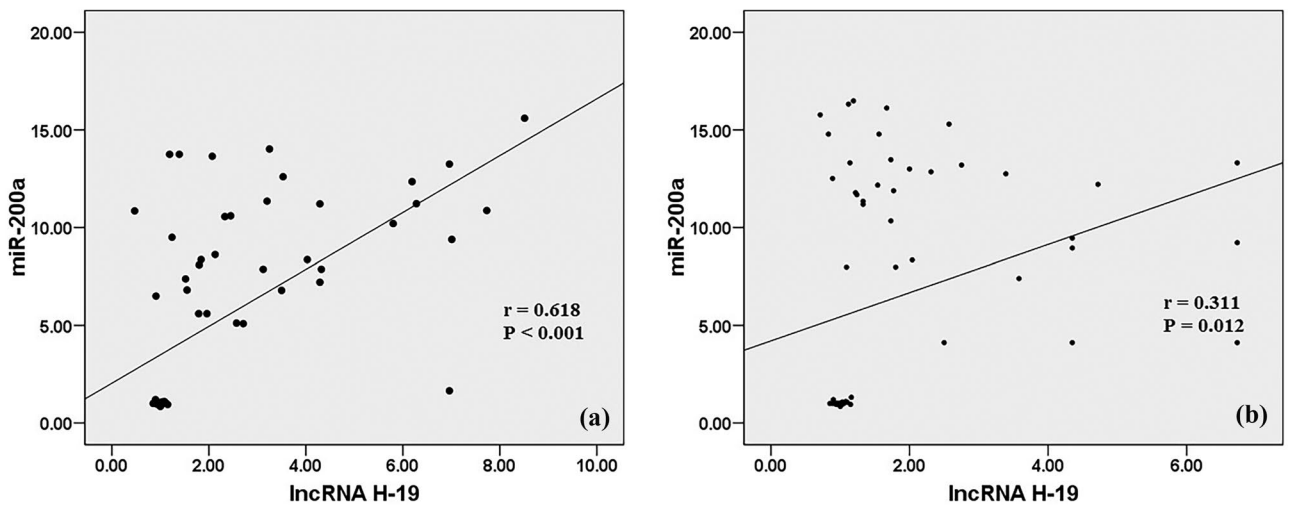

Fig. 1 Correlations analysis between **a** miR-200a and lncRNA H-19 in ulcerative colitis. **b** miR-200a and lncRNA H-19 in Crohn's disease

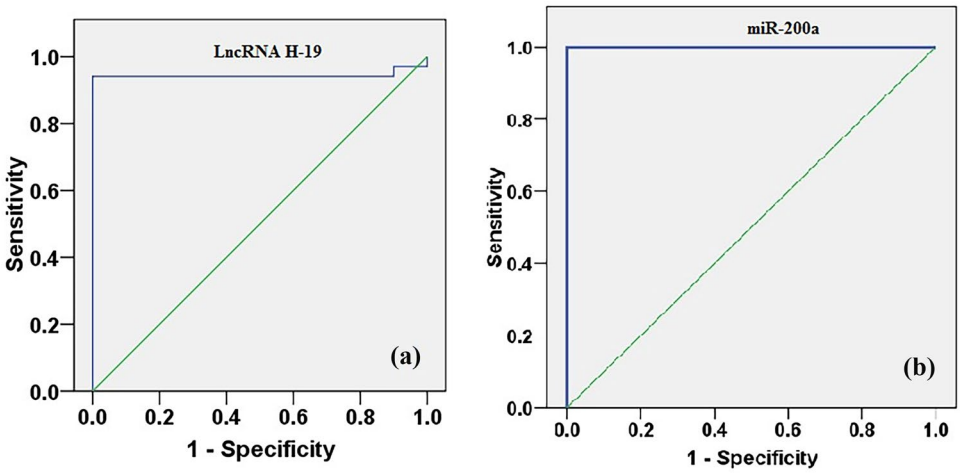

Fig. 2 ROC analysis regarding **a** lncRNA H-19 between ulcerative colitis and healthy control participants. **b** miR-200a between ulcerative colitis and healthy control participants

IEC proliferation and epithelial regeneration, lncRNA H-19 appears to inhibit the p53 protein, as well as microRNA-34a and let-7.

No doubt that proper intestinal function is regulated by different mediators, and the activation or inhibition of certain target genes involved in miRNA signaling displays a wide range of alterations in biological functions, including cell proliferation and apoptosis (Runtsch et al. 2014). Among the many molecular biomarkers, the free circulating miRNA expression patterns could be potential diagnostic as well as prognostic indicators for intestinal inflammation. Accordingly, previous studies reported that miRNAs could be used as diagnostic as well as prognostic biomarkers, through investigation of their differential expression pattern (Condrat et al. 2020). Here, the miR-200a expression was quantified by RT-qPCR representing overexpression in both ulcerative colitis and Crohn's disease, relative to healthy participants. Accordingly, high levels of miR-200a expression in patients with ulcerative colitis were associated with the target gene for therapy (Chen et al. 2013; Lewis et al. 2017). Additionally, in hepatic cancer cells, miR200a was considerably up-regulated, and regulates the oxidative stress response by targeting p38 (Xiao et al. 2015). Moreover, up-regulation of miR-200a has been associated to visceral hypersensitivity in a diarrhea-predominant irritable bowel syndrome model. It also directly targets CNR1 and SERT (Hou et al. 2018). Moreover, Wang et al. (Wang et al. 2021) demonstrated the PI3K-Akt signaling pathway through miR-200a expression.

Herein, the investigation of the influence of expression folding alterations of lncRNA H-19 caused by single nucleotide polymorphism demonstrated the crucible roles of rs2170425 in the incidence of UC and CD via signaling alteration of lncRNA H-19 and disrupting its differential expression. Accordingly, previous investigations have revealed the co-segregation and frequency of rs2170425 variants in various diseases (Naz et al. 2021; Khalil et al. 2022). In addition, recent studies have demonstrated that the regulation of SNPs in lncRNAs is mediated via the interactions between lncRNAs and microRNAs (miR) (Ratti et al. 2020).

The additional potential SNPs identification has been viewed as a promising route for clinical trials in IBD and provides the earlier application of proper therapeutic

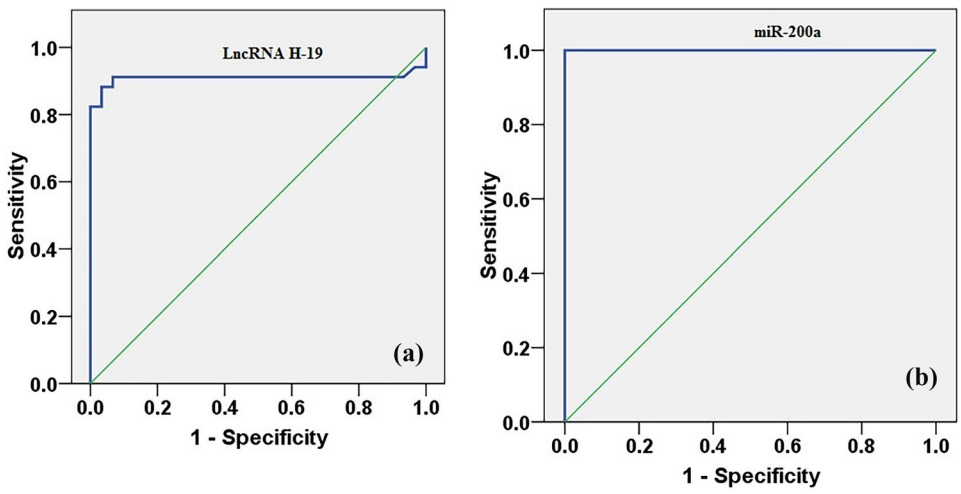

Fig. 3 ROC analysis regarding **a** lncRNA H-19 between Crohn's disease and healthy control participants. **b** miR-200a between Crohn's disease and healthy control participants

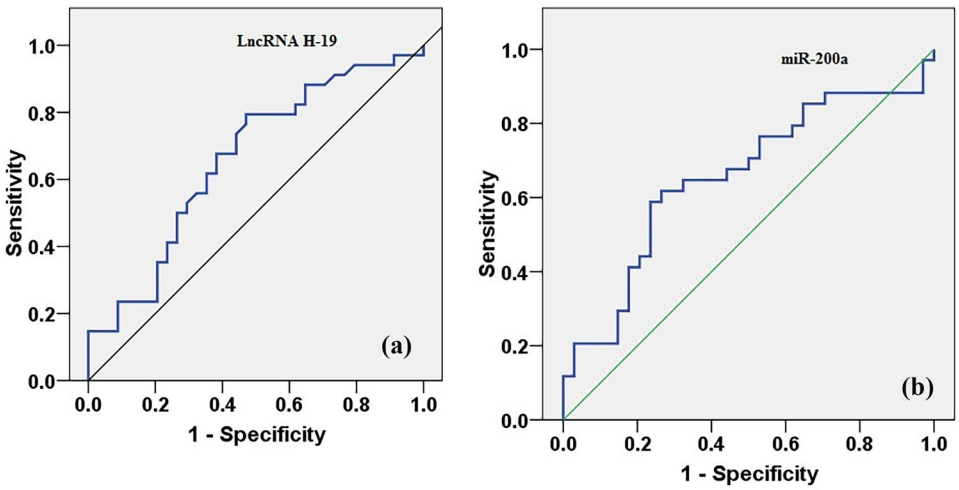

Fig. 4 ROC analysis regarding **a** lncRNA H-19 between ulcerative colitis and Crohn's disease patients. **b** miR-200a between ulcerative colitis and Crohn's disease patients

strategies (Dudzińska et al. 2018). Interestingly, the CT + TT genotype of the rs2170425 lncRNAH-19 SNP was associated with UC and CD susceptibility in our study. In Crohn's disease, the frequency of CT and TT genotypes was considerably higher than in ulcerative colitis. Accordingly, recent studies revealed a link between distinct lncRNA H19 polymorphisms and susceptibility to diseases. lncRNAH-19 genetic polymorphisms (rs2839698) modify and predict the susceptibility to kidney cancer and its mortality (Cao et al. 2020). Additionally, the rs2107425 lncRNA H-19 SNP was implicated in the susceptibility of colorectal cancer (Khalil et al. 2022). All of these suggest that genetic variants of LncRNA H-19 may have a significant impact on many disorders' susceptibilities.

As far as we know, this is the first study that has explored the association of lncRNA H-19 rs2107425 SNP with ulcerative colitis and Crohn's disease. Moreover, the relationship between the expression folds of lncRNA H-19 and miR-200a in individuals with ulcerative colitis and Crohn's disease has been assessed. Thus, further and well-designed investigation and clinical trials are required to confirm the exact role of lncRNA H-19 polymorphisms in IBD progression. In addition, the lncRNA H-19/miR-200a axis can open therapeutic avenues for IBD treatments.

Conclusion

In this pilot investigation study, we have determined the frequency of rs2107425 lncRNA H-19 SNP in a small population sample of Egypt. The frequency of the CT + TT genotype of the LncRNAH-19 polymorphism was linked to susceptibility to UC and CD. In Crohn's disease, the frequency of CT and TT genotypes was considerably higher than in ulcerative colitis. Our study revealed that lncRNA H-19 and miR-200a can be used as non-invasive diagnostic biomarkers for follow-up patients with ulcerative colitis and Crohn's disease. More studies are needed to determine the correlation between different lncRNA H-19 SNPs and susceptibility for various disorders and opening therapeutic avenue in a variety of IBD interventions.

Availability of data and materials All data generated or analysed during this study are included in this published article.

Compliance with ethical standards

Funding The authors declare that no funding for the research received. This study was not supported by any funding.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Approval of the study was granted by research Ethics Committee at Faculty of Medicine, Beni-Suef University. The study was conducted in compliance with the Declaration of Helsinki. This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent All study participants provided their informed consent permission for participation in this study.

Consent for publication For this type of study, consent for publication is not required.

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