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Association of the myosin heavy chain 9 gene single nucleotide polymorphism with inflammatory bowel disease

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ABSTRACT

Background: To date, the cause of inflammatory bowel disease (IBD) remains a mystery. A balance between cell proliferation and apoptosis maintains intestinal tissue homeostasis. Dissociation-induced myosin-actin contraction results in stem cell apoptosis. This study aiming to evaluate the influence of the myosin heavy chain 9 (*MYH9*) gene single nucleotide polymorphisms (SNPs) on inflammatory bowel disease.

Subjects: and methods: The study carried on eighty patients with IBD and seventy controls. All participants subjected to history taking, thorough physical examination, colonoscopy and laboratory investigations. Genotyping performed for rs4821480 and rs3752462 by SNP assay real-time PCR methods.

Results: On analyzing rs3752462 CT and TT genotypes were significantly more frequent in IBD patients as compared to controls with 4.6 fold increase in the risk of IBD. While on analyzing rs4821480, The TG and GG genotypes have significant increased distribution among the IBD patients as compared to the controls with 5.3 fold increase in the risk of IBD and higher prevalence of GG genotype in patients with low hemoglobin level and higher BMI.

Conclusion: The rs3752462 T allele and rs4821480 G allele of *MYH9* are associated with more susceptibility to IBD.

1. Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disease affecting the intestine. It affecting many patients in Egypt and the Middle East. However, starting a disease registry is highly crucial for IBD, and establishing a specific unit for IBD is extremely important for better diagnosis, treatment, and patients to care [1,2].

The intestinal mucosa acts as a barrier to protect the host from dangerous pathological organisms and it is the site at which the interactions with commensal organisms take place. These interactions modify by the immune system in the intestine and play a part in immune homeostasis. IBD can take place in the condition of disruption of this homeostasis [3].

There are 2 types of stem cells of the gastrointestinal tract mucosa: the rapid proliferating leucine-rich repeat having G protein-coupled receptor 5 + ve (Lgr5 þ) cells which preserve the intestinal homeostasis, and the Bmi1 þ (þ 4) cells which play a part in the intestinal regeneration after injury. These 2 stem cell types can interconvert in the mucosa lining the intestine [4].

The *MYH9* is a large gene localized on long arm of chromosome 22 at position q12.3, spanning more than 106 kbp, encodes the non-muscle myosin heavy chain IIA encodes the heavy chain of the non-muscle myosin IIA (NMM-IIA) protein [5]. This protein is included in many significant functions, involving the motility of the cell, cytokinesis, cell shape maintenance, and specific functions like secretion. The *MYH9* mutations are also, correlated with the occurrence of other disorders like the giant platelet syndrome [6].

The NMM-IIA produced force for cell motility through catalyzing ATP hydrolysis and plays a role in a broad range of cellular functions in several cells, like mitosis, cell migration, and cell adhesion [7]. Many studies documented that the dissociation-induced myosin-actin contraction resulted in induced and embryonic stem cell apoptosis [8].

A number of correlated *MYH9* SNPs, including four tagging SNPs (rs4821480, rs2032487, rs4821481 and rs3752462) spanning introns

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12–23 (≈14.9 kb), are highly associated with diseases. *MYH9* rs3752462 SNP is located in intron 13, while rs 4821480 is located in intron 23 of *MYH9* gene. Their functional effect might be that this SNPs may affecting the alternative splicing, or altering messenger RNA half-life [9], this might introduce changes in a variable portion of the non-helical tailpiece of the protein resulting in accumulation of a non-functional protein**.** studies in mice provide evidence that *Myh9* acts as a tumor suppressor in certain types of cancer [10].

This study carried out to reveal if there is an association between the rs 4821480 and rs3752462 SNPs of the *MYH9* gene and IBD.

2. Subjects and methods

This prospective case-control study conducted at Menoufia University Hospitals. The subjects included in the study were divided into two groups; group I included 80 cases diagnosed with inflammatory bowel disease and group II which included age and sex-matched 70 healthy subjects as a control group. Informed consent obtained from all the participants before starting the study. Besides, the local ethical committee of Menoufia University approved the study. All patients subjected to complete history taking, thorough physical examination, colonoscopy and laboratory investigation include occult blood tests.

The Research Ethical Committee of faculty of Medicine, Menoufia University, approved the protocol. Written informed consent was obtained from each participant.

Blood samples were taken from patients and controls to detect the SNP of the MYH9 gene. This done in two main steps, first, whole blood DNA extraction by Quick-genomic DNA™ MiniPrep kit, Zymo Research. Second, the MYH9 SNPs (rs 3753462& rs4820480) were genotyped using Real-Time PCR Instrument, Applied Biosystems®7500.

The genotype reaction mix was prepared using TaqMan universal master mix II (2x), supplied by Applied Biosystems, Foster City, USA, 2010. The manufacturer described probes: [VIC/FAM] for **SNP2** (rs4821480) was: TTTTCCTAGATCAAAGGATAATTTT[G/T]AAAGGTCACGAGCTCCCCTGAAACA. For **SNP1** (rs3752462) was: AGGTGTGAGGTCAAAGCAAGCCTGG[C/T]

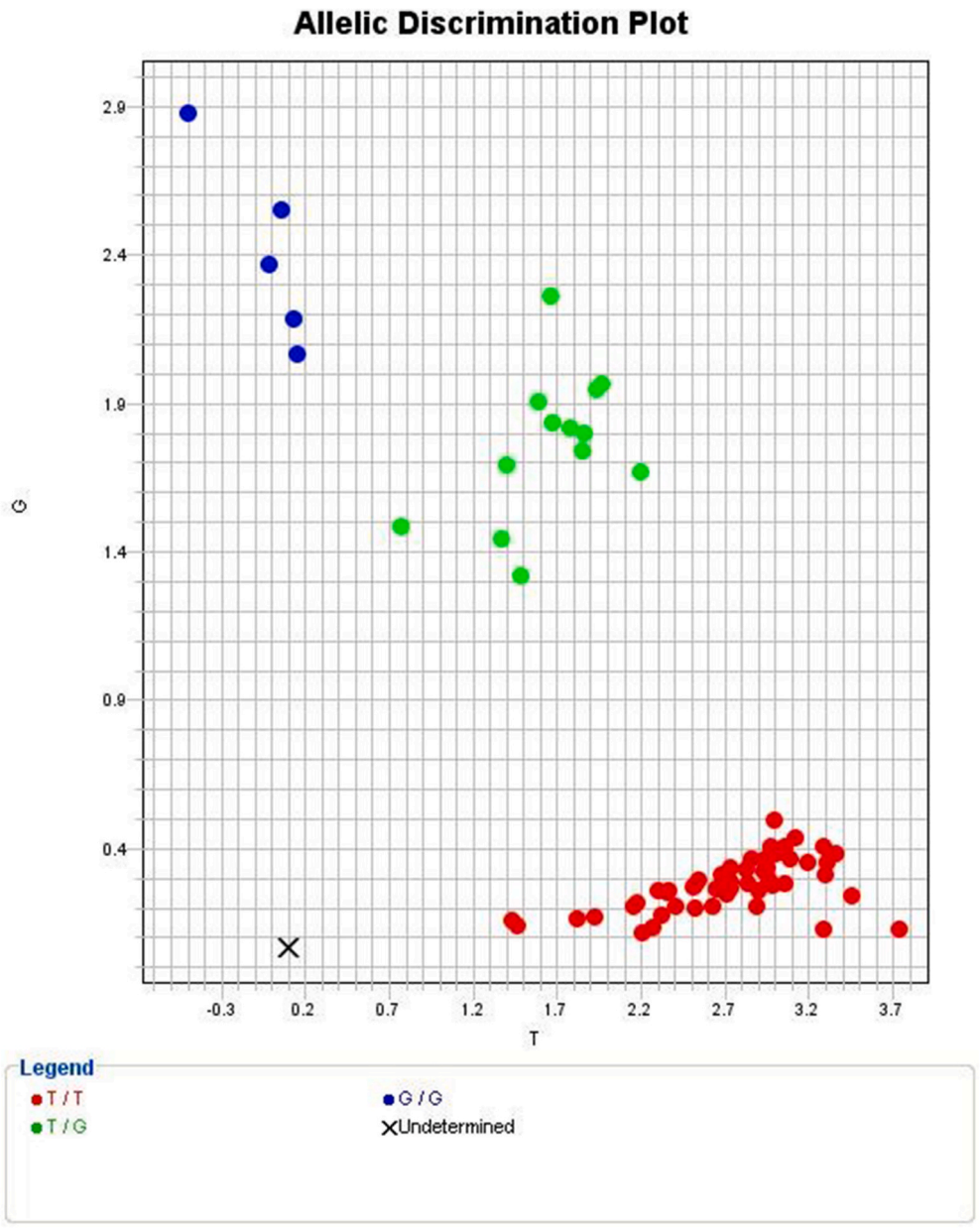

Fig. 1. Allelic discrimination plot of rs4820480 SNP of MYH 9 gene.

ACTCACTGGCTTCTCAATGAGGTCG. Both primers and probes purchased from an Applied Biosystem, Foster City, USA, 2010. The fluorescence generated by PCR amplification indicates which alleles are present in the sample. Figure (1) shows the allelic discrimination plot of rs4820480 SNP of the *MYH 9* gene and figure (2) shows the allelic discrimination plot of rs3752462 SNP of *MYH 9* gene.

3. Statistical analysis

Data entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS 21.0, IBM/SPSS Inc., Chicago, IL) software for analysis. Baseline characteristics of the study population were presented as frequencies and percentages (%) or mean values and standard deviations (SD) or median and interquartile range (IQR) (after testing of normality by Kolmogorov-Smirnov and Shapiro-Wilk's tests).

For comparison of data, the Chi-Square test (or Fisher's exact test) was used to compare two independent groups of qualitative data. For quantitative data, *t*-test and The Mann-Whitney test were used to compare two groups of parametric and non-parametric quantitative data respectively. F-test (ANOVA) and Kruskal Wallis test were used to compare between more than two groups of parametric and non-parametric quantitative data respectively. The Hardy-Weinberg (HMW) test was used to show the equilibrium of alleles and genotypes frequency in this population. Odds ratio: describe the probability that people who are exposed to a certain factor will have a disease compared to people who are not exposed to the factor. If one calculates the 95% CI of the difference in means between two samples, and zero is within the range of the 95% CI, then the *P* value will not be significant at the level less than 0.05.

4. Results

Starting with demographics, age and gender were not significantly different between cases and controls ($p > 0.05$). However, there was a statistically significant difference between cases and controls regarding

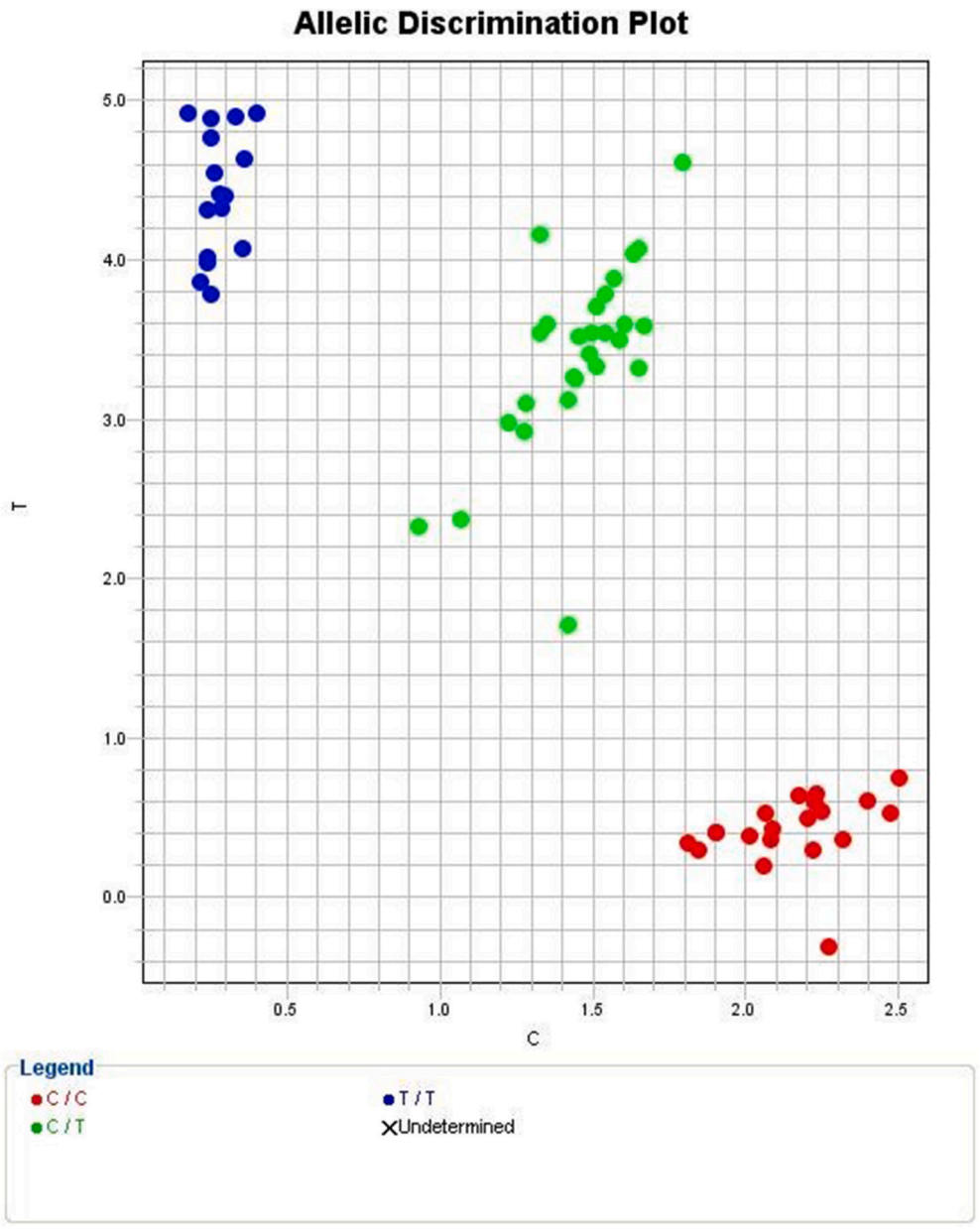

Fig. 2. Allelic discrimination plot of rs3752462 SNP of MYH 9 gene.

BMI ($p < 0.001$). Table (1) illustrates these data.

Regarding the presentations reported, a fecal occult blood test was positive in all cases while it was negative in all controls included in the current study ($p < 0.001$). As regards CBC parameters analyzed in the included subjects, it was evident that hemoglobin, leucocytes count, and platelets were significantly higher in controls compared to IBD cases ($p < 0.05$). These data are not shown.

The genotypes distribution of rs4821480, which consistent with HMW in the IBD cases and control group exposed that, the TG, GG genotypes, and the combination of TG + GG genotypes were significantly more prevalent in the IBD group as compared to the control group. The odds ratio of the G allele in the IBD group was 5.93 fold Table (2) illustrates these results.

While, the genotypes distribution of rs3752462, which consistent with HMW in the IBD and control group revealed that, The CT, TT genotype, and the combination of CT + TT genotypes were significantly more frequent in the IBD group as compared to the control group. The odds ratio of the T allele in the IBD group was 3.792 fold. Table (3) illustrates these results.

The most frequent haplotype in IBD patients was GT' (the two mutant alleles) while the most frequent haplotype in controls was TC' (the two wild alleles with a non-significant linkage disequilibrium of haplotypes of these two SNPs, Table (4).

On analyzing rs4821480 in IBD cases, although the GG genotype had significantly lower hemoglobin levels compared to the other two genotypes, genotype, it was significantly associated with higher BMI, Table (5).

Univariate and multivariate analysis revealed that BMI, hemoglobin level, WBC count, platelet count and TT genotype of rs3752462 were independent predictors, Table (6).

5. Discussion

Inflammatory bowel disease is a multifactorial disease that affected by a combination of environmental and genetic factors; the definite IBD etiology is still unrecognized [1].

Many studies utilized genetic and pharmacologic inhibition of the heavy chains NM II to evaluate their importance in the monolayers model of the intestinal mucosa. These studies concluded that first, the motor activity of NM II is critical for the standard barrier properties preservation of these layers. Second, NM II has a significant responsibility in regulating the junctional remodeling by motivating 2 phases against each other: junctional assembly and reassembly. Third, the heavy chain of NM IIA works as a vital AJ/TJ functions regulator [11–13].

In several previous studies, the expression of MYH9 proved to be as an indicator to observe the progression and prognosis of gastrointestinal tract [14–19].

Another study found that MYH9 down-regulated many small interfering RNAs (siRNAs) in pancreatic cancer patients, and the down-regulation of tumor suppressor genes led to the occurrence of tumors [20].

A modern study on mice evaluating the specific NM IIA knockout in the epithelium of the intestine documented that the NM IIA loss was reasonable to increase the GIT barrier permeability and to stimulate low-grade inflammation in the intestine and elevates the sensitivity of the animal to colitis, which lead to severe erosion of the epithelium and more barrier breakdown exacerbation [21].

The interactions of heavy chain with proteins, which bind to myosin, as well as specific heavy chain of NM IIA phosphorylation may have a relation with abnormal cytoskeleton organization in the intestinal epithelium lead to inflammation development in the intestine [22].

Several mutations have been identified in *MYH9* gene lead to what is called *MYH9 related diseases* (*MYH9*-RD). In most cases, they are single nucleotide substitutions that affect either the head domain or the coiled-coil region of the tail domain [23].

Table 1
Demographic data of the studied groups.

	IBD (n = 80)		Control (n = 70)		Test of Sig.	p
	No.	**%**	**No.**	**%**		
Sex						
Male	40	50.0	41	58.5	χ^2 =	0.798
Female	40	50.0	29	41.5	0.453	
Age (years)						
Mean ± SD.	31.77 ± 10.05		29.10 ± 9.07		U = 3.126	0.210
Median (IQR)	30.0(27.0–35.0)		29.0(21.0–34.0)			
BMI (Kg/m^2)						
Mean ± SD.	23.98 ± 2.43		27.95 ± 4.39		U = 16.033*	<0.001*
Median (IQR)	24.0(22.0–26.0)		27.34 (24.79–29.76)			
Hb level (gm/dl)						
Mean ± SD.	11.83 ± 1.47		12.77 ± 0.80		t = 6.26*	0.002*
Median (IQR)	11.80 (11.0–13.0)		13.10 (12.2–13.2)			
TLC (x10^3/μl)						
Mean ± SD.	5.68 ± 1.42		6.83 ± 0.55		t = 7.96*	0.001*
Median (IQR)	5.35(4.60–6.90)		6.90(6.40–7.40)			
Platelets (x10^3/μl)						
Mean ± SD.	172.17 ± 52.57		223.2 ± 42.04		t = 10. 4*	<0.001*
Median (IQR)	170.0 (153.0–191.0)		218.0 (217.0–265.0)			

IQR: Interquartile Range BMI: body mass index χ^2: Chi Square.
U: Mann-Whitney test t: *t*-test *: Statistically significant at $p \leq 0.05$.

Table 2
MYH9 SNP rs4821480 in IBD and Controls groups.

rs4821480	IBD (n = 80)		Control (n = 70)		p	OR (95%CI)
	No.	%	No.	%		
SNP						
TT®	44	55	60	85.7	1.000	–
TG	24	30	10	14.3	χ^2 = 6.02 P = 0.038*	OR 3.706 (1.075–12.772)
GG	12	15	0	0.0	–	–
TG + GG	36	45	10	14.3	χ^2 = 7.4 p = 0.005*	OR 5.353 (1.640–17.473)
Allele						
T®	112	70	130	92.8	1.000	–
G	48	30	10	7.2	χ^2 = 8.4 P = 0.001*	OR 5.930 (2.044–17.208)

OR: Odds ratio CI: Confidence interval The results are consistent with HMW.

Table 3
MYH9 SNP rs3753462 in IBD and Controls groups.

rs3752462	IBD (n = 80)		Control (n = 70)		p	OR (95%CI)
	No.	%	No.	%		
SNP						
CC®	26	32.5	49	70.0	1.000	–
CT	32	40.0	15	21.4	χ^2 = 4.9 P = 0.022*	OR 3.733 (1.211–11.513)
TT	22	27.5	6	8.6	χ^2 = 5.3 P = 0.009*	OR 7.467 (1.648–33.821)
CT + TT	54	67.5	21	30.0	χ^2 = 6.8 P = 0.003*	OR 4.667 (1.689–12.898)
Allele						
C®	84	52.5	113	80.7	1.000	–
T	76	47.5	27	19.3	χ^2 = 8.8 P = 0.001*	OR 3.792 (1.779–8.080)

OR: Odds ratio CI: Confidence interval The results are consistent with HMW.

Table 4
Linkage disequilibrium between *MYH9* rs4821480 and rs3753462 gene polymorphisms.

	Total sample (n = 300)	Group I (n = 160)	Group II (n = 140)
D	−0.053	−0.051	−0.026
D'	−0.056	−0.337	−0.202
r^2	0.003	0.045	0.013
χ^2	0.458	3.640	1.074
P	>0.05	>0.05	>0.05

D: Linkage disequilibrium D': standardization of D.

Outside the gastrointestinal tract, the polymorphisms of the (*MYH9*) gene have been claimed in dissimilar kidney diseases, as well as in diabetic nephropathy [24].

The role of MYH9 in cell motility and division, as it is crucial in the development and differentiation of skeletal muscle, Ablation of MYH9 resulted in the alteration of podocyte actin cytoskeletal structure and focal adhesion distribution, decreased cell attachment and contractility as well as increased cell motility [25].

In the present study, The CT and TT genotypes of *MYH9* rs3752462 were significantly higher prevalence in the IBD patients with T allele has 3.79-fold increase risk of IBD. While, on analyzing rs4821480 of *MYH9*, it was evident that the GG genotype had a significantly higher prevalence in IBD cases with G allele has 5.93-fold increase risk of IBD. Moreover, the GG genotype had significantly lower hemoglobin levels and higher BMI compared to the other two types. To the best of our knowledge, the polymorphisms in the *MYH9* gene concerning IBD not tested before.

MYH9 protein is one of the differentially expressed proteins functioned in digestive system development and its function, inflammatory disease, and developmental disorders [26].

MYH9 overexpression in colorectal cancer (CRC) have a positive correlation with poorer prognosis. *MYH9* may acts as an enhancer of cancer aggressiveness by promoting EMT via MAPK/AKT signaling activation [27]. Also, studies have also found that *MYH9* interacts with Deleted in liver cancer 1 (Dlc1) gene and Rac 1 activation [28].

Further studies are required to explain the mechanism regulate functions of NM IIA in the epithelium of the intestine in the state of health and inflammation of gastrointestinal tract.

6. Conclusion

The MYH9 gene polymorphism may be associated with the pathogenesis of IBD. The rs4821480 G allele and rs3752462 T allele of MYH9 gene associated with more susceptibility to IBD and GG genotypes of rs4821480 associated with anemia and overweight.

Author's contribution

Elsayed El-Shayeb, Abd El-naser Gadallah and Ahmed Ezz El-Arab design study, Eman badr do the lab investigation, Elsayed El-Shayeb analyzes the results, Ahmed Megahed Taman collect the sample and follow the patients. All authors write and revise of the manuscript and approve the final manuscript for submission.

Table 6
Univariate and multivariate analysis for the parameters affecting patient's vs control.

	Univariate		#Multivariate	
	p	OR (95%C.I)	p	OR (95%C.I)
Sex (female)	0.502	1.353 (0.560–3.267)	–	–
Age (years)	**0.463**	1.018 (0.971–1.066)	–	–
BMI (Kg/m2)	**0.001***	1.302 (1.111–1.525)	0.004*	1.413(1.118–1.786)
Hb level (gm/dl)	**0.002***	0.473 (0.295–0.758)	0.041*	0.497(0.255–0.971)
TLC (x103/μl)	**0.001***	0.462 (0.291–0.735)	0.026*	0.511(0.282–0.924)
Platelets (x103/μl)	**<0.001***	0.979 (0.969–0.990)	0.041*	0.985(0.971–0.999)
rs4821480				
TT®				
TG	**0.052**	3.208 (0.988–10.419)	–	–
GG	**0.999**	–	–	–
rs3753462				
CC®				
CT	**0.046***	2.904 (1.020–8.266)	0.342	2.016(0.475–8.562)
TT	**0.008***	6.844 (1.651–28.382)	0.006*	22.552 (2.454–207.261)

OR: Odd's ratio, C.I: Confidence interval, *: Statistically significant at $p \leq 0.05$.
- All variables with $p < 0.05$ was included in the multivariate.

Table 5
Relation between rs4821480 and different parameters in IBD group.

	rs4821480						Test of sig.	p
	TT (n = 44)		TG (n = 24)		GG (n = 12)			
	No.	%	No.	%	No.	%		
Sex								
Male	23	52.27	10	45.8	6	50.0	$\chi^2 = 0.347$	1.000
Female	21	47.73	14	58.2	6	50.0		
Age (years)								
Mean ± SD.	30.65 ± 9.66		34.33 ± 12.70		30.75 ± 4.57		H = 0.971	0.615
Median	29.0		30.0		32.50			
BMI (Kg/m^2)								
Mean ± SD.	24.31 ± 3.86		26.35 ± 3.27		28.99 ± 3.82		H = 7.822*	0.020*
Median	24.37		26.66		28.10			
Hb level (gm/dl)								
Mean ± SD.	12.64 ± 1.06		11.30 ± 0.94		9.58 ± 1.05		F = 16.229*	<0.001*
Median	12.60		11.0		9.35			
TLC (x10^3/μl)								
Mean ± SD.	5.93 ± 1.66		5.43 ± 1.18		5.13 ± 0.35		F = 0.698	0.506
Median	5.90		5.40		5.30			
Platelets (x10^3/μl)								
Mean ± SD.	186.47 ± 54.99		167.56 ± 47.15		121.75 ± 6.85		F = 2.817	0.077
Median	180.0		160.0		123.50			

χ^2: Chi square test H: Kruskal Wallis test F: ANOVA test *: Statistically significant at $p \leq 0.05$.

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Summary

Inflammatory bowel disease is a multifactorial disease, affected by a combination of environmental and genetic factors. The genetic etiology of IBD is still unclear. This is the first study carried out to reveal if there is any association between two SNPs of MYH9 gene and IBD. This study concluded that MYH9 gene polymorphism might be associated with the pathogenesis of IBD.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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