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***Case Control Study***

**Genetic associations of inflammatory bowel disease in a South Asian population**

NiriellaMA *et al.*Genetic associations of IBD in Sri Lanka

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**Abstract**

***AIM***

To estimate prevalence and phenotypic associations of selected inflammatory bowel disease (IBD) associated genetic variants among Sri-Lankan patients.

***METHODS***

A case [histologically confirmed ulcerative colitis (UC) or Crohn’s disease (CD) of ≥ 1 year duration] control (unrelated, gender matched, healthy individuals) study was conducted at four major centers in Sri Lanka. Phenotypic data of cases were obtained, all participants were genotyped for 16 selected genetic variants (*IL12B:rs1045431, IL23R:rs11805303, ARPC2:rs12612347, IRGM:rs13361189, IL26/IL22:rs1558744, CDH1:rs1728785, IL10:rs3024505, FCGR2A:rs3737240, PTGER4:rs4613763, IL17REL/PIM3:rs5771069, HNF4a:rs6017342, STAT3:rs744166, SMURF1:rs7809799, LAMB1:rs886774, HLA-DRB5, DQA1, DRB1, DRA:rs9268853, MST1, UBA7, APEH:rs9822268*). Genotypes of all variants were in Hardy-Weinberg Equilibrium (*P* > 10−3). To account for multiple hypotheses testing a *P*-value < 0.003 were considered significant.

***RESULTS***

A total of 415 patients and 465 controls were recruited. Out of the single nucleotide polymorphisms (SNPs) tested majority were not associated with IBD in Sri Lankans. Significant positive association was noted between *rs886774* (*LAMB1*-gene) with UC [odd ratio (OR) = 1.42, *P* = 0.001]. UC patients with *rs886774* had mild disease (OR = 1.66, *P* < 0.001) and remained in remission (OR = 1.48, *P* < 0.001). A positive association was noted between *rs10045431* (*IL 12B* gene) and upper gastrointestinal involvement in CD (OR = 4.76, *P* = 0.002).

***CONCLUSION***

This confirms heterogeneity of allelic mutations in South Asians compared to Caucasians. Most SNPs and disease associations reported here have not been described in South Asians.

 **Key words:** Inflammatory bowel disease; Genetics of inflammatory bowel disease; Ulcerative colitis; Crohn's disease; *LAMB1* gene mutation; *IL-12B* gene mutation

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**Core Tip:** This is a case-control study looking at prevalence of common genetic mutations associated with inflammatory bowel disease (IBD) among Caucasians, in a South Asian population from Sri Lanka. Most of allelic variants studied were not seen in this population, confirming the heterogeneity of genetic composition of IBD between South Asians and Caucasian patients. We found positive associations between *rs886774* (*LAMB1*-gene) with UC which was also associated with a milder disease and increased remission rate. Patients with upper gastrointestinal involvement of Crohn’s disease were more likely to have the mutation *rs10045431* (*IL 12B* gene).

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**INTRODUCTION**

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the intestines that includes Crohn’s disease (CD) and ulcerative colitis (UC). It was initially considered a disease of developed countries but it has now become a global health problem[1]. In Europe, the annual incidence of IBD per 100000 population is reported to range from 3-7 cases for CD and 4-11 cases for UC[2]. Although the evidence base in the Asian region is limited, studies such as the Asia Pacific Crohn’s and Colitis Epidemiology Study carried out in Australia, China, Hong Kong, Indonesia, Macau, Malaysia, Singapore, Sri Lanka and Thailand have demonstrated an overall incidence per 100000 population of 0.76 for UC and 0.54 for CD[3,4].

Prevalence of IBD is relatively higher in East Asia, when compared to South Asia. Japan has the highest prevalence (121.9 per 100000) for UC in East Asia[5], while India has the highest prevalence for UC (44.3 per 100000) in South Asia[5-7]. The reported prevalence and incidence of IBD per 100000 population in Sri Lanka are 6.5 (UC-5.3, CD-1.2) and 1.6 (UC-1, CD-0.6) respectively[4,8]. Genetic heterogeneity within the region along with diverse socio-economic, environmental and cultural factors may contribute to these differences.

Since identification of Neucleotide Oligomerisation Domain 2 (*NOD2*) gene in 2001, a multitude of genome-wide association scans (GWAS) and candidate gene association studies have identified more than 160 genes associated with IBD in Caucasians[8-10]. However, genetic contribution to IBD varies between regions and ethnicities and there is only limited data for Asians[11]. Results of a large trans-ancestry study demonstrated wide heterogeneity of genetic risk between European, East Asian and South Asian populations[14]. Therefore it is important to study genetic associations of IBD for individual Asian ethnic populations.

Many genetic variants that are correlated with increased disease risk in Caucasians such as variants found in *NOD2*/*CARD15*, autophagy-related protein16-liked 1 (*ATG16l1*), immunity-related GTPase family (IRG)-M, interleukin 23 receptor (*IL23R*), tumour necrosis factor superfamily gene (*TNFSF*)*-15*, Toll-like receptor (*TLR)-4, DLG-5*, and *SLC22A4* genes have been investigated in Asian populations. A systematic review and meta-analysis by Ng *et al*[13] in 2012 based on results of 93 reports from 8 countries with data from 17976 patients found that only *ATG16L1*, *IL23R*, *TNFSF15*, *TNF308*, *CTLA-4* and *MHC* were significantly associated with IBD among Asians. However, more studies representative of the Asian population are required to identify additional underlying genetic risk factors[3,6]. This study was conducted in a population that had not been studied before in South Asia – among Sri Lankans with the objective of identifying prevalence and phenotypic associations of common genetic risk alleles for IBD.

**MATERIALS AND METHODS**

***Study population***

This multicenter, case-control study was conducted among 415 patients with IBD and 465 healthy controls from five major centres in three major cities of Sri Lanka. Patients were recruited from Gastroenterology Units of Colombo North Teaching Hospital, Ragama, National Hospital of Sri Lanka, Colombo, Colombo South Teaching Hospital, Kalubovila, Teaching Hospital, Kandy and Teaching Hospital Karapitiya, Galle. These centers collectively provide tertiary level specialist gastroenterology care for the majority of Sri Lankan patients.

Cases were patients with endoscopically and histologically confirmed IBD, who had had the condition for more than one year duration. From the commencement of data collection, consecutive, consenting patients were recruited from the five study centres. Approximately equal number of unrelated, healthy, gender-matched subjects, with no chronic bowel symptoms, from the above five locations were recruited as controls.

Ethical approval for the study was obtained from the Ethical Review Committee (ERC) of the Faculty of Medicine, University of Kelaniya and Hospital ERCs where relevant.

***Data collection***

Data were obtained using an interviewer administered, structured questionnaire. Clinical data were obtained by direct questioning and by review of medical records. Phenotypic data (type, location, severity, treatment types, response to treatment and complications) of patients were recorded. Patients were categorized into UC and CD using clinical, endoscopic and histological features. Disease characteristics were listed according to Montreal classification[15]. Comorbid conditions, details of the disease and treatment were confirmed using medical records. Complicated disease was defined as having stricturing or penetrating disease in CD, and extensive colitis or pancolitis in UC. Patients with a disease course that was frequently relapsing, steroid dependent, steroid refractory or requiring biologics was classified as treatment refractory. Presence of disease complications was considered if either perforation, significant bleeding, requirement of colectomy or malignant change had taken place.

***Single nucleotide polymorphism selection and genotyping***

Previous candidate gene studies and GWAS were reviewed to select 16 frequently replicated single nucleotide polymorphisms (SNPs) which were associated with inflammatory bowel disease. DNA from the cases and controls were extracted from peripheral blood samples using. These DNA samples were quantified, normalized and arrayed on 96 well plates. Thereafter genotyping was carried out for 16 SNPs, which tag confirmed IBD susceptibility loci, using Agena MassARRAY system (Agena Bioscience, San Diego, USA) following manufacturer’s instructions. Genotypes of all variants were in Hardy-Weinberg Equilibrium (*P* > 10−3 in the control population).

***Statistical analysis***

After Bonferroni correction a *P*-value of< 0.003 was considered significant to account for multiple hypotheses. Association analysis utilized logistic regression within STATA version 13 (Chicago, IL) with routines available fromhttp://www-gene.cimr.cam.ac.uk/clayton/software/stata. Different genetic models were tested using statistical modeling in univariate and multivariate analyses, for associations with UC and CD. Individual SNPs and various combinations were tested against disease phenotypes. Chi-square test/Fisher’s exact test were used where appropriate for significance testing.

**RESULTS**

The demographic and clinical characteristics of patients are summarized in Table 1.

The result of the case-control comparison of variants in cases and controls is in Table 2. The variant allele of *rs11805303*, *rs1558744* and *rs886774* occurred at a higher frequency in cases than in controls.

The presence of variant alleles was tested for the phenotypes (either CD or UC) that are currently established in Western populations. Only SNP *rs886774* was associated with the described phenotype (Table 3).

Most of the tested phenotypic characteristics were not associated with individual SNPs and combinations that were tested. Table 4 shows SNPs that were significantly associated with clinical characteristics of UC and CD.

**DISCUSSION**

The aim of this study was to identify the association of selected SNPs with IBD, its clinical manifestations and treatment outcomes. Of the 16 SNPs tested, only the variant allele of *LAMB1* gene (*rs886774*) was associated with the main phenotype of UC in this population. We also present a few disease characteristics that are associated with *LAMB1* gene (*rs886774*) and *IL 12B* gene (*rs10045431*) that have not been reported previously among South Asians.

The most significant mutation associated with UC in this study was *rs886774*of the *LAMB1* gene. The *LAMB1* gene codes for a subunit of Laminin, which is a component of the cell basement membrane. Mutation *rs886774* in *LAMB1* gene has been reported in GWAS to be associated with increased susceptibility to UC[16]. Although mutations of this gene are postulated to alter intestinal permeability, a study carried out in Netherland has failed to demonstrate an association with disrupted intestinal permeability[17]. In this Sri Lankan patient population with UC, *rs886774* was associated with mild disease [odd ratio (OR) =1.66, *P* < 0.001] and maintained remission (OR=1.48, *P* < 0.001). Therefore findings of this study indicate that although rs886774 increases susceptibility to UC, patients with this mutation develop a milder version of the disease that is easier to control. This is in keeping with our clinical observations that Sri Lankan patients with UC tend to have a milder and easily controllable form of the disease[18].

The variant allele of *IL-12B* gene (*rs10045431*) that is known to increases susceptibility to CD in Caucasians[19] had been absent in a study conducted among North Indian patients with CD[20]. Similarly, we did not observe a significant association of this mutation with the main phonotype of CD (OR = 2.5, *P* = 0.178 for homozygous individuals). However, among patients with CD, *rs10045431* was associated with upper gastrointestinal involvement (OR = 4.42, *P* =0.002) in our population. This relationship has not been demonstrated in IBD patients prior to this study.

Variant allele (*rs11805303* ) in the region of *IL23R*, which is an extensively studied genetic association of CD was not present in this group of patients[21,22]. In contrast to the Caucasians, this allele of *IL23R* has been reported to be associated with UC in Chinese patients by several study groups[23-25]. This variant however, have not been observed in South Asia[26], which is in agreement with the findings of our study.

Variant *rs9268853* located in the MHC class II molecule/*HLA DRB9* region is another significant associations of UC previously reported among Caucasians[27,28]. In our population this SNP was not associated with UC. Interestingly, our UC patients with this variant allele had a trend towards less extensive disease compared to others (OR = 0.59, *P* = 0.009). Further, CD patients with this variant were more likely to receive biologics compared to others (OR = 3.36, *P* = 0.004). This variant was not associated with any of the other characteristics of severe CD in this population.

Majority of previously reported variants, associated with IBD in Caucasians and Asians of Chinese origin, were not replicated in this study. This difference may be due to other factors such as gene-gene interactions or gene-environment interactions. It is also possible that yet undiscovered genetic variants, unique to the South Asian populations, which were not investigated in this study, may contribute. Further, it is noted that familial aggregation is less among South Asian IBD patients. This contributed to the hypothesis, that genetic contribution to IBD is less among Asians compared to their Caucasian counterparts, which however is refuted by some scientists[12].

We only studied 16 selected SNPs that were reported to be associated with IBD in previous studies, and which were known to be polymorphic in the Sri Lankan population. The limited number of patients with IBD and the genetic variants included in this study may be a limitation. Hence, more comprehensive studies, including GWAS, involving larger and wider, cross country patient populations among South Asia are needed.

In conclusion,this study, confirms the heterogeneity of allelic mutations in South Asians compared to Caucasians. Most SNPs and disease associations reported here have not been studied in South Asians previously. Further studies, involving a wider South Asian population, are required to confirm or refute these findings.

**ARTICLE HIGHLIGHTS**

 ***Research background***

Genetic factors play an important role in etiology and nature of disease in inflammatory bowel disease (IBD). Genome wide association studies and meta-analyses have discovered 230 disease loci linked to IBD and its various phenotypic characteristics. Majority of these studies are conducted among Caucasian populations.

***Research motivation***

Genetic factors that determine disease patterns are known to vary across different populations and regions. Hence there is an increased need to study the South Asian population in whom there is only sparse evidence on genetic associations of IBD.

***Research objectives***

We aimed to study the association of 16 selected single nucleotide polymorphisms (SNPs) in a South Asian multiethnic population of IBD patients in Sri Lanka.

***Research methods***

A case control multi-center study was conducted. Patients were recruited from the four main gastroenterology units in Sri Lanaka who were diagnosed with IBD for over 1 year duration. A roughly equal number of unrelated gender matched healthy adult volunteers were recruited. DNA was extracted from peripheral blood and genotyping was performed for 16 selected SNPs using Agena MassARRAYay system. Data on disease characteristic including disease behavior, treatment response and severity were obtained. Genotypes of all variants were in Hardy-Weinberg Equilibrium. Data analysis included testing for individual SNPs and various combinations with ulcerative colitis (UC), Crohn’s disease (CD) and different clinical characteristics of these diseases.

***Research results***

A total of 415 (CD= 158, UC = 258, indeterminate colitis = 4) patients and 465 controls were studied. SNP *rs886774* (*LAMB1*-gene) was associated with UC [odd ratio (OR) = 1.42, *P* = 0.001]. Other tested mutations failed to demonstrate and associated with UC or CD in this population. The following phenotypic associations were noted within the patient population; among UC patients *rs886774* was associated with mild disease (OR = 1.66, *P* < 0.001) and remained remission (OR = 1.48, *P* < 0.001). SNP *rs10045431* (*IL 12B* gene) was associated with upper gastrointestinal involvement in CD (OR = 4.76, *P* = 0.002).

***Research conclusions***

This study demonstrated the presence of SNP *rs886774* (*LAMB1*-gene) among Sri Lankan patients with UC. Out of the SNPs tested majority were not associated with IBD in Sri Lankans. This confirms genetic heterogeneity of South Asians compared to Caucasian populations.

***Research perspectives***

Future research should direct to genome-wide association scans and identification of other genetic risk factors specific to South Asian populations.

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**Table 1 Characteristics of the patient population *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **CD ( *n* = 153)** | **UC (*n* = 258)** | ***P*1** |
| Male gender  | 77 (50.3) | 123 (47.7) | **0.80** |
| Age in years (mean, SD) | 41.0 (16.9) | 47.6 (14.9) | < 0.01 |
| Race |  |  |  |
| Sinhala | 129 (84.31) | 229 (88.75) |  |
| Tamil | 11 (7.19) | 13 (5.06) |  |
| Muslim | 11 (7.19) | 13 (5.03) |  |
| Other | 2 (1.31) | 3 (1.17) |  |
| Body mass index mg/m2 (mean, SD) |  21.4 (4.6) |  22.9 (4.5) | <0.01 |
| Family history of IBD | 7 (4.6) | 12 (4.7) | 0.98 |
| **Comorbidities** |  |  |  |
|  | Diabetes |  11 (7.1) |  41 (15.9) | 0.01 |
|  | Hypertension |  16 (10.5)  | 37 (14.3) | 0.26 |
|  | BA/COPD | 9 (5.8) |  22 (8.5) | 0.33 |
|  | Tuberculosis |  7 (4.6) |  1 (0.4) |  < 0.01 |
|  | Tobacco smoking | 25 (16.3) | 49 (18.9) | 0.39 |
| **Disease characteristics** |  |  |  |
|  | Duration of the disease (yr) | 4.8 (4.2) | 7.3 (5.7) | < 0.01 |
|  | Extensive disease in UC | 76 (29.5) | - | - |
|  | Upper GI disease in CD | 11 (7.2) | - | - |
|  | Severe/complicated disease | 47 (30.7) | 130 (50.4) | < 0.01 |
|  | Maintained remission | 142 (92.9) | 245 (95.0) | 0.83 |
|  | Treatment refractory disease | 24 (15.68) | 24 (9.3) | < 0.05 |
|  | Use of biologics | 16 (10.5) | 7 (2.7) | < 0.01 |

1Unadjusted univariate *P* value. IBD:Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; GI: Gastrointestinal; BA: Bronchial asthma; COPD: Chronic obstructive pulmonary disease.

**Table 2 Results of the cases control analysis for the association of single nucleotide polymorphisms with inflammatory bowel disease**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **SNPs** | **Variant allele** | **Genotypes** | **Controls (465), *n* (%)** | **Cases****(415) *n* (%)** | **Odds ratio1** | **95% CI** | ***P*** |
| rs10045431 | C | AA | 5 (1.08) | 5 (1.2) |  |  |  |  |
|   |   | CA | 114 (24.52) | 83 (20) | 0.77 | 0.56 | 1.06 | 0.11 |
|   |   | CC | 346 (74.41) | 327 (78.8) | 1.06 | 0.30 | 3.69 | 0.93 |
| rs11805303 | T | CC |  93 (20) |  53 (12.77) |  |  |  |  |
|   |   | TC |  236 (50.75) |  207 (49.88) | 1.54 | 1.05 | 2.26 | 0.03 |
|   |   | TT |  136 (29.25) |  155 (37.35) | 2.00 | 1.33 | 3.01 | 0.00 |
| rs12612347 | G | AA |  67 (14.41) |  69 (16.63) |  |  |  |  |
|   |   | GA |  229 (49.25) |  191 (46.02) | 0.81 | 0.55 | 1.19 | 0.29 |
|   |   | GG |  169 (36.34) |  155 (37.35) | 0.89 | 0.60 | 1.33 | 0.57 |
| rs13361189 | C | TT |  267 (57.42) |  235 (56.63) |  |  |  |  |
|   |   | CT |  172 (36.99) |  153 (36.87) | 1.01 | 0.76 | 1.34 | 0.94 |
|   |   | CC |  26 (5.59) |  27 (6.51) | 1.18 | 0.67 | 2.08 | 0.57 |
| rs1558744 | A | GG |  347 (74.62) |  289 (69.64) |  |  |  |  |
|   |   | AG |  116 (24.95) |  118 (28.43) | 1.22 | 0.90 | 1.65 | 0.19 |
|   |   | AA |  2 (0.43) |  8 (1.93) | 4.80 | 1.01 | 22.79 | 0.04 |
| rs1728785 | A | CC |  261 (56.13) |  253 (60.96) |  |  |  |  |
|   |   | CA |  184 (39.57) |  139 (33.49) | 0.78 | 0.59 | 1.03 | 0.08 |
|   |   | AA |  20 (4.3) |  23 (5.54) | 1.19 | 0.64 | 2.21 | 0.59 |
| rs3024505 | A | GG |  373 (80.22) |  322 (77.59) |  |  |  |  |
|   |   | GA |  89 (19.14) |  89 (21.45) | 1.16 | 0.83 | 1.61 | 0.38 |
|   |   | AA |  3 (0.65) |  4 (0.96) | 1.54 | 0.34 | 6.95 | 0.57 |
| rs3737240 | T | CC |  262 (56.34) |  215 (51.81) |  |  |  |  |
|   |   | TC |  172 (36.99) |  167 (40.24) | 1.18 | 0.90 | 1.56 | 0.24 |
|   |   | TT |  31 (6.67) |  33 (7.95) | 1.30 | 0.77 | 2.19 | 0.33 |
| rs4613763 | C | TT |  461 (99.14) |  408 (98.31) | 1.98 | 0.57 | 6.80 | 0.28 |
|   |   | CT |  4 (0.86) |  7 (1.69) | 0.89 | 0.77 | 1.01 | 0.07 |
|   |   | CC |  0 (0) |  0 (0) |  |  |  |  |
| rs5771069 | A | GG |  264 (56.77) |  248 (59.76) |  |  |  |  |
|   |   | GA |  160 (34.41) |  144 (34.7) | 0.96 | 0.72 | 1.27 | 0.77 |
|   |   | AA |  41 (8.82) |  23 (5.54) | 0.60 | 0.35 | 1.02 | 0.06 |
| rs6017342 | A | CC |  217 (46.67)  | 223 (53.73) |  |  |  |  |
|   |   | CA | 200 (43.01) | 154 (37.11) | 0.75 | 0.57 | 0.99 | 0.04 |
|   |   | AA | 48 (10.32) | 38 (9.16) | 0.77 | 0.48 | 1.23 | 0.27 |
| rs744166 | G | AA | 86 (18.49) | 100 (24.1) |  |  |  |  |
|   |   | AG | 238 (51.18) | 203 (48.92) | 0.73 | 0.52 | 1.03 | 0.08 |
|   |   | GG | 141 (30.32) | 112 (26.99) | 0.68 | 0.47 | 1.00 | 0.05 |
| rs7809799 | G | AA | 405 (87.1) | 361 (86.99) |  |  |  |  |
|   |   | GA | 58 (12.47) | 50 (12.05) | 0.97 | 0.65 | 1.45 | 0.87 |
|   |   | GG | 2 (0.43) | 4 (0.96) | 2.24 | 0.41 | 12.32 | 0.35 |
| rs886774 | G | AA | 154 (33.12) | 104 (25.06) |  |  |  |  |
|   |   | GA | 214 (46.02) | 199 (47.95) | 1.38 | 1.01 | 1.89 | 0.05 |
|   |   | GG | 97 (20.86) | 112 (26.99) | 1.71 | 1.18 | 2.47 | 0.00 |
| rs9268853 | C | TT | 210 (45.16) | 203 (48.92) |  |  |  |  |
|   |   | CT | 208 (44.73) | 164 (39.52) | 0.82 | 0.62 | 1.08 | 0.16 |
|   |   | CC | 47 (10.11) | 48 (11.57) | 1.06 | 0.68 | 1.65 | 0.81 |
| rs9822268 | A | GG | 284 (61.08) | 280 (67.47) |  |  |  |  |
|   |   | GA |  163 (35.05) | 117 (28.19) | 0.73 | 0.55 | 0.97 | 0.03 |
|   |   | AA | 18 (3.87) | 18 (4.34) | 1.01 | 0.52 | 1.99 | 0.97 |

1Report the odds of being a case for heterozygous and homozygous individuals with the recessive allele compared to the controls. SNPs: Single nucleotide polymorphisms.

**Table 3 Associations of variants with Cohn’s disease and ulcerative colitis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **SNPs** | **Candidate gene** | **Associated subtype** | **Heterogenous**  | **Homogenous** |
|  **Odds ratio1** | ***P*** | **Odds ratio1** | ***P*** |
| rs10045431 | *IL 12B* | CD | 0.579 | 0.027 | 2.491 | 0.178 |
| rs11805303 | *IL23R* | CD | 0.909 | 0.609 | 1.505 | 0.010 |
| rs12612347 | *ARPC2* | UC | 0.896 | 0.479 | 0.991 | 0.957 |
| rs13361189 | *IRGM* | CD | 1.093 | 0.578 | 1.355 | 0.331 |
| rs1558744 | *IFN-c, IL26, IL22* | UC | 1.043 | 0.811 | 5.560 | 0.036 |
| rs1728785 | *CDH1* | UC | 0.829 | 0.244 | 1.410 | 0.314 |
| rs3024505 | *IL10* | UC | 1.194 | 0.351 | 2.446 | 0.244 |
| rs3737240 | *FCGR2A* | UC | 1.182 | 0.291 | 1.187 | 0.564 |
| rs4613763 | *PTGER4* | CD | 2.325 | 0.273 | 2 | - |
| rs5771069 | *IL17REL/PIM3* | UC | 0.915 | 0.589 | 0.599 | 0.109 |
| rs6017342 | *HNF4a, SERINC3* | UC | 0.690 | 0.021 | 0.920 | 0.746 |
| rs744166 | *STAT3* | CD | 0.841 | 0.266 | 0.900 | 0.541 |
| rs7809799 | *SMURF1* | UC | 1.149 | 0.542 | 2.747 | 0.270 |
| rs8867743 | *LAMB1* | UC | 1.163 | 0.330 | 1.494 | 0.001 |
| rs9268853 | *HLA DRB5* | UC | 0.684 | 0.017 | 1.049 | 0.850 |
| rs9822268 | *APEH* | UC | 0.748 | 0.748 | 1.116 | 0.779 |

1Odds ratios when compared to patients with the healthy controls; 2No heterozygous individuals were present in this study population; 3Significantly associated with the relevant phenotype after Bonferroni correction. SNPs: Single nucleotide polymorphisms; CD: Cohn’s disease; UC: Ulcerative colitis.

**Table 4 Association of single nucleotide polymorphisms with clinical characteristics of ulcerative colitis and Cohn’s disease**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristic** | **SNPs** | **OR1** | ***P*** | **95% CI** |
| Risk for UC | rs11805303 | 1.35 | 0.009 | 1.08  | 1.69 |
| Extensive disease in UC | rs9268853 | 0.59 | 0.009 | 0.37 | 0.82 |
| Upper GI disease in CD | rs10045431 | 4.42 | 0.002 | 1.75 | 12.92 |
| Mild disease in UC | rs886774 | 1.66 | < 0.001 | 1.13 | 2.17 |
| Maintained remission UC | rs886774 | 1.48 | < 0.001 | 1.19 | 1.85 |
| Use of biologics in CD | rs9268853 | 3.36 | 0.004 | 1.48 | 7.58 |

1Univariate odds of presence of single nucleotide polymorphisms in patients with characteristic tested against the healthy controls. OR: Odds ratio; SNPs: Single nucleotide polymorphisms; GI: Gastrointestinal; CD: Cohn’s disease; UC: Ulcerative colitis.