Genetic associations of inflammatory bowel disease in a South Asian population

Madunil Anuk Niriella, Isurujith Kongala Liyanage, Senerath Kuleesha Kodisinghe, Arjuna Priyadarsin De Silva, Nimna Rajapakse, Sunali D Nanayakkara, Dunya Luke, Thilakshi Silva, Metthananda Nawarathne, Ranjith K Peiris, Udaya P Kalubovila, Sujeewa R Kumarasena, Vajira Harshadeva Weerabaddana Dissanayake, Rohan W Jayasekara, Hithanadura Janaka de Silva

Author contributions: Niriella MA, de Silva HJ and Jayasekara RW conceptualized the study design; Liyanage IK, Kodisinghe SK, De Silva AP, Rajapakse N, Nanayakkara SD, Luke D and Silva T were researchers involved in data collection, analysis and preparation of this manuscript; Nawarathne M, Peiris RK, Kalubovila UP and Kumarasena SR assisted with providing access to consenting patients from their respective units; Liyanage IK carried out the data analysis under the supervision of Niriella MA, De Silva AP, Dissanayake VH, Jayasekara RW and de Silva HJ who were overall supervisors leading data acquisition, analysis and formulation of this manuscript; Dissanayake VH was the lead of the genetics analysis; all authors read and accepted the final version of this manuscript.

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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 people is reported to range from 3-7 cases for CD and 4-11 cases for UC[2]. Although the evidence based in the Asian region is limited, studies such as the Asia Pacific Crohn’s and Collitis Epidemiology Study carried out in Australia, China, Hong Kong, Indonesia, Macau, Malaysia, Singapore, Sri Lanka and Thailand have demonstrated an overall incidence per 100000 people of 0.76 for UC and 0.54 for CD[3,4].

The prevalence of IBD is relatively higher in East Asia 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 people in Sri Lanka are 6.5 (UC-5.3, CD-1.2) and 1.6 (UC-1, CD-0.6), 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

Core tip: This is a case-control study looking at the prevalence of genetic mutations, ones that are commonly associated with inflammatory bowel disease (IBD) among Caucasians, in a South Asian population from Sri Lanka. Most allelic variants studied were not seen in this population, confirming the heterogeneity of the genetic composition of IBD between South Asians and Caucasian patients. We found positive associations between rs886774 (LAMB1-gene) and ulcerative colitis, 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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Genetic heterogeneity within the region, along with diverse socio-economic, environmental and cultural factors, may contribute to these differences. Since identification of the 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. However, genetic contribution to IBD varies between regions and ethnicities, and there is only limited data for Asians. Results from a large trans-ancestry study demonstrated a wide heterogeneity of genetic risk between European, East Asian and South Asian populations. 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 protein 16-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. in 2012 based on results of 93 reports from eight 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.

This study was conducted in Sri Lankans, a population that had never before been studied in South Asia, 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 centers 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 the condition for more than one year duration. From the commencement of data collection, consecutive, consenting patients were recruited from the five study centers. Approximately equal numbers 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 the Montreal classification. Comorbid conditions, details of the disease and treatment were confirmed using medical records. Complicated disease was defined as having strictureing 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. The presence of disease complications was considered if either perforation, significant bleeding, requirement for colectomy or malignant changes had taken place.

**Single nucleotide polymorphism selection and genotyping**

Previous candidate gene and GWAS studies were reviewed to select 16 frequently replicated single nucleotide polymorphisms (SNPs) that were associated with inflammatory bowel disease. DNA from the cases and controls were extracted from stored peripheral blood samples using Qiagen QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany) to yield DNA concentration > 10 ng/μL. These DNA samples were quantified, normalized and arrayed on 96-well plates. Thereafter, genotyping was carried out for 16 SNPs, which confirmed IBD susceptibility loci, using the Agena MassARRAY system (Agena Bioscience, San Diego, United States) and by following the 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, United States) with routines available from http://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 tests/Fisher’s exact tests were used where appropriate for significance testing.

**RESULTS**

The demographic and clinical characteristics of patients...
The results of the case-control comparison of variants in cases and controls is included in Table 2. The variant alleles 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 for 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 the 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 the 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 the LAMB1 gene (rs886774) and the IL12B 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 the LAMB1 gene has been reported in GWAS to be associated with increased susceptibility to UC[26]. Although mutations in this gene are postulated to alter intestinal permeability, a study carried out in the Netherlands 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, this study's findings 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 consistent with our clinical observations that Sri Lankan patients with UC tend to have a milder and easily controllable form of the disease[48].

The variant allele of the IL-12B gene (rs10045431) that is known to increase susceptibility to CD in Caucasians[29] was 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 phenotype 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 had not been demonstrated in IBD patients prior to this study.

The 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 Caucasians, this allele of IL23R was reported by several study groups to be associated with UC in Chinese patients[23-25]. This variant, however, has 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

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

| Characteristic                  | CD (n = 153) | UC (n = 258) | P*  |
|--------------------------------|-------------|-------------|-----|
| 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 kg/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|

*Unadjusted univariate P value. IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; GI: Gastrointestinal; BA: Bronchial asthma; COPD: Chronic obstructive pulmonary disease.
molecule/HLA DRB9 region, is also significantly associated with UC, which has been 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, \(P = 0.009\)). Furthermore, 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.

The 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 other undiscovered genetic variants unique to South Asian populations, which were not investigated in this study, may contribute. Furthermore, it is noted that familial aggregation is lower among South Asian IBD patients. This contributed to the hypothesis that genetic contribution to IBD is lower among Asians compared to their Caucasian counterparts, which is refuted by some

| SNPs          | Variant allele | Genotypes | Controls (465), n (%) | Cases (415), n (%) | Odds ratio\(^1\) | 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 |
| 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 |
| 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              | 0.00            | 22.79  | 0.00 |
| rs1728785 A   | CC             | 261 (56.13)| 253 (56.96)           |                   |                 |        |      |
|               | CA             | 184 (39.57)| 139 (33.49)           | 0.78              | 0.59            | 1.03   | 0.08 |
| rs3024505 A   | GG             | 373 (80.22)| 322 (77.59)           |                   |                 |        |      |
|               | GA             | 89 (19.14) | 89 (21.45)            | 1.16              | 0.83            | 1.61   | 0.38 |
| rs3737240 T   | CC             | 262 (56.34)| 215 (51.81)           |                   |                 |        |      |
|               | TC             | 172 (36.99)| 167 (40.24)           | 1.18              | 0.90            | 1.56   | 0.24 |
| rs4613763 C   | TT             | 461 (99.14)| 408 (96.31)           | 1.98              | 0.57            | 6.80   | 0.28 |
|               | CT             | 4 (0.86)  | 7 (1.69)              | 0.89              | 0.77            | 1.01   | 0.07 |
| rs5771069 A   | GG             | 264 (56.77)| 248 (59.76)           |                   |                 |        |      |
|               | AG             | 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 |
| rs744166 G    | AA             | 48 (10.32)| 38 (9.16)             | 0.77              | 0.48            | 1.23   | 0.27 |
| rs7809799 G   | AA             | 86 (18.49)| 100 (24.1)            |                   |                 |        |      |
|               | AG             | 238 (51.18)| 203 (48.92)           | 0.73              | 0.52            | 1.03   | 0.08 |
| rs886774 G    | AA             | 405 (87.1)| 361 (86.99)           |                   |                 |        |      |
|               | GA             | 58 (12.47)| 50 (12.05)            | 0.97              | 0.65            | 1.45   | 0.87 |
| rs9268853 C   | TT             | 210 (45.16)| 203 (48.92)           |                   |                 |        |      |
| rs9822268 A   | AA             | 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 |

\(^1\)Reports the odds of being a case for heterozygous and homozygous individuals with the recessive allele compared to the controls. SNPs: Single nucleotide polymorphisms.
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 that involves larger and wider, cross country populations throughout South Asia, are needed.

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

**ARTICLE HIGHLIGHTS**

**Research background**

Genetic factors play an important role in the etiology and nature of inflammatory bowel disease (IBD). Genome-wide association studies and meta-analyses have discovered 230 disease loci linked to IBD and its various phenotypic characteristics. A 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 of 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, who were diagnosed with IBD for more than a 1 year duration, were recruited from the four main gastroenterology units in Sri Lanka. 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 the Agena MassARRAYay system. Data on disease characteristics 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 rs986774 (LAMB1-gene) was associated...
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with UC [odds ratio (OR) = 1.42, P = 0.001]. Other tested mutations failed to demonstrate an association 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 = 1.86, P < 0.001) and remained significant (OR = 1.48, P < 0.001), and SNAP rs0064531 (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, the majority were not associated with IBD in Sri Lankans. This confirms the genetic heterogeneity of South Asians compared to Caucasian populations.

Research perspectives

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

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