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ORIGINAL ARTICLE

Case Control Study

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 Rajapakshe, 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

Madunil Anuk Niriella, Arjuna Priyadarsin De Silva, Nimna Rajapakshe, Sunali D Nanayakkara, Dunya Luke, Thilakshi Silva, Hithanadura Janaka de Silva, Faculty of Medicine, University of Kelaniya, Ragama GQ 10110, Sri Lanka

Isurujith Kongala Liyanage, Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda 10250, Sri Lanka

Senerath Kuleesha Kodisinghe, University Medical Unit, Colombo North Teaching Hospital, Ragama 0025, Sri Lanka

Metthananda Nawarathne, Gastroenterology Unit, National Hospital of Sri Lanka, Colombo 0010, Sri Lanka

Ranjith K Peiris, Gastroenterology Unit, Colombo South Teaching Hospital, Kalubovila 80000, Sri Lanka

Udaya P Kalubovila, Gastroenterology Unit, Teaching Hospital Kandy, Kandy 20400, Sri Lanka

Sujeewa R Kumarasena, Gastroenterology Unit, Teaching Hospital Karapitiya, Galle 80000, Sri Lanka

Vajira Harshadeva Weerabaddana Dissanayake, Rohan W Jayasekara, Human Genetics Unit, Faculty of Medicine, University of Colombo, Colombo 0010, Sri Lanka

ORCID number: Madunil Anuk Niriella (0000-0002-7213-5858); Isurujith Kongala Liyanage (0000-0003-3477-4576); Senerath Kuleesha Kodisinghe (0000-0003-2956-5008); Arjuna Priyadarsin De Silva (0000-0002-0559-8721); Nimna Rajapakshe (0000-0002-4702-0928); Sunali D Nanayakkara (0000-0003-4693-2041); Dunya Luke (0000-0002-6225-1994); Thilakshi Silva (0000-0002-8155-0770); Metthananda Nawarathne (0000-0002-0098-4017); Ranjith K Peiris (0000-0003-0748-6253); Udaya P Kalubovila (0000-0002-5806-6171); Sujeewa R Kumarasena (0000-0002-2221-5649); Vajira Harshadeva Weerabaddana Dissanayake (0000-0002-3264-6856); Rohan W Jayasekara (0000-0002- 4176-7705); Hithanadura Janaka de Silva (0000-0003-1119-1802).

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Corresponding author to: Madunil Anuk Niriella, MBBS, MD, MRCP, FRCP, Professor, Department of Clinical Medicine, Faculty of Medicine, University of Kelaniya, Ragama GQ 10110, Sri Lanka. maduniln@yahoo.co.uk
Telephone: +94-714820948
Fax: +94-112958337

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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 study of histologically confirmed ulcerative colitis (UC) or Crohn's disease (CD) patients with $\geqslant$ 1 year disease duration, who were compared to unrelated, gender-matched, healthy individuals as controls, was conducted at four major centers in Sri Lanka. Phenotypic data of the cases were obtained and 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*, and *APEH*:*rs9822268*. The genotypes of all variants were in Hardy-Weinberg Equilibrium ($P > 10^{-3}$). To account for multiple hypothesis testing, *P*-values < 0.003 were considered significant.

RESULTS

A total of 415 patients and 465 controls were recruited. Out of the single nucleotide polymorphisms (SNPs) tested, the majority were not associated with IBD in Sri Lankans. Significant positive associations were noted between *rs886774* (*LAMB1*-gene) and UC (odds 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 the 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

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).

Niriella MA, Liyanage IK, Kodisinghe SK, De Silva AP, Rajapakshe N, Nanayakkara SD, Luke D, Silva T, Nawarathne M, Peiris RK, Kalubovila UP, Kumarasena SR, Dissanayake VH, Jayasekara RW, de Silva HJ. Genetic associations of inflammatory bowel disease in a South Asian population. *World J Clin Cases* 2018; 6(15): 908-915 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i15/908.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i15.908

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 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 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),

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 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[8-10]. However, genetic contribution to IBD varies between regions and ethnicities, and there is only limited data for Asians[11]. Results from a large trans-ancestry study demonstrated a 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 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*[13] 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[3,6]. 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[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. 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

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/m^2 (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

[1]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.

are summarized in Table 1.

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 *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 the *LAMB1* gene has been reported in GWAS to be associated with increased susceptibility to UC[16]. 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[18].

The variant allele of the *IL-12B* gene (*rs10045431*) that is known to increase susceptibility to CD in Caucasians[19] 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 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 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

Table 2 Results of the case's control analysis for the association of single nucleotide polymorphisms with inflammatory bowel disease

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
		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

[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.

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

Table 3 Associations of variants with Crohn's disease and ulcerative colitis

SNPs	Candidate gene	Associated subtype	Heterogenous		Homogenous	
			odds ratio[1]	*P*	odds ratio[1]	*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
rs886774[3]	*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

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

Table 4 Association of single nucleotide polymorphisms with clinical characteristics of ulcerative colitis and Crohn's disease

Characteristic	SNPs	OR[1]	*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 UC remission	rs886774	1.48	< 0.001	1.19	1.85
Use of biologics in CD	rs9268853	3.36	0.004	1.48	7.58

[1]Univariate odds for the presence of single nucleotide polymorphisms in patients with characteristics tested against healthy controls. OR: Odds ratio; SNPs: Single nucleotide polymorphisms; GI: Gastrointestinal; CD: Crohn's disease; UC: Ulcerative colitis.

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 that involves larger and wider, cross country patient 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 over 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 *rs886774* (*LAMB1*-gene) was associated

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 = 1.66, $P < 0.001$) and remained in remission (OR = 1.48, $P < 0.001$), and 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, 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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