

The Role of Interleukin-22 Genetic Polymorphism in A Cohort of Egyptian Patients With Ulcerative Colitis

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ABSTRACT

BACKGROUND: Ulcerative colitis (UC) is characterized by an exaggerated mucosal immune response to luminal gut contents in genetically susceptible individuals. Interleukin-22 (IL-22) is a recently described IL-10 family cytokine that is produced by T-helper (Th)-17 cells, Th1 cells, NKT cells and newly described innate lymphoid cells (ILCs). Role for IL-22 has been identified in

numerous tissues including the intestines, lung, liver, kidney, thymus, pancreas and skin.

AIM: studying the polymorphism of interleukin-22 in a cohort of Egyptian ulcerative colitis patients.

METHODS: The study included two groups Group A: fifty Egyptian patients suffering from ulcerative colitis. Group B: fifty Egyptian healthy persons as a control group. Genotypes of 3 common polymorphisms of the IL-22 gene were determined by the 5' nuclease Allelic discrimination assay.

RESULTS: The comparison of IL22 rs2227485, rs1182844, and rs1179246 SNP genotype frequency between UC patients and controls revealed a statistically significant difference. Assessment of IL22 rs2227485, rs1182844, and rs1179246 SNPs as risk factors for UC using logistic regression analysis revealed that subject carrying one T, A and C alleles of the respective SNPs had 2.006, 2.676 and 4.416 folds increased risk for development of UC compared to the C, T and A alleles carriers respectively (OR=2.006, 95% C.I=1.044 - 3.854 for rs2227485 & OR=2.676, 95% C.I=1.394 - 5.135 for rs1182844 and OR=4.416, 95% C.I=2.372 - 8.221 for rs1179246).

CONCLUSION: There was a significantly associated of IL-22 gene polymorphisms (rs2227485, rs1182844, rs1179246) with Egyptian UC patients. The validation of our results require additional well-designed large studies.

Key words: Interleukin-22; Gene polymorphism; Ulcerative colitis

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INTRODUCTION

Ulcerative colitis (UC) is one of the two major types of inflammatory bowel disease (IBD), along with Crohn's disease (CD). UC is a lifelong illness that has a profound emotional and social impact on the affected patients. IBD occur with different frequencies around the world. The United States, the United Kingdom and Sweden

have the highest incidence of UC^[1]. In Egypt, the frequency of IBD increased in the last 10 years, the mean age at presentation was in the late twenties, a smaller peak occurs at 55-70 years, although it can occur at any age^[2]. It affects men and women equally and appears to run in families with reports of up to 20 percent of people with UC having a family member or relative with UC or CD^[2]. The hallmark of IBD is chronic, uncontrolled inflammation of the intestinal mucosa. The exact etiology of ulcerative colitis (UC) is unknown, but some hypotheses and certain factors have been associated with the disease. Etiologic factors include genetic factors, immune system dysregulation, environmental factors as non-steroidal anti-inflammatory drug (NSAID) use, oral contraceptive pills, low levels of antioxidants, psychological stress factors, a smoking history, and certain types of food composition as milk products^[3]. The current hypothesis is that genetically susceptible individuals have abnormalities of humoral and cell-mediated immunity and/or generalized enhanced reactivity against commensal intestinal bacteria, and this will lead to dysregulation in the mucosal immune response which predisposes to colonic inflammation^[4]. The Genome-Wide Association Studies (GWAS) of UC have identified more than 25,000 possible single nucleotide polymorphisms (SNP) for IBD in susceptible regions on several chromosomes such as 1, 3, 4, 5, 6, 7, 10, 12, 14, 16, 19, and X^[5].

It is established that mucosal inflammation is triggered by various cytokines produced by different pathways, such as the Th1, Th2, and recently the Th17 immunological response^[6].

Interleukin-22 (IL-22) is a α -helical cytokine that belongs to a group of cytokines called the IL-10 family, this class is formed of potent mediators of cellular inflammatory responses including IL-19, IL-20, IL-24, and IL-26^[7]. IL-22 binds to a heterodimeric cell surface receptor composed of IL-10R2 and IL-22R1 subunits^[8]. IL-22 is produced by activated NK and T cells and initiates innate immune responses against bacterial pathogens especially in epithelial cells such as respiratory and gut epithelial cells. This cytokine acts as an effector of the Th17 pathway in response to IL-23 with pro-inflammatory and anti-inflammatory properties that may be implicated in the pathogenesis of IBD^[9]. The IL-22 gene is a 5.3 Kb region located in the 12q15 loci of the chromosome 12, close to the genes encoding IFN- γ and IL-26^[10].

IL-22 responsiveness is mainly determined by IL-22R1 expression. IL-22R1 is specifically expressed in non leukocytic cells such as those of the pancreas, skin, kidney, liver, and colon. IL-22R1 expression can be detected in epithelial cells of these organs, but not in their immune cells^[11]. IL22 cannot mediate autocrine or paracrine functions among leukocytes Therefore, it is unique among the cytokines. Instead, IL 22 transmits information between leukocytes and the non leukocytic cell compartment^[12]. Whether genetic polymorphisms of IL22 influence UC risk is still unknown. The aim of this study was to determine the role of interleukin-22 genetic polymorphism (IL22 rs2227485, rs1182844, and rs1179246) in Egyptian ulcerative colitis patients.

PARTICIPANTS AND METHODS

The current study included one hundred native Egyptian participants divided into two groups; group (I): fifty patients diagnosed with ulcerative colitis, group (II): fifty sex and age matched healthy subjects acts as a control group. All participants were selected from internal medicine and gastroenterology outpatient clinics, patients admitted to gastroenterology inpatient ward, faculty of medicine, Alexandria University. This study was carried out according to the

principles in the Declaration of Helsinki. The Ethics and Research Committee of our hospital approved the present study and all participants signed a written statement of informed consent.

UC was diagnosed based on clinical, radiological, endoscopic and histological examinations^[13]. According to Montreal classification the disease location was defined as (ulcerative proctitis, leftsided colitis, and extensive colitis)^[14]. The severity of UC was determined according to Truelove and Witts criteria (mild colitis, moderate colitis, and severe colitis)^[15]. The control group had undergone endoscopic examinations in the same period as the UC patients, without evidence of UC.

Genomic DNA was extracted from peripheral blood samples using QIAamp DNA Blood Mini Kit (Qiagen, USA) according to the manufacturer's instructions. The quantity and purity of the extracted DNA were assessed using the NanoDrop 2000 (Thermo Scientific, USA). The IL22 rs2227485 and rs1179246 SNPs genotyping was performed using the 5' nuclease Allelic discrimination assay. For each SNP, the PCR reaction mix contained 10 μ L TaqMan® Universal PCR Master Mix (Applied biosystems, USA), 1 μ L of TaqMan® SNP Genotyping Assay 20x (IL22 rs2227485 Cat.no. 4351379 and IL22 rs1179246 Cat.no 4351379), 20 ng DNA/reaction and DNAase free water to a final reaction volume of 20 μ L. Thermal cycling profile was done using Rotorgene Q real-time PCR system (Qiagen, Germany) as follows: initial AmpliTaq Gold enzyme activation at 95 °C for 10 min, and 40 cycles of denaturation at 95°C for 15 seconds and annealing/extension at 60 °C for 1 min.

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The normality of distribution of variables was verified by using the Kolmogorov- Smirnov test, Comparisons between groups for categorical variables were assessed using Chi-square test (Fisher or Monte Carlo). Student t-test was used to compare two groups for normally distributed quantitative variables. Mann Whitney test was used to compare between two groups for not normally distributed quantitative variables while Kruskal Wallis test was used to compare different groups. Odd ratio (OR) and 95% Confidence Interval were used. Significance of the obtained results was judged at the 5% level.

RESULTS

The current study included two native Egyptian groups; group (1): 50 patients diagnosed with UC, and group (2): 50 age and sex-matched healthy participants.

Table 1 represents the demographic and laboratory parameters of studied groups, no statistical significant differences were found between the group (I) and control group regarding age, sex and laboratory parameters except for fecal calprotectin. The mean level of faecal calprotectin was 600.3 ± 405.1 μ g/g in group (I), and 30.2 ± 8.1 μ g/g in group (II), with a high statistical significant difference between both groups. $P < 0.001$.

Table 2 represents the family history of ulcerative colitis (UC) in both groups, a significant statistical significant difference was noticed between the two studied groups.

As regards the severity of the disease, figure 1 showed the distribution of the studied cases according to Truelove and Witts' severity index and figure 2 showed the location of the disease in studied cases according to Montreal classification.

IL-22 gene polymorphisms and UC

1.1. Association between IL22 rs2227485, rs1182844, and rs1179246 polymorphism and UC risk

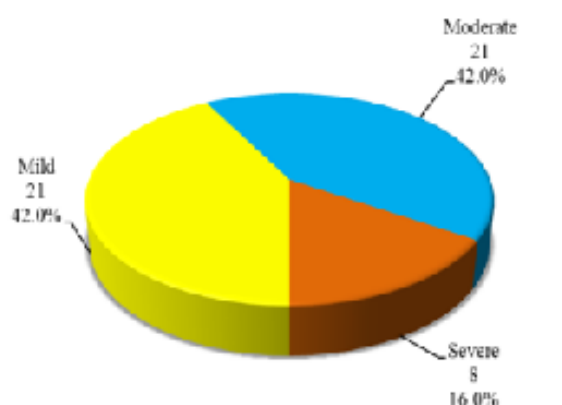


Figure 1 Distribution of the studied cases according to severity, it showed the distribution of the studied cases according to Truelove and Witts' severity index. 21 cases (42%) were mild, 21 cases (42%) were moderate, 8 cases (16%) were severe.

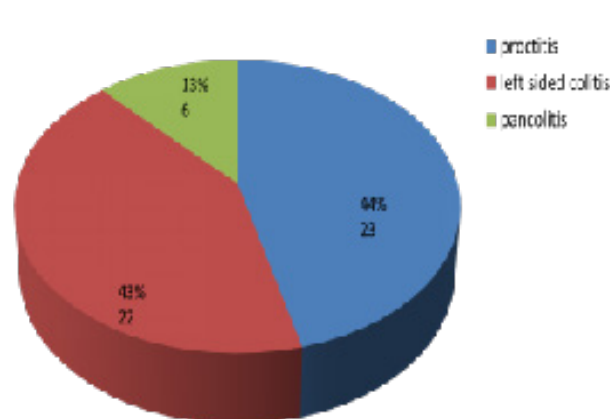


Figure 2 Classification of the studied cases according to disease location, it showed the location of the disease in studied cases according to Montreal classification. 23 cases (44%) had proctitis, 21 cases (43%) had left sided colitis, 6 cases (13%) had pancolitis.

Table 1 Comparison between the studied groups according to demographic and laboratory parameters.

	Group (I) (n = 50)	Group (II) (n = 50)	Test of sig.	P
Sex				
Male	14 (28%)	21 (42.0%)	$\chi^2 = 2.154$	0.142
Female	36 (72%)	29 (58.0%)		
Age (years)				
Mean \pm SD.	34.1 \pm 10.6	37.6 \pm 9.6	t= 1.774	0.079
Median (Min.-Max.)	33 (20 - 80)	35.5(27.0 - 77.0)		
Hemoglobin (g/dl)				
Mean \pm SD.	13 \pm 1.4	13.5 \pm 2.3	t= 1.393	0.167
Median (Min.-Max.)	12.9(10 - 16.5)	13.6 (5.1 - 17.3)		
WBCs ($\times 10^9/l$)				
Mean \pm SD.	7 \pm 1.8	6.2 \pm 2.4	t= 1.869	0.065
Median (Min.-Max.)	6.8 (4 - 10.7)	6.3 (1.8 - 12.7)		
PLT ($\times 10^9/l$)				
Mean \pm SD.	274.1 \pm 69.3	244.8 \pm 46.3	U= 988.5	0.071
Median (Min.-Max.)	270 (154 - 534)	255.5(104.0-308.0)		
SGOT				
Mean \pm SD.	24.3 \pm 10.1	26.5 \pm 12.7	U= 1028.5	0.126
Median (Min.-Max.)	23 (14 - 85)	24.5(13.0-102.0)		
SGPT				
Mean \pm SD.	20.8 \pm 6.3	26.9 \pm 19.5	U= 1012.5	0.101
Median (Min.-Max.)	19.5 (11-48)	22.5 (11.0-136.0)		
Albumin				
Mean \pm SD.	4.1 \pm 0.4	3.9 \pm 0.8	t= 1.573	0.12
Median (Min.-Max.)	4 (3.5-6)	4.0 (1.8-5.2)		
ALP				
Mean \pm SD.	67.9 \pm 7.9	62.7 \pm 23.0	t= 1.504	0.138
Median (Min.-Max.)	66 (57-98)	64.0 (37.0-166.0)		
Urea				
Mean \pm SD.	26.3 \pm 5.5	30.8 \pm 19.2	1130	0.407
Median (Min.-Max.)	25.5 (18-39)	26.0 (17.0-139.0)		
Creatinine				
Mean \pm SD.	0.8 \pm 0.1	0.9 \pm 0.5	1101.5	0.292
Median (Min.-Max.)	0.8 (0.5-1.3)	0.8 (0.5-4.0)		
Calprotectin				
Mean \pm SD.	600.3 \pm 405.1	30.2 \pm 8.1	0.0*	<0.001*
Median (Min.-Max.)	395.5 (164-1600)	30 (10-44)		

U: Mann Whitney test, p: p value for comparing between the studied groups, *: Statistically significant at $p \leq 0.05$.

Table 2 Family history to UC in relation to the two Groups.

		Groups			Total
		Patients		Control	
Family history to UC	No	No.	31	50	81
		%	62.00%	100.00%	81.00%
	Yes	No.	19	0	19
		%	38.00%	0.00%	19.00%
Total		No.	50	50	100
		%	100.00%	100.00%	100.00%
X ²		23.457			
P		0			

The distribution of IL22 rs2227485, rs1182844, and rs1179246 SNPs genotypes in patients with UC and controls was in accordance with Hardy-Weinberg equilibrium^[16] and were showed in table 3.

The comparison of IL22 rs2227485 SNP genotype frequency between UC patients and controls revealed a statistically significant difference. The CC genotype was significantly more frequent in the control group (62%) than UC patients (42%), whereas CT and TT genotypes were more common in UC patients (58% and 38% respectively) ($p = 0.045$). As regard allelic frequency, the T allele was significantly more prevalent in patients with UC compared to controls with a predominance of 37% versus 18% respectively ($p = 0.035$).

Similarly, The TT genotype of rs1182844 SNP was significantly lower in UC patients (34%) compared to the control group (64%) while the TA and AA genotypes were found in 66% of UC patients versus 36% of controls ($p = 0.003$). The A allele of IL22 rs1182844 SNP was significantly prevalent in UC compared to controls with predominance of 37% in UC patients versus 18% in controls ($p = 0.003$).

Regards the IL22 rs 1179246 SNP the C allele was significantly associate with UC as it was found in 54% of UC patients and only 21% of controls ($p < 0.001$). The AC and CC genotypes were significantly higher in UC patients compared to the controls with a prevalence of 82% versus 42% ($p < 0.001$) (Table 3).

Assessment of IL22 rs2227485, rs1182844, and rs1179246 SNPs as risk factors for UC using logistic regression analysis revealed that subject carrying one T, A and C alleles of the respective SNPs had 2.006, 2.676 and 4.416 folds increased risk for development of UC compared to the C, T and A alleles carriers respectively (OR=2.006, 95% C.I=1.044 - 3.854 for rs2227485 & OR=2.676, 95% C.I=1.394 - 5.135 for rs1182844 and OR=4.416, 95% C.I=2.372 - 8.221 for rs1179246) (Table 3).

Table 3 Comparison between the studied groups according to genotypes.

	UC PAT (n = 50)	Control (n = 50)	p	OR	95% C.I
rs 2227485					
CC®	21(42%)	31(62%)	0.045*	1	-
CT	26(52%)	19(38%)	0.159	2.02	0.898 - 4.543
TT	3(6%)	0(0%)	0.242	10.256	0.504 - 208.8
CC®	21(42%)	31(62%)		1	-
CT + TT	29(58%)	19(38%)	0.045*	2.253	1.011 - 5.019
Allele frequency					
C®	68(68%)	81(81%)		1	-
T	32(32%)	19(19%)	0.035*	2.006	1.044 - 3.854
rs 1182844					
TT®	17(34%)	32(64%)	0.003*	1	-
TA	29(58%)	18(36%)	0.028*	3.033	1.32 - 6.97
AA	4(8%)	0(0%)	0.117	16.714	0.849 - 328.7
TT®	17(34%)	32(64%)		1	-
TA + AA	33(66%)	18(36%)	0.003*	3.451	1.517 - 7.852
Allele frequency					
T®	63(63%)	82(82%)		1	-
A	37(37%)	18(18%)	0.003*	2.676	1.394 - 5.135
rs 1179246					
AA®	9(18%)	29(58%)	<0.001*	1	-
AC	28(56%)	21(42%)	0.161	4.296	1.682 - 10.974
CC	13(26%)	0(0%)	<0.001*	83.842	4.541 - 1548.1
AA®	9(18%)	29(58%)		1	-
AC + CC	41(82%)	21(42%)	<0.001*	6.291	2.521 - 15.696
Allele frequency					
A®	46(46%)	79(79%)		1	-
C	54(54%)	21(21%)	<0.001*	4.416	2.372 - 8.221

p: p value for Chi square test for comparing between the two groups;
*: Statistically significant at $p \leq 0.05$; OR: Odds Ratio; C.I: Confidence interval.

Table 4 Relation between rs 2227485 with severity, family history and calprotectin in UC PAT.

	rs 2227485			Test of sig.	P
	CC (n = 21)	CT (n = 26)	TT (n = 3)		
Severity					
Mild	10(47.6%)	10(38.5%)	1(33.3%)	$\chi^2 = 3.389$	0.533
Moderate	6(28.6%)	13(50.0%)	2(66.7%)		
Severe	5(23.8%)	3(11.5%)	0(0.0%)		
Family history					
No	17(81.0%)	24(92.3%)	2(66.7%)	$\chi^2 = 2.749$	0.244
Yes	4(19.0%)	2(7.7%)	1(33.3%)		
Calprotectin					
Mean \pm SD.	677.8 \pm 470.5	542.6 \pm 362.7	558.0 \pm 231.6	H= 0.544	0.762
Median (Min. - Max.)	391 (242-1600)	380.5 (164-1345)	638 (297-739)		

χ^2 : Chi square test, H: H for Kruskal Wallis test, p: p value for comparing between the studied groups.

1.2. Association between IL22 rs2227485, rs1182844, and rs1179246 genotypes and clinical features

No significant association was observed between IL22 rs2227485, rs1182844, and rs1179246 SNPs genotypes or alleles with severity ($p = 0.533$, $p = 0.356$ and $p = 1.00$ respectively), family history ($p = 0.244$, $p = 1.00$ and $p = 0.744$ respectively) or fecal calprotectin ($p = 0.762$, $p = 0.574$ and $p = 0.914$ respectively) in UC patients. On the other hand, initial PB blast count was significantly associated with GG genotype with a median count of 10% in AA, 66% in AG and 86% in GG genotype ($p < 0.001$). Both initial and post induction BM

Table 5 Relation between rs 1182844 with Severity, Family history and Calprotectin in UC PAT.

	rs 1182844			Test of sig.	p
	TT (n = 17)	TA (n = 29)	AA (n = 4)		
Severity					
Mild	8(47.1%)	12(41.4%)	1(25.0%)	$\chi^2 = 4.108$	0.365
Moderate	8(47.1%)	12(41.4%)	1(25.0%)		
Severe	1(5.9%)	5(17.2%)	2(50.0%)		
Family history					
No	15(88.2%)	24(82.8%)	4(100.0%)	$\chi^2 = 0.527$	1
Yes	2(11.8%)	5(17.2%)	0(0.0%)		
Calprotectin					
Mean \pm SD.	604.2 \pm 427.1	584.3 \pm 414.7	699.3 \pm 295.5	H = 1.110	0.574
Median (Min.-Max.)	500 (164-1345)	361 (166-1600)	752.5 (306-986)		

χ^2 : Chi square test; H: H for Kruskal Wallis test; p: p value for comparing between the studied groups.

Table 6 Relation between rs 1179246 with Severity, Family history and Calprotectin in UC PAT.

	rs 1179246			Test of sig.	p
	AA (n = 9)	AC (n = 28)	CC (n = 13)		
Severity					
Mild	4(44.4%)	11(39.3%)	6(46.2%)	$\chi^2 = 0.543$	1
Moderate	4(44.4%)	12(42.9%)	5(38.5%)		
Severe	1(11.1%)	5(17.9%)	2(15.4%)		
Family history					
No	7(77.8%)	24(85.7%)	12(92.3%)	$\chi^2 = 1.064$	0.744
Yes	2(22.2%)	4(14.3%)	1(7.7%)		
Calprotectin					
Mean \pm SD.	584.7 \pm 418.4	603.0 \pm 396.2	605.3 \pm 447.2	H= 0.179	0.914
Median (Min. - Max.)	332 (224-1345)	450 (164-1600)	361 (190-1352)		

χ^2 : Chi square test; H: H for Kruskal Wallis test; p: p value for comparing between the studied groups.

blast count were significantly higher in ALL patients with G allele as the median count of initial BM blast count was 45%, 75% and 95% in AA, AG and GG genotypes respectively ($p < 0.001$) while on day 28, the median of BM blast count was 2% in AA, 5% in AG versus 28.5% in GG genotype ($p = 0.001$) (Table 3).

The relation between rs 2227485 with severity, family history and calprotectin in UC PAT was showed in table 4, there was no significant difference (Table 4). The relation between rs 1182844 with severity, family history and calprotectin in UC PAT was showed in table 5, there was no significant difference (Table 5). The relation between rs 1179246 with severity, family history and calprotectin in UC PAT in UC PAT was showed in table 6, there was no significant difference (Table 6).

DISCUSSION

In the present study, there was an association between 3 polymorphisms of the IL-22 gene (rs2227485, rs1182844, rs1179246) and the development of UC in Egyptian patients. Recently, many studies have identified the association of many SNPs with UC. A study in china investigates the expression of interleukin IL-22, IL-22R1, IL-23, and STAT3 in ulcerative colitis (UC) and UC-related carcinogenesis (UC-CRC) tissues from human and mouse. The results showed that IL-22 and related proteins were closely related to the severity of colitis, and the expression level of IL-22 and related proteins was higher in dysplasia tissues. IL-22/ STAT3 signaling pathway was related to UC and UC CRC^[17].

In a case-control study of Sivaram G et al which was performed

on 139 and 176 patients with UC and controls, found that polymorphisms in CD14 -159 C/T and TLR4 -299 A/G significantly affected mCD14 and mTLR4 expression levels and also increased susceptibility to UC^[18]. There was a case-control study that provided an evidence for an association of IL-22 -429 C/T gene polymorphisms with UC risk, this study comprised of 180 patients with UC and 180 age and gender-matched controls, genotypes of 3 common polymorphisms of the IL-22 gene were determined by fluorogenic 5' exonuclease assays (TaqMan)^[19].

On the other hand, a Mexican study included a total of 199 Mexican patients with confirmed UC and 697 healthy controls, studying IL-22 polymorphisms (rs2227485, rs2272478, rs2227491) in UC but there was no statistical significance in the gene and genotype frequencies of three SNPs of IL-22 (rs2227485, rs2272478, rs2227491) between the UC patients and healthy controls and no association was found between those IL-22 SNPs and clinical features of UC^[20].

IL-22 expression was studied on several human inflammatory conditions and autoimmune diseases and showed its involvement in these diseases. A study included 631 HCV patients found that IL-22 polymorphisms were involved in the progression of persistent hepatitis C virus infection^[21].

Polymorphism of IL-22 receptor alpha 1 was associated with the development of childhood IgA nephropathy which was suggested in a case-control study in 194 patients and 287 normal controls ($p = 0.002$)^[22]. In patients suffering from severe chronic rhinosinusitis, A case-control study was done on 206 cases and 196 controls suggested that Polymorphisms in the IL-22 receptor alpha-1 gene were associated with them ($p = 0.0014$)^[23]. As regards allergic asthma, there was a study which included allergic asthma patients ($n = 18$), controlled asthma patients ($n = 17$) and healthy controls ($n = 12$) found that IL-22 might be involved in the pathogenesis of allergic asthma in human and its level might have some relationship with the severity of the disease ($p < 0.05$)^[23]. A study in 18 cases and 21 controls suggested that increased expression of IL-22 was associated with disease activity in Behcet's disease^[25].

CONCLUSION

In conclusion, this study provides an association of 3 polymorphisms of the IL-22 gene (rs2227485, rs1182844, rs1179246) and the development of UC in Egyptian patients. The validation of our results require additional well-designed large studies.

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