ORIGINAL ARTICLE

Correlation between Interleukin-22 (IL- 22) Genetic Polymorphism and Inflammatory Bowel Disease

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ABSTRACT

Background: *Inflammatory bowel disease belongs to digestive system chronic inflammatory disorders of unknown etiology. This disease is represented with two considerable conditions ulcerative colitis and Crohn's disease. Novel studies illustrated that interleukine-22 has prominent effect on inflammatory processes during the disease.* ***Objective:*** *This research aimed to detect the correlation of IL-22 gene polymorphism (rs2227485) with inflammatory bowel disease.* ***Methodology:*** *A Case-control study was conducted at Internal Medicine and Gastroenterology Outpatient Clinics and patients admitted to Gastroenterology Inpatient Ward, Ain Shams University Hospital. Genomic DNA was extracted and amplified using TaqMan Genotyping master mix and ready-made TaqMan SNP Genotyping assay.* ***Results:*** *Patients groups were presented in two groups (30 patients diagnosed as UC and 30 patients with CD) and 30 control subjects. Correlation between genotype & allele frequency among the study groups showed no statistically significant differences between the three groups (P = 0.925). C allele and T allele had been detected in almost all patients and controls with CT genotype predominance. There was a statistically significant differences between both genotypes with Clinical Score (Mayo) in UC, while there was a non-statistically significant differences between both genotypes with Clinical Score (CDAI) in CD.* ***Conclusion:*** *There is no statistically significant correlation between IL-22 gene polymorphism (rs2227485) and the susceptibility to inflammatory bowel disease. More researches are demanded to detect the actual role of IL-22 polymorphism in inflammatory bowel disease.*

INTRODUCTION

Inflammatory Bowel Disease (IBD) is detected in subjects characterized with a genetic susceptibility and defects of the immune system, mostly in presence of special environmental factors[1]. They are known by disease activity and remission. The site and extent of the inflammation can affect the attitude and severity of the disease[2]. Ulcerative colitis (UC) and Crohn's disease (CD) can appear in both of sex through all ages. Lifestyles in western countries are major cause of increasing the incidence of IBD over years[3].

It is also observed that there are differences in environmental factors and genetic susceptibility between eastern and western populations[4]. Nonetheless, all over the world, the financial burden of IBD in hospitals goes on to elevate, referring to the requirement to fight coming burdens. According to the higher ages and the predominance of multiple chronic diseases, the degree of severity in CD or UC may be more aggressive[3,5].

Ulcerative colitis (UC) is the most popular type of inflammatory bowel disease that might presented with unique ulcers, or open sores[6]. The incidence of ulcerative colitis reached 1 to 20 cases per 100,000 individuals per year, and a prevalence of 8 to 246 per 100,000 individuals [7]. In Egypt, the occurrence of IBD jumped in the last decade, as the common age of incidence was in the late twenties, a tiny increase occurs at 55-70 years, moreover any age can be affected[8].

The pathogenesis of UC has not been completely understood, although it is known that genetic and environmental factors share in an obvious immune response to enteric flora[9,10]. Several studies demonstrated that genetic, immunological, environmental and microbiological factors may act together leading to the occurrence of IBD[11]. Many single-nucleotide polymorphisms associated with UC have been detected with genome-wide association studies[12,13].

T- and NK-cells are considered main cells for synthesis of IL-22, and it is known to mediate the

talking language between inflammatory cells and keratinocytes[14,15]. The expression of IL-22 detected with immunohistochemical analysis in tissues with mild-moderate and severe IBD showed significantly higher values than those with inactive IBD and normal colon tissue, which confirmed that the severity of UC was related to IL-22[16]. So, IL-22 can be considered as a marker to determine the severity of IBD. Several studies have been identified many SNPs in the IL-22 gene. Whether the fact of influence of IL-22 genetic polymorphisms on UC risk is still unknown[17,18].

This study aims to correlate genetic polymorphism of interleukin-22 **(rs2227485)** with IBD in Egyptian patients and assessment will be within the confines of Faculty of Medicine   Ain Shams University Hospital.

METHODOLOGY

Sixty patients were enrolled from Internal Medicine and Gastroenterology Outpatient Clinics, and Gastroenterology Inpatient Ward, Ain Shams University Hospital. Thirty apparently normal healthy controls were enrolled from subjects attend to blood bank at Ain Shams university Hospital for blood donation.

Three milliliters (3mL) of blood were withdrawn into a sterile K3 EDTA vacutainer and were preserved at -70 °C to be used for detection of Interleukin-22 gene polymorphism.

Genomic DNA purification:

Genomic DNA was extracted using the Gene JET whole blood genomic DNA purification mini kit (ThermoFisher Scientifc Inc, Bleiswijk, Netherlands), according to the manufacturer's instructions.

Interleukin-22 genotyping (rs2227485)

The extracted DNA was amplified using TaqMan Genotyping master mix and ready-made TaqMan SNP Genotyping assay (SNP ID: **rs2227485,** assay ID C_15955719_20; ThermoFisher Scientifc Inc, Bleiswijk, Netherlands). Thermal cycling was performed in a Rotorgene Q real-time PCR system (Qiagen, Germany) under the following conditions: Initial activation at 95°C for 10 min followed by denaturation 40 cycles of 95°C for 15 sec, annealing/extension at 60°C for 60 sec, and finally 60°C for 7 min.

Ethical approval:

The current study was approved by the Ethical Committee of College of Medicine, Ain Shams University in Cairo (IRB: FWA000017585)

RESULTS

Sixty patients were enrolled from Internal Medicine and Gastroenterology Outpatient Clinics, and Gastroenterology Inpatient Ward, Ain Shams University Hospital. Patients were divided to two groups (30 with ulcerative colitis, 30 with Crohn's diseases). Thirty apparently normal healthy controls were enrolled for the study. Males represent only 45.6% while females represent 54.4 % with mean age 27.68± 8.56 ranged from 16 to 54 years. **(Table 1)**

Table 1: Correlation between demographic data and study groups

(N= 90)		Mean± SD			Range	
Age		27.68 ± 8.56			(16 - 54)	
		Diagnosis			Test of significance	
		Controls	UC	CD		
		Mean ± SD N (%)	Mean ± SD N (%)	Mean ± SD N (%)	p-Value	Sig.
Age		27.17 ± 7.65	28.87 ± 9.54	27 ± 8.54	0.651*	NS
Weight		68.7 ± 14.37	67.03 ± 14.52	67 ± 14.6	0.874*	NS
Height		165.37 ± 8.61	164.87 ± 9.25	168 ± 10.07	0.380*	NS
BMI		25.01 ± 4.24	24.42 ± 3.54	23.63 ± 4.23	0.416*	NS
Gender	Male	14 (46.67%)	10 (33.33%)	17 (56.67%)	0.191**	NS
	Female	16 (53.33%)	20 (66.67%)	13 (43.33%)		
Smoking state	No	22 (73.33%)	23 (76.67%)	23 (76.67%)	0.942**	NS
	Yes	8 (26.67%)	7 (23.33%)	7 (23.33%)		

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant. *One Way ANOVA test, **Chi-Square test.

Correlation between demographic data of the research groups including (age, weight, height, Body mass index, gender and smoking status) was done showing non statistically significant difference between three groups. **(Table 1)**

Correlation of clinical history, signs and symptoms within cases groups showed non statistically significant difference regarding onset of symptoms, disease duration, and presence of extraintestinal manifestation, abdominal masses and perianal abscesses. There was a statistically significant differences between Crohn's and ulcerative colitis diseases regarding total number of diarrhea/ day (P value = 0.001) and number of bloody motions / days (p< 0.001*) as some of these symptoms are characterized for one disease more than another. **(Table 2)**.

Table 2: Correlation between clinical history and signs & symptoms within cases group

		Diagnosis		Test of significance	
		UC	CD		
		Median (IQR) N (%)	Median (IQR) N (%)	p-Value	Sig.
Onset of symptoms		3.5 (2.5 - 5)	4 (2 - 5)	0.958*	NS
Disease duration		2.75 (2 - 4)	3 (1 - 4)	0.758*	NS
Total no. of diarrhea / day		**5 (4 - 6)**	**3 (1 - 4)**	**0.001***	**S**
No. of bloody motions / day		**2 (0 - 3)**	**0 (0 - 0)**	**<0.001***	**S**
EIM	No	15 (50%)	20 (66.67%)	0.19**	NS
	Yes	15 (50%)	10 (33.33%)		
EIM	Non	15 (50%)	20 (66.67%)	0.019^	S
	Vasculitis	2 (6.67%)	0 (0%)		
	Peripheral arthritis	5 (16.67%)	2 (6.67%)		
	Oral ulcer	2 (6.67%)	4 (13.33%)		
	Axil arthritis	5 (16.67%)	0 (0%)		
	EN	0 (0%)	1 (3.33%)		
	PSC	1 (3.33%)	0 (0%)		
	Psoriasis	0 (0%)	3 (10%)		
Abdominal mass	No	30 (100%)	25 (83.33%)	0.052^	NS
	Yes	0 (0%)	5 (16.67%)		
Perianal disease	No	30 (100%)	26 (86.67%)	0.112^	NS
	Yes	0 (0%)	4 (13.33%)		

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant.
*Mann-Whitney test, **Chi-Square test, ^Fisher's Exact test.

There was a statistically significant differences between the clinical activity status of the patients in both diseases (mild, moderate, severe and remission) (P = 0.003). Moderate cases were more in CD 17 cases (56.67%) while severe cases were high in UC 9 cases (30%). Moreover, remission of the disease was observed more in CD 7 (23.33%). **(Table 3)**

Table 3: Relation between clinical activity status and diagnosis within cases group.

		Diagnosis		Fisher's Exact test	
		UC	CD		
		N (%)	N (%)	p-Value	Sig.
Clinical activity status	Mild	8 (26.67%)	6 (20%)	0.003	S
	Moderate	10 (33.33%)	17 (56.67%)		
	Severe	9 (30%)	0 (0%)		
	Remission	3 (10%)	7 (23.33%)		

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant.

Correlation between genotype and allele frequency among the study groups showed no statistically significant differences between the three groups (P = 0.925). **(Table 4)**

C allele and T allele were detected in almost all patients and controls with CT genotype predominance. **(Table 4 &5)**

Table 4: Correlation between genotype & allele frequency among the study groups.

		Diagnosis			Fisher's Exact test	
		Controls	UC	CD		
		N (%)	N (%)	N (%)	p-Value	Sig.
C allele	No	5 (16.67%)	3 (10%)	4 (13.33%)	0.925	NS
	Yes	25 (83.33%)	27 (90%)	26 (86.67%)		
T allele	No	0 (0%)	0 (0%)	0 (0%)		
	Yes	30 (100%)	30 (100%)	30 (100%)		
Genotype	CT	25 (83.33%)	27 (90%)	26 (86.67%)	0.925	NS
	TT	5 (16.67%)	3 (10%)	4 (13.33%)		

Table 5: Correlation between genotype & allele frequency among the cases groups.

		Diagnosis		Fisher's Exact test	
		UC	CD		
		N (%)	N (%)	p-Value	Sig.
C allele	No	3 (10%)	4 (13.33%)	1.00	NS
	Yes	27 (90%)	26 (86.67%)		
T allele	No	0 (0%)	0 (0%)		
	Yes	30 (100%)	30 (100%)		
Genotype	CT	27 (90%)	26 (86.67%)	1.00	NS
	TT	3 (10%)	4 (13.33%)		

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant.

Statistically significant difference was detected among the two genotypes regarding the clinical activity status of the diseases. **(Table 6)**

Table 6: Correlation between clinical activity status and genotype within cases group.

		Genotype		Fisher's Exact test	
		CT	TT		
		N (%)	N (%)	p-Value	Sig.
Clinical activity status	Mild	13 (24.53%)	1 (14.29%)	0.054	NS
	Moderate	26 (49.06%)	1 (14.29%)		
	Severe	6 (11.32%)	3 (42.86%)		
	Remission	8 (15.09%)	2 (28.57%)		

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant.

Regarding Correlation between clinical severity scores and genotype within cases group. There was a statistically significant difference between both genotypes with Clinical Score (Mayo) in UC, while there was a non-statistically significant differences between both genotypes with Clinical Score (CDAI) in CD **(Table 7)**

Table 7: Correlation between clinical severity scores and genotype within cases group.

	Genotype		Mann-Whitney test	
	CT	TT		
	Median (IQR)	Median (IQR)	p-Value	Sig.
Clinical Score (Mayo) in UC	5 (4 - 6)	7 (7 - 8)	0.039	S
Clinical Score (CDAI) in CD	267.5 (168 - 341)	103.5 (49.5 - 285)	0.272	NS

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant.

Correlation between response and failure of treatment with genotype within cases group showed no statistically significant difference between both genotypes in cases groups as the predominant one is CT genotype. **(Table 8)**

Table 8: Correlation between response and genotype within cases group.

		Genotype		Fisher's Exact test	
		CT	TT		
		N (%)	N (%)	p-Value	Sig.
Response	Respond	34 (64.15%)	5 (71.43%)	0.558	NS
	1ry failure	4 (7.55%)	1 (14.29%)		
	2ry failure	15 (28.3%)	1 (14.29%)		

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant.

There was a statistically significant difference between both genotypes in disease behavior in CD (P value = 0.001) as responder to conventional therapy represent 11 (42.3%) of all cases with CT genotype. **(Table 9)**

Table 9: Relation between Disease behavior and genotype within cases groups.

UC group		Genotype		Fisher's Exact test	
		CT	TT		
		N (%)	N (%)	p-Value	Sig.
Disease behaviour	Non	4 (14.8%)	0 (0%)	1.00	NS
	Steroid dependant	23 (85.2%)	3 (100%)		

CD group		Genotype		Fisher's Exact test	
		CT	TT		
		N (%)	N (%)	p-Value	Sig.
Disease behaviour	Responder to conventional therapy	11 (42.3%)	0 (0%)	0.001	S
	Steroid dependant	1 (3.8%)	0 (0%)		
	Penetrating	0 (0%)	3 (75%)		
	Stricturing	1 (3.8%)	0 (0%)		
	Penetrating / Stricturing	7 (26.9%)	0 (0%)		
	Fistulizing	6 (23.1%)	1 (25%)		

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant.

DISCUSSION

Demographic and clinical data of study participants were illustrated in (Table 1&2). There were no significant differences between the UC & Crohn's disease cases and controls in age, sex, body mass index (BMI), smoking status and family history of inflammatory bowel disease (IBD). This finding was in consistence with Chi et al., [19] who illustrate that no significant differences were detected between the UC cases and controls in demographic characteristics.

Regarding clinical characteristics between case groups, it was observed that there were statistically significant differences between cases regarding total number of diarrhea motions, bloody diarrhea and presence of extraintestinal manifestation. This came in contrast to Yamamoto-Furusho et al.[20] who found that extraintestinal manifestation appeared only in 32.6% of UC patients (50% in our study). While Vavricka et al.[21] illustrated that 43% of patients with CD showed EIMs, and can affect multiple body systems (33.3% in our study).

In the present study, there were predominance of CT genotype among all studied groups with no statistically significant differences between them. Moravej A et al. [22] studied the frequencies of allele and genotypes in patients and control group for IL-22 gene polymorphism (rs2227503). They illustrated that the frequency of G allele was increased and A allele was decreased in patients compared with control group, but the difference was not statistically significant.

Chi et al.[19] reported that IL-22 −429 TT genotype and −429 T allele in patients with UC showed a significantly higher frequency than controls. While by clinical type, site and disease severity of UC, no significant differences were found in any groups.

Yamamoto-Furusho et al.[20] found that 3 polymorphisms of the IL-22 gene (rs2227485, rs2272478, rs2227491) showed no association with the frequency of UC in Mexican patients. The frequency of allele C in the rs2227485 SNP was found in 46% of the control group and 50% of the UC patients.

In Crohn's disease, Yoganathan et al.[23] discovered that having the predominant allele of the single

nucleotide polymorphisms (SNPs) rs10733113, rs4353135, and rs55646866 is related to a greater likelihood for CD. Matthews et al.[24] figured out that rs6651252 establishes a WRE and that the disease-associated allele potentiates stimulate activity through higher affinity binding of TCF7L2.

There was no statistically significant difference among the two genotypes regarding the clinical activity status of both of the diseases. While Yoganathan et al.[23] pointed to the presence of the main allele (G) of rs10733113 in CD patients was related to lesser operations and a lower maximal CDAI, and a similar issues was noticed for rs55646866 and rs4353135. The presence of the main allele for all three SNPs was found to be inversely associated with maximal CDAI. In UC patients, homozygous genotype for the main allele (CC) for rs55646866 was related to an older age at disease diagnosis and a higher MTWAI index. A larger number of ambulatory visits and longer hospital stays were related to homozygous genotype for the main allele of all three polymorphisms.

Many SNPs have been linked to UC in numerous studies. A study of 139 UC patients and 176 controls discovered that polymorphisms in CD14 159 C/T and TLR4 299 A/G significantly influenced mCD14 and mTLR4 expression levels in addition to increasing the liability to UC [25].

Another study including 198 Mexican Mestizo patients diagnosed as UC and 698 matched healthy controls concluded that the GG genotypes of the IL-20 polymorphisms (rs2981573 and rs2232360) might have a pivotal role in the occurrence of UC in the Mexica (as p-Value= 0.017) [26].

Some limitations affected with our results. First, the patients' numbers included of the research were little, and were not enough to clarify the correlations between the IL-22 gene polymorphisms and IBD. Secondly, the participants in our research are only from Ain shams university hospitals. It would be of great value to perform similar studies in different populations for comparison.

CONCLUSION

In the present study, Correlation between genotype and allele frequency among the study groups illustrated no statistically significant differences between the three groups (P = 0.925). C allele and T allele were detected in almost all patients and controls with CT genotype predominance.

The absence of correlation of IL-22 SNPs and IBD does not exclude the potential role of other SNPs of IL-22 in other autoimmune diseases as in IBD, as IL-22 act as a cytokine with both pro-inflammatory and anti-inflammatory effects, depending on the type of tissue target.

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