

Association of Interleukin-10 gene promoter polymorphisms in Saudi patients with Vitiligo

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Abstract. The promoter region of human Interleukin -10 gene is highly polymorphic and has been associated with numerous autoimmune diseases. Recent studies have linked vitiligo with defective autoimmune system. This study is aimed to explore a possible association between IL-10 gene polymorphism and vitiligo in Saudi population. This case control study consisted of 184 Saudi subjects including 83 vitiligo patients (40 males, 43 females mean age 27.85 ± 12.43 years) and 101 matched controls. Genomic DNA was extracted from the blood samples of healthy controls and Vitiligo patients visiting out patient clinic of Department of Dermatology, Riyadh Armed Forces Hospital, using QIA amp^R DNA mini kit (Qiagen CA, USA). Interleukin-10 gene was amplified by polymerase chain reaction (PCR) using Arms primers to detect any polymorphism involved at positions -592, -819 and -1082.

The frequencies of GG genotype at -1082, and CC genotype at positions -592 and 819 were significantly higher in vitiligo patients compared to healthy subjects suggesting that GG and CC genotypes might be susceptible to vitiligo in Saudis. On the other hand genotypes -1082 GA, -819 CT, and -592 CA of IL-10 were more prevalent in healthy controls suggesting protective effects of GA, CT and CA genotypes against vitiligo. This study indicates that the IL-10 gene may play a significant role in the etiology of vitiligo among Saudis.

Keywords: Interleukin-10, polymorphism, vitiligo, Saudis

1. Introduction

Vitiligo is a puzzling disorder characterized by the appearance of white patches resulting from the loss of functional melanocytes and melanin from the skin. This common disorder involves 1–4% of the world population. Several theories concerning the etiopathology of vitiligo have been suggested including autoimmunity, inherent defects in melanocyte biochemistry and neuronal dysfunction [23]. In fact, familial aggregation of vitiligo is quite common with up to 20% of vitiligo patients having at least one first degree relative affected with the disease, clearly indicating genetic basis of

vitiligo susceptibility [1,47]. It has been proposed that genes at different loci may contribute to the pathogenesis of vitiligo [1,15,38,43,49,56].

Recently, significant changes in cytokines levels were reported in vitiligo affected skin compared with pre-lesional, non-lesional and healthy skin suggesting that the cytokine production in epidermal microenvironment may play a role in pathogenesis of vitiligo [2, 58]. Individual differences in the inheritance of polymorphic gene lead to variation in their immune responses [3,24] clearly indicating that cytokine gene polymorphism may reflect or control severity and progression of various diseases [25]. Several studies have addressed the role of peripheral blood and lesional cytokine expression in patients with vitiligo [58,63]. These authors suggested a role for epidermal cytokine imbalance in the pathogenesis of vitiligo.

Interleukin-10 (IL-10) is a cytokine functionally characterized by anti-inflammatory effects [39]. IL-

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IL-10 is produced by a wide variety of cell types, including Th-cells, monocytes, macrophages, mast cells, eosinophils and keratinocytes [33]. This cytokine is a global suppressor of immune responses as well as an immunoregulator of the Th-cell response [34]. Moreover, a direct ability of IL-10 to down-regulate TNF α , IL-1, IL-8 and interferon- γ , production makes it one of the most important immunoregulators as well as a mediator of inflammatory process [44,50,51]. IL-10 is also a potent up-regulator of B-cell production and differentiation [18,59].

IL-10 gene maps to the junction of 1q31–q32 [27] and exhibits substantial polymorphism in the promoter region which appears to correlate with variations in transcription [14,61]. Various single nucleotide polymorphisms (SNPs) have also been identified in the promoter region of IL-10 gene, three of which (–1082G/A, –819C/T, –592C/A) have been found to be associated with a number of diseases [7,9,17,20,30,35,36,42,54,55,57,64]. Recently Grimes et al. [45] suggested that IL-10, IFN- γ and TNF- α may play a role in the pathogenesis of vitiligo and a statistically significant increase in the expression of these cytokines was observed in the lesional and perilesional skin of vitiligo patients as compared to controls.

Therefore, in this study it was aimed to investigate the association between genotype and allele frequencies of IL-10 gene especially in promoter region at –1082, –819 and –592 loci and vitiligo in Saudi patients.

2. Results

Eighty three Saudi vitiligo patients (40 male, 43 female, aged 6 to 79, mean age 27.85 ± 12.43 years) and 101 healthy matched controls (71 males and 30 females) from same population were genotyped for three polymorphisms of IL-10 gene. Results of analysis of single nucleotide polymorphism (SNP) for IL-10 G(–1082)A, IL-10 C(–592)A, IL-10 C(–819)T, and corresponding genotypes using ARMS-PCR method are summarized in Tables 1–3.

The frequency of –1082GG genotype was found to be significantly higher ($P = 0.05$) in vitiligo patients (18.07%) as compared to controls subjects (8.91%). On the contrary, the frequency of heterozygous genotype GA was significantly lower ($P = 0.04$) in patients (60.24%) as compared to control subjects (73.26%). No significant difference in the frequency of homozygous AA genotype was observed in patients (21.68%)

and controls (17.82%). Genotype –1082GG seems to be susceptible to vitiligo (RR = 2.25, EF = 0.34) while genotype GA is resistant to vitiligo (RR = 0.55, PF = 0.24, Table 1).

The frequency of –819 CC genotype was significantly higher ($P = 0.02$) in the vitiligo patients (56.62%) compared to controls (39.60%) while CT showed a reverse pattern with lower frequency (31.32%) in vitiligo patients as compared to 50.49% in controls ($P = 0.01$). The homozygous TT genotype was detected in 12.04% of vitiligo and 9.9% of control samples, with insignificant difference ($P = 0.64$). The CT genotype is more common among the healthy controls indicating that the C-819T polymorphism may have a protective effect on the susceptibility to vitiligo (RR = 0.44, PF = 0.29) whereas CC genotype appears to be susceptible to vitiligo (RR = 1.99, EF = 0.99, Table 2).

The frequencies of –592 CC genotype was significantly higher in vitiligo patients as compared to controls (56.62% vs 39.60%, $P = 0.02$) while CA genotype was found to be significantly lower ($P = 0.01$) in vitiligo patients (31.32%) compared to control subjects (50.49%). The homozygous AA genotype was detected in 12.04% of vitiligo and 9.9% of control samples with no significant difference. The higher frequency of CA genotype among the healthy controls indicated that the individuals with –592CA genotype are protected against vitiligo (RR = 0.44, PF = 0.29) while CC genotype at position –592 of IL-10 seems to be susceptible to vitiligo ($P = 0.02$, RR = 1.99, EF = 0.99, Table 3).

3. Discussion

IL-10 is a major immunoregulatory cytokine with diverse immunomodulating effects on the immune system. IL-10 is a potent anti-inflammatory Th2 cytokine that down regulates the expression of major histocompatibility complex (MHC) class I and class II molecules, as well as the production of pro-inflammatory Th1 cytokines [10,18,19,26,50,51,60]. It also has potent stimulatory effects on B lymphocytes resulting in increased production of immunoglobulin and DNA replication [18].

The gene encoding IL-10 has been mapped to chromosome I [29] and the capacity for IL-10 production appears to be genetically encoded. It has been reported that up to 75% of the variation in IL-10 production is genetically controlled [52]. Moreover, the expression of IL-10 is regulated by different mechanisms in different cell types [34]. The three promoter polymor-

Table 1
Genotype and allele frequencies of (–1082G/A) IL-10 variants in Vitiligo and matched controls

Genotype/allele	Vitiligo (N = 83)		Control (N = 101)		p-value	RR	EF**/PF
	NO.	%	NO.	%			
GG	15	18.07	9	8.91	0.05*	2.25	0.34**
GA	50	60.24	74	73.26	0.04*	0.55	0.24
AA	18	21.68	18	17.82	0.57	1.27	0.10**
G-allele	80	48.19	92	45.54	0.67	1.11	0.04**
A-allele	86	51.80	110	54.45	0.67	0.89	0.05

*1-tailed P values.

Table 2
Genotype and allele frequencies of (819C/T) IL-10 variants in Vitiligo and matched controls

Genotype/ allele	Vitiligo (N = 83)		Control (N = 101)		p-value	RR	EF*/PF
	NO.	%	NO.	%			
CC	47	56.62	40	39.60	0.02	1.99	0.99*
CT	26	31.32	51	50.49	0.01	0.44	0.29
TT	10	12.04	10	9.9	0.64	1.24	0.24*
C-allele	120	72.28	131	64.85	0.14	1.41	0.15*
T-allele	46	27.71	71	35.14	0.14	0.70	0.13

Table 3
Genotype and allele frequencies of (–592C/A) IL-10 variants in Vitiligo and matched controls

Genotype/allele	Vitiligo (N = 83)		Control (N = 101)		p-value	RR	EF*/PF
	NO.	%	NO.	%			
CC	47	56.62	40	39.60	0.02	1.99	0.99*
CA	26	31.32	51	50.49	0.01	0.44	0.29
AA	10	12.04	10	9.9	0.64	1.24	0.24*
C-allele	120	72.28	131	64.85	0.14	1.41	0.15*
A-allele	46	27.71	71	35.14	0.14	0.70	0.13

phisms namely –1082A/G, –819C/T, and –592C/A lie in putative transcription binding site [11,12], making them important loci to be studied in relation to various disorders and diseases. These polymorphisms exhibit strong linkage disequilibrium and appear in three potential haplotypes (GCC, ACC and ATA) for three loci (–1082, –819, –592) which have been described in various populations [12,28,41]. IL-10 production is associated with these haplotypes; it has been suggested that GG genotype is associated with high production, AG genotype is an intermediate producer whereas AA genotype as low producer of IL-10 [12].

In our study, the GG genotype of IL-10 (–1082) was more prevalent in vitiligo patient as compared to healthy control (Table 1) suggesting that the polymorphism at position –1082 could be associated with susceptibility to vitiligo. Our finding is in agreement with earlier genetic studies suggesting that many diseases/conditions like septic shock [4,21,48], acute respiratory syndrome [42], chronic hepatitis C [46], non small cell lung cancer [7], Crohn's disease [36] trauma [53] and mortality in acute renal failure [16] are directly associated with –1082 GG and high circulating IL-10.

In present study intermediate IL-10 producer genotype –1082 G/A showed negative association with vitiligo as majority of control subjects have this genotype, suggesting that individuals having 1082 G/A genotype are less likely to get vitiligo. Interestingly, another study showed that intermediate IL-10 producer genotype –1082 AG exerts protective effect against multiple sclerosis while, high IL-10 producer –1082 GG and low producer 1082-AA genotypes had no association with multiple sclerosis [40].

The frequency of IL-10-819CC was significantly higher in our vitiligo patient as compared to healthy controls, whereas the frequency of IL-10 –819 CT, was significantly lower in vitiligo patients. Recently genotype –819 CC has been reported to be a high producer of IL10 whereas CT and TT as intermediate and low producer [37]. These findings further indicated that genotypes associated with high production of IL-10 are more prevalent in vitiligo patients. The genotypes of IL-10-592, being in linkage disequilibrium with the genotypes of IL-10-819 followed the pattern similar to those for frequencies of -819 in vitiligo patients and healthy controls.

Table 4
Showing sets of sense and antisense primers used to amplify the IL-10 promoter region to detect polymorphism

Locus	Generic (antisense) primer	Sense primers
IL-10 (-1082)	5'-CAG TGC CAA CTG AGA ATT TGG-3'	5'-CTA CTA AGG CTT CTT TGG GAG-3' 5'-ACT ACT AAG GCT TCT TTG GGA A-3'
IL-10 (-819/-592)	5'-AGG ATG TGT TCC AGG CTC CT-3'	5'-CCC TTG TAC AGG TGA TGT AAC-3' 5'-ACC CTT GTA CAG GTG ATG TAA T-3'

The genotypes of IL-10 (–1082GG, –819CC, –592CC) known to be associated with high production of IL-10 are more prevalent in our vitiligo patients indicating the possible association with susceptibility of vitiligo which is supported by the recent finding that the vitiligo patients show statistically significant increased expression of IL-10, IFN- γ and TNF α in involved and adjacent uninvolved skin as compared to controls [45].

It is clear from our results and earlier published reports that some genotypes of IL-10 may enhance the vulnerability of some diseases [4,7,21,36,42,46,62], on the other hand others may exert a protective effect against diseases like breast cancer [62], tuberculosis [22] and leprosy [13]. These findings do not support the inflammatory theory of vitiligo according to which dramatic inflammatory changes including cytotoxic T-lymphocyte (CTL) influx were reported in the lesional margin and in the center of newly formed vitiligo lesions [31]. In fact, inflammatory infiltrates from vitiliginous lesions have been found to contain T-cells specific to melanocytes antigen [6]. IL-10, being a potent anti-inflammatory cytokine produced by T-cells and macrophages strongly inhibits antigen specific T-cell proliferation, cytokine production and MHC class 2 expression. Thus, our findings are not in agreement with the hypothesis that high IL-10 may dampen the disease process involving inflammatory mechanism. However, some immune stimulating effects of IL-10 have also been documented where it induces activated B cells to secrete large amounts of IgG, IgA, and IgM and in combination with IL-4 results in the secretion of four immunoglobulin isotypes. Thus high levels of IL-10 may also play a role in the amplification of humoral responses as suggested by Rousset et al. [18] which may cause melanocyte damage and lead to depigmentation.

In conclusion, our results of IL-10 polymorphism in vitiligo suggested that GG genotype at –1082 position together with CC genotypes at positions –592 and –819 of IL-10 are susceptible to the development of vitiligo. The three polymorphisms C592A, C819T and G1082A in IL-10 gene promoter region, which were more prevalent in healthy Saudi subjects, might possibly, exert protective effect against vitiligo. This study

presents first report of possible association between human IL-10 gene and vitiligo susceptibility and/or heritability in Saudi patients. However, further studies are warranted to investigate IL-10 polymorphism in families with vitiligo.

4. Materials and methods

4.1. Patients and controls

A total of 184 subjects visiting Armed Forces Hospital, Riyadh, Saudi Arabia were involved in this study. Eighty three Saudi vitiligo patients (40 male, 43 female) and 101 healthy matched voluntary blood donors from same population were recruited. This study was approved by the research and ethics committee of RMH and a written informed consent was obtained prior to recruitment of subjects.

Genomic DNA was extracted from the blood of Vitiligo patients and controls using QIA amp^R DNA mini kit (Qiagen CA, USA). Interleukin-10 gene was amplified using amplification refractory mutation systems (ARMS)-PCR methodology [8] to detect any polymorphism involved at various loci viz: –592, –819, –1082. The set of primers used to amplify various types of polymorphism are summarized in Table 4.

4.2. PCR amplification

PCR amplification was carried out in Ready to Go PCR Beads (Amersham Biosciences, USA). Reaction consisted of 10 temperature cycles of denaturation for 15 s at 94°C, annealing for 50 s at 65°C and extension for 40 s at 72°C. Then 25 cycles of denaturation for 20 s at 94°C, annealing for 50 s at 59°C, extension for 50 s at 72°C. Final extension was performed at 72°C for 7 m. A positive control was included in the PCR assay by amplification of the human growth hormones (MGH) gene. Electrophoreses of the PCR product was performed in 1.5% agarose gel, stained with ethidium bromide and photographed.

4.3. Statistical analysis

The differences in genotype and allele frequencies between patients and controls were analyzed by the Fisher's exact test. *P* values less than 0.05 were considered significant. The strength of the association of disease with respect to a particular genotype/ allele is expressed by odd ratio interpreted as *relative risk* (RR) following the method of Woolf as outlined by [32]. It is calculated only for those genotypes which are increased or decreased in vitiligo patients as compared to normal Saudis.

Etiologic Fraction (EF): The EF indicates the hypothetical genetic component of the disease. Values >0.00 are of significance. It is calculated for positive association ($RR > 1$) [5].

Preventive Fraction (PF): The PF indicates the hypothetical protective effect of one specific antigen for the disease. It is calculated for negative association ($RR < 1$) [5]. Values <1.0 indicate the protective effect of the genotype against the manifestation of disease.

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