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Association of Interleukin 10 Gene Polymorphism with Psoriasis in Chinese Population

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Abstract

Background: Psoriasis is a chronic, inflammatory, T cell-mediated cutaneous dermatosis. It is found to be associated with an over expression of T helper1 and Th17 cytokines and relative under expression of Th2 and T-regulatory cytokines. Interleukin-10 is an immunosuppressive cytokine produced mainly by Th2 and T regulatory cells. Genetic polymorphism of the IL-10 gene can lead to the imbalance of Th1/Th17 and Th2/T reg cytokines and results in a decrease in the production of anti-inflammatory cytokines like, IL-10. Relative deficiency of IL-10 and T reg cells play a main role in the pathogenesis of psoriasis. We aimed to find out the association of IL-10 gene (rs1800871 and rs1800896) polymorphism and susceptibility to psoriasis in Han Chinese population.

Methods: This study included 44 patients with psoriasis recruited from outpatient and inpatient department of dermatology, Zhongnan Hospital, China. Out of 44 patients, 40 were males and 4 were females. Their age group ranged from 9 to 86 years. Their genotypes were compared with 50 healthy controls of same age group and locality. Psoriasis patients and healthy controls were genotyped for IL-10 gene (rs1800871 and rs1800896) polymorphism by polymerase chain reaction.

Results: The genotypic frequencies of IL-10 rs1800871 in psoriasis patients were found to be GA (40.91%), GG (6.82%), AA (52.27%) and in controls GA (34%), GG (20%), and AA (46%). The frequency of minor allele G was found to be 54.55% in cases and 74% in controls. The genotypic frequencies of rs1800896 were found to be CT (11.36%), TT (88.64%), in psoriasis patients and CT (26%), TT (74%), in controls. The frequencies of minor allele C was found to be 11.36% in psoriasis patients and 26% in controls. The p-value, odds ratio (OR) and 95% CI of genotypes of rs1800871 are as follows, GA (p = 0.8990, OR =1.06 & 95% CI = (0.44-2.52), GG (p = 0.0840, OR = 0.30 and 95% CI = (0.08-1.17) and for the minor allele G (p = 0.1550, OR= 0.64 and 95% CI = (0.34-1.18) which are not statistically significant. The p value, OR & 95% CI of genotypes of rs1800896 are CT (p=0.0720, OR=0.36, 95% CI = 0.12-1.09) and for the

minor allele C (p=0.0890, OR=0.40, 95% CI=0.14-1.15) which are also not statistically significant. Genetic model analysis also showed no significant association. We observed that IL 10 gene (rs1800871 and rs1800896) polymorphism were not associated with risk of psoriasis. (p >0.05).

Conclusion: Our results suggest that IL-10 gene (rs1800871 and rs1800896) polymorphism have no association with risk of psoriasis in the Han Chinese population. The Chinese population is not susceptible to psoriasis associated with IL-10 gene polymorphism.

Keywords: psoriasis, cytokines, IL-10, genetic polymorphism.

1. Introduction

Psoriasis is a common, chronic, T cell-mediated inflammatory cutaneous dermatosis affecting the skin, nails, and joints. Psoriatic lesions are seen particularly over the extensor surfaces and scalp [1]. It can occur at any age group and there is no sexual predilection. But Chang et al, in his study, found out that there is a male predilection with a sex ratio of 1.49:1 in Chinese population [2]. The Prevalence rate of psoriasis is found to be increasing globally [3]. Prevalence rate of psoriasis in adults ranged from 0.51% (USA) to 11.43% (Norway) population worldwide [4]. Prevalence of psoriasis is found to be higher in countries far to the equator and lower in countries near to the equator. Both genetic and environmental factors have a critical role in the etiopathogenesis of psoriasis [5]. Common clinical variants of psoriasis include generalized plaque type, guttate psoriasis, pustular psoriasis, erythrodermic psoriasis, and psoriatic arthritis. Generalized plaque-type psoriasis is the most common type of psoriasis seen in adults, whereas guttate psoriasis is most commonly seen in children. The hyper proliferation and abnormal differentiation of the epidermis are found to be the major pathogenetic mechanisms in psoriasis [6,7]. Psoriatic patients experience increased morbidity and mortality associated with systemic manifestations in multiple organ systems. Classic co-morbidities include psoriatic arthritis, inflammatory bowel disease, psychiatric disorders, uveitis, metabolic syndrome and its components, cardiovascular disease, atherosclerosis, lymphomas, chronic obstructive pulmonary disease, osteoporosis, erectile dysfunction, and hepatobiliary diseases [8-10]. Psoriatic arthritis is the most common inflammatory disease associated with psoriasis [11]. Psoriasis is found to be chronic and persistent over years in most of the patients. In some patients, psoriasis is found to have less stable course and exhibits a great variation in the extent and degree of inflammation. This may be due to various relapse factors like climate change, stress, infection, medications, cigarette smoking, alcohol and other environmental factors [12-14]. The severity of psoriasis varies greatly between patients. The PASI is the most widely used severity assessment method for psoriasis in clinical practice. In a Swedish based population study of assessment of severity of psoriasis in men and women, it has been reported that severity of psoriasis is found to be more common in women.[15]

The exact etiopathogenesis of psoriasis is still not clearly understood. But there is strong evidence supporting that psoriasis has an important immunogenetic component. Psoriasis is found to be seen more common among the first degree relatives and also there is a higher concordance rate among monozygotic twins [16]. Genome-wide association studies have found at least nine chromosomal loci associated with psoriasis (PSORS1-PSORS9). Psoriasis Susceptibility Region 1 (PSORS1) is found to be the main genetic loci associated with psoriasis. PSORS1 lies in the major histocompatibility complex (MHC) on chromosome 6p and it constitutes about 35-50% of the heritability of psoriasis [17-20]. From the

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immunological point of view, psoriasis is found to be associated with an increased expression of Th1 and Th17 cytokines and decreased expression of Th2 and Treg cytokines. Th1, Th17 lymphocytes and their cytokines play a major role in the inflammation of psoriasis. Their activity is regulated by Treg cells. Studies have evidenced that the activity and number of Treg cells is decreased in the sera and skin lesions of psoriatic patients [21-23]. Treg cells are a group of T lymphocytes which maintains immunological homeostasis and regulates the immune response. The number and activity of Treg cells are found to be decreased in psoriasis which can interfere the normal immune responses. So the decreased expression of these Th2 and Treg cells plays a crucial role in the pathogenesis of psoriasis [24-26].

The Th2 cells produce anti-inflammatory cytokines like IL-4 and IL-10. IL-10 is an important immunoregulatory cytokine with anti-inflammatory and immunosuppressive properties. It is produced by many cells. It is synthesized mainly by T cell subsets like Th2 cells, Treg cells and macrophages. It is also produced by B cells, natural killer cells (NK cells), monocytes, and dendritic cells [27,28]. IL-10 binds with IL-10 receptor (IL-10R) which is present on a variety of immune cells. IL-10R has two chains, IL-10R1 and IL-10 R2 [29]. Apart from its immunosuppressive properties, some studies also reported that IL-10 also has immunomodulatory properties which help to eliminate the infectious agents with limited inflammation. IL-10 promotes B cell mediated proliferation, functions and antibody production [30,31]. Recent studies have also reported another subset of IL-10 producing B regulatory cells (Bregs). These Bregs can inhibit Th1 and Th17 differentiation. Psoriasis is characterized by a decrease in the number and function of Bregs [32-34]. The IL-10 cytokine is a homodimer having a molecular weight of 37kDa. Each monomer has a molecular mass of 18.5 kDa [35]. The human IL-10 exhibits 80% homology with murine IL-10. The human IL-10 gene is located on chromosome 1 at 1q31.32. It spans about 4.7 kb and encodes for 5 exons. Its promoter region is highly polymorphic with three frequent point mutations -1082 G/A, -819 C/T and -592 C/A. The promoter region also has two microsatellites, IL.10.G and IL.10.R [30]. These SNP's lies on the regulatory areas in the promoter region of the IL-10 gene which contains various transcription factor binding sites. IL-10 secretion is regulated by various endogenous and exogenous factors like catecholamines, tumor necrosis factor (TNF-α). Stress axis also plays a significant role in the regulation of IL-10 secretion through the release of catecholamines which in turn leads to the production of IL-10. IL-10 exhibits its immunosuppressive effects mainly by inhibiting NF-κ_β [30,36]. It inhibits the secretion of various proinflammatory cytokines such as TNF-α, IFN-γ, IL-2, IL-3, and GM-CSF, thereby inhibiting the inflammatory processes. So, a relative deficiency of IL-10 founds to play a main role in the pathogenesis of psoriasis. Suppressor of cytokine synthesis (SOCS-3) acts as a mediator in the inhibitory functions of IL-10 [29]. IL-10 has been suggested as a potential treatment for several localized and systemic inflammatory diseases, autoimmune diseases and tumors due to its multiple inhibitory actions [37].

Prevalence of psoriasis in China ranged from 0.11% to 0.47%. The prevalence rate in China and world-wide is found to be increasing which makes psoriasis a serious global problem [3]. Studies showing the association of IL-10 gene polymorphism with risk of psoriasis in the Chinese population is scanty. The reported studies showed that there is no association of IL-10 gene polymorphism with psoriasis [38,39]. So, we attempt to conduct a case-control study to find out whether there is any association of IL-10

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single nucleotide polymorphism (SNP) with psoriasis in the Han Chinese population.

2. Materials And Methods

2.1 Cases and controls

This study is a case-control immune genetic study. Our study was conducted in the Department of Dermatology in collaboration with the Department of Biochemistry, Zhongnan Hospital of Wuhan University China. This study was approved by the Ethics Committee of Zhongnan Hospital and conducted according to the declaration of Helsinki Principles. All the study subjects signed the written informed consent before enrolment in the study.

This study included 44 patients with psoriasis recruited from the dermatology department of Zhongnan Hospital. The data of all study subjects were collected from October 2017 to September 2018. We took a detailed history of the study subjects. Psoriasis patients were classified as early onset psoriasis (age <40 years) and late onset psoriasis (age ≥40 years). The clinical profile such as PASI score, ESR, leucocyte count, ASO titre, Family history, age of onset of disease, duration of disease, comorbidities associated with psoriasis, associated skin diseases, smoking and alcoholic history, triggering factors were recorded in a predetermined proforma. The severity of psoriasis was assessed by PASI score. [<10 = mild psoriasis, ≥10 = moderate to severe psoriasis]. All study subjects were chosen from the Han Chinese population having no blood relationship with each other.

The control group comprised of 50 healthy subjects selected from the physical examination centre of Zhongnan Hospital. The control group includes age, sex and ethnicity matched healthy subjects with no family history of psoriasis and no history of any autoimmune diseases, infectious diseases, tumors or skin diseases.

2.2 Genotyping

5 ml of whole peripheral blood were collected in an EDTA coated anticoagulant tube and preserved at 4^0C. Genomic DNA was isolated from whole peripheral blood by Phenol protease method. The content and concentration of DNA were determined by ultraviolet spectrophotometer and kept at -20^0C until used for genotyping. The polymorphism in the IL-10 gene was typed by using PCR technique by Wuhan Optimus Family Innovational Biotechnology. The amplification conditions were 94^0C for 3 min, 94^0C for 30 s, 56^0C for 30 s, 72^0C for 30 s, followed by 35 cycles for 30 s, and 72^0C for 5 min. The amplified PCR products were then subjected to electrophoresis on 2% agarose gel. These products were then analyzed by SNAPshot method which is conducted by Wuhan Zhengke Innovation Biotechnology Ltd. The amplified results were then verified.

2.3 Statistical Analysis

Statistical analysis of the data was done using the Statistical Package of Social Science (SPSS version 10) software. The Hardy-Weinberg equilibrium in cases and controls were tested for significance using the x^2 test. The frequency of genotypes was calculated by direct gene counting method. The difference in the allele and genotype frequencies were compared between cases and controls using the x^2 test. Odds ratio and 95% CI were calculated to test the association of genetic polymorphism with psoriasis. We also performed the genetic model analysis. A p-value of < 0.05 was considered as statistically significant.

3. Results

3.1 Demographic characteristics

The demographic features of the study subjects are shown in Table 1. Out of 44 patients, 40 were males (91%) and 4 were females (9%). Their age group ranged from 9 to 86 years. Their mean age and standard deviations were 47.59

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years and 18.34 respectively. Psoriasis patients were classified into early onset psoriasis (age < 40 years) and late onset psoriasis (age ≥ 40 years). 24 patients (54.55%) had early onset psoriasis and 20 patients (45.45%) had late-onset psoriasis. Their mean age of onset of disease in years and SD is 37.02 and 17.20 respectively. The PASI score which assess the clinical severity of psoriasis ranged from 3.5 to 23.6 with mean and standard deviation of 11.02 and 5.5 respectively. 20 patients (45.45%) had mild psoriasis (PASI < 10), and 24 patients (54.55%) had moderate to severe psoriasis. 3 patients had a family history of psoriasis in their first-degree relatives. Out of total 44 patients recruited 30 patients (68.18%) presented with chronic plaque psoriasis, 7 patients (15.91%) with guttate psoriasis, 3 patients (6.82%) with pustular psoriasis, 2 patients (4.55%) with psoriatic arthritis, 1 patient (2.27%) with erythrodermic psoriasis, 1 patient (2.27%) presented with both plaque and pustular psoriasis. The control group included 50 healthy volunteers with age, sex and ethnicity matched.

3.2 Association of IL-10 (rs1800871) polymorphism with risk of psoriasis. The genotype and allele frequencies of IL-10 (rs1800871) polymorphism in cases and controls are shown in Table 2. The genotype and allele frequencies of both psoriatic patients and control group were concordant with Hardy-Weinberg equilibrium. (p-value >0.05). The genotype frequencies of IL-10 (rs1800871) in psoriasis were found to be GA (40.91%), GG (6.82%), AA (52.27%). In controls GA (34%), GG (20%), and AA (46%). The frequency of minor allele G was 54.55% in patients with psoriasis and 74% in the control group. The p-value, odds ratio (OR) and 95% CI of genotypes of rs1800871 are as follows, GA (p = 0.8990, OR =1.06 & 95% CI = (0.44-2.52), GG (p = 0.0840, OR = 0.30 and 95% CI = (0.08-1.17) and for the minor allele G (p = 0.1550, OR= 0.64 and 95% CI = (0.34-1.18) which are not statistically significant. There was no significant difference between allele and genotype frequencies among patients with psoriasis and control groups. (p-value > 0.05). By the χ^2 test also we found no significant association between the patients with psoriasis and controls. (Table.4) (χ^2 = 3.4291, P value = 0.1800).

3.3 Association of IL-10 (rs1800896) polymorphism with risk of psoriasis.

The genotype and allele frequencies of IL-10 (rs1800896) polymorphism in cases and controls are shown in Table.3. The genotype frequencies of both psoriatic patients and control groups were concordant with Hardy-Weinberg equilibrium. (p -value >0.05). The genotype frequencies of IL-10 (rs1800896) in patients with psoriasis were found to be CT (11.36%), and TT (88.64%). In the control group CT (26%) and TT (74%). The frequency of the minor allele C was found to be 11.36% in cases and 26% in controls. The p value, OR & 95% CI of genotypes of rs1800896 are CT (p=0.0720, OR=0.36, 95% CI = 0.12-1.09) and for the minor allele C (p=0.0890, OR=0.40, 95% CI=0.14-1.15) which are also not statistically significant. No significant difference was observed between genotype and allele frequencies among psoriasis patients and control group (p-value > 0.05). By the χ^2 test also, we found that there is no significant association of IL-10 polymorphism between patients with psoriasis and controls. (Table 4). (χ^2 = 3.2380, P value= 0.0720).

4. Discussion

Psoriasis is an immune-mediated skin disease in which T cells play an important role in its pathogenesis. Interleukin 10 is an important anti-inflammatory cytokine produced mainly by the T cell subsets. IL-10 has a main role in the regulation of immune responses in various diseases including psoriasis. IL-10 gene polymorphism can alter the transcription factor binding sites and influence the production of IL-10 and thereby influencing the

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inflammatory processes. So, IL-10 gene SNP have become a focus of interest in many scientific research studies for a better understanding about its role in many diseases including psoriasis. Several genetic studies have reported a significant association of IL-10 SNP's with susceptibility, and severity for various inflammatory, infectious, autoimmune diseases, and malignancies [40-43] . IL-10 SNP's is also a study of interest in psoriasis. There are a number of studies showing both significant and not significant association of IL-10 SNP's with psoriasis in different populations.

From the above case-control immune genetic study, Han Chinese population were screened for any association of IL-10 gene (rs1800871 and rs1800896) polymorphism with risk of psoriasis. We found that both IL-10 (rs1800871 and rs1800896) polymorphism have no association with risk of psoriasis in the Han Chinese population.

There are several genetic studies that reported the association of IL-10 gene SNP and psoriasis, but they are presented with contradictory results. There are some similar studies reported in the literature in accordance with our results. A study conducted in Taiwan Chinese population also reported that IL-10 (rs1800871) polymorphism have no association with risk of psoriasis [38] . Another study conducted in Polish population by Baran et al also found that rs1800871 polymorphism has no influence with the risk of psoriasis [44] . Kingo et al, in his study among Estonian population also reported that IL -10 polymorphisms are not found to be the risk factor for psoriasis, but they are disease modifiers [45]. A recent study conducted by Adil et al [46] among North Indian population reported that rs1800871 polymorphism did not influence the development of psoriasis, whereas another IL-10 promoter SNP's was associated with risk of psoriasis. But in contrary to our results, Indhumathi et al [47] suggested that rs1800871 polymorphism was a risk factor for psoriasis.

We observed in our study that rs1800896 polymorphism was also not associated with the susceptibility of psoriasis in the Chinese population. Similar to our results, Chang et al [38] also reported that rs1800896 polymorphism has no significant association with risk of psoriasis in Taiwan Chinese population. There are also similar studies which conducted recently among Indians (northern and southern areas) on the same polymorphisms. Among the two studies, Indhumathi et al [47] reported that rs1800896 polymorphism was not a risk factor for psoriasis, whereas another study conducted by Adil et al [46] in north Indian population found out that rs1800896 polymorphism influences the development of psoriasis. A Thailand population-based study conducted by Wongpiyabovan also reported that rs1800896 polymorphism has no association with the risk for psoriasis [48] . Baran et al also reported that there is no link between -1082 G/A (rs1800896) polymorphism with psoriasis in Polish population [44]. Another population-based study conducted by Balding et al also found out that the cytokine gene polymorphism IL-10 (rs1800896) was not associated with risk of development of psoriasis and psoriatic arthritis [49]. Reich et al [50], also conducted a population-based study which showed that IL-10 polymorphism has no influence with the risk of psoriasis. Kingo et al [45] also reported that IL 10 polymorphisms are not risk factors for psoriasis, but they are disease modifiers. In a recent study conducted in Romanian population, reported that the severity of psoriasis is not influenced by rs1800896 polymorphism[51]. Majority of the European population-based study showed that -1082 G/A (rs1800896) polymorphism has no association with risk of psoriasis.

But in contrary to our results, some studies showed that IL-10 (rs1800896) polymorphism is a major risk factor for

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psoriasis. This includes a study conducted by Windermuth et al in Ireland which reported that rs1800896 polymorphism has a significant association with the susceptibility of psoriasis [52]. Lee et al, in his meta-analysis also demonstrated that IL-10 (rs1800896) polymorphism was an important risk factor for psoriasis in Asians [53] . Craven et al, in his study, reported that there is a significant association of rs1800896 polymorphism only with late-onset psoriasis. He found that late-onset psoriasis patients were heterozygous at -1082 position. He found no significant association of the same polymorphism with early-onset psoriasis [54]. There are two Egyptian population-based studies reported in the literature named Karam et al [55] and Settin et al [56]. Both studies showed a link between rs1800896 polymorphism with psoriasis in the Egyptian population.

The above study was an attempt to find out the association of IL 10 gene polymorphisms (rs1800871 and rs1800896) in the Chinese population, which were already reported as a risk factor for psoriasis in some populations. But in the Chinese population, our study observed that rs1800871 and rs1800896 polymorphisms are neither a risk factor nor a protective factor for psoriasis. However, our study results were limited by small sample size and inability to analyze other SNP's and haplotypes in the IL-10 gene. So, we recommend larger and multicentric population-based studies involving more SNP's and haplotype analysis of IL-10 gene to ascertain our findings and to define its role and influence in the pathogenesis of psoriasis in different populations.

5. Conclusion

We concluded that IL-10 polymorphism (rs1800871 and rs1800896) has no association with the susceptibility of psoriasis in the Han Chinese population. Further large population-based studies are necessary to confirm our findings.

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Table 1: Demographic and clinical information of the study subjects.

Characteristics **Demographics**	Cases (n= 44)	Controls (n=50)
Males	40	30
Females	4	20
Male: female	10:1	
Mean age in years +/- SD	47.59 +/- 18.34	
Clinical Mean age of disease onset in years+/- SD	37.02+/- 17.20	
Mean PASI score	11.02+/- 5.5	
Early-onset psoriasis (age of onset < 40 years)	24 (54.55%)	
Late-onset psoriasis (age of onset ≥ 40 years)	20 (45.45%)	
Mild psoriasis (PASI < 10)	20 (45.45%)	
Moderate to severe psoriasis (PASI ≥ 10)	24 (54.55%)	
Family history	3 (6.82%)	
Smoking history	26 (59.09%)	
Alcoholic history	21 (47.73%)	
Chronic plaque psoriasis	30 (68.18%)	
Guttate psoriasis	7 (15.91%)	
Pustular	3 (6.82%)	
Psoriatic arthritis	2 (4.55%)	
Erythrodermic psoriasis	1 (2.27 %)	
Plaque and pustular	1 (2.27%)	

Table 2: Genotype and allele frequencies of IL-10 gene (rs1800871) in psoriasis and healthy controls.

Gene & SNP	Genotype/allele	Psoriasis (n= 44)	Control(n= 50)	OR (95% CI)	p-value
IL-10 (rs1800871)	GA	18 (40.91%)	17 (34%)	1.06 (0.44-2.52)	0.8990
	GG	3 (6.82%)	10 (20%)	0.30 (0.08-1.17)	0.0840

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	AA	23 (52.27%)	23 (46%)	-ref-	
	G	24 (54.55%)	37 (74%)	0.64 (0.34-1.18)	0.1550
	A	64 (145.45%)	63 (126%)	-ref-	

SNP- Single nucleotide polymorphism, OR- Odds ratio, CI- Confidence interval, ref-referent genotype.

Table 3: Genotype and allele frequencies of IL-10 gene (rs1800896) in psoriasis and healthy controls.

Gene & SNP	Genotype/allele	Psoriasis (n=44)	Controls(n=50)	OR (95% CI)	p-value
IL-10rs1800896	CT	5 (11.36%)	13 (26%)	0.36 (0.12-1.09)	0.0720
	CC	0	0		
	TT	39 (88.64%)	37 (74%)	-ref-	
	C	5 (11.36%)	13 (26%)	0.40 (0.14-1.15)	0.0890
	T	83 (188.64%)	87 (174%)	-ref-	

SNP- Single nucleotide polymorphism, OR- Odds ratio, CI- Confidence interval, ref- referent geneotype.

Table.4. Genotypic distributions of IL-10 (rs1800871 and rs1800896) between patients with psoriasis and controls.

Gene & SNP	Genotype/allele	Psoriasis (N= 44)	Control (N=50)	Chi-square	p-value
IL-10 gene (rs1800871)	GA	18 (40.91%)	17 (34%)	3.4291	0.1800
	GG	3 (6.82%)	10 (20%)		
	AA	23 (52.27%)	23 (46%)		
IL-10 gene (rs1800896)	CT	5 (11.36%)	13 (26%)	3.2380	0.0720
	CC	0	0		
	TT	39 (88.64%)	37 (74%)		

SNP-single nucleotide Polymorphism.

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