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Original article

Association of proinflammatory cytokine IL-20 gene polymorphism with psoriasis in north Indian population

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ABSTRACT

Background: IL-20 plays an important role in the inflammatory and hyperproliferative dermatosis of psoriasis.
Aim: The aim of the study was to determine whether the IL-20 gene polymorphism, haplotype and serum level confer pathogenesis of psoriasis.
Subjects and methods: 200 psoriatic patients and 200 controls were genotyped for four IL-20 polymorphic sites by polymerase chain reaction. Serum levels of IL-20 were measured by ELISA.
Results: Our results demonstrated that polymorphism of IL-120 −1380 A/G (adjusted* OR 5.52; (95% CI = 2.43–12.55) was found to be in association with increased risk of psoriasis while as IL-20–1462 G/A (adjusted* OR = 0.11 95; (95% CI = 0.03–0.34) was found to be in association with decreased risk of psoriasis and IL-20–1053 G/T adjusted* OR 1.99; (95% CI = 0.86–4.64), IL-20–3978 T/C(adjusted* OR = 12.87; (95% CI = 0.97–79.54) polymorphism does not show any significant association with the risk of psoriasis. HT4 TG haplotype is associated with decreased risk of psoriasis. Serum IL-20 level significantly increases in patients, as compared to controls with non-significant correlation between serum IL-20 and psoriasis severity.
Conclusion: These findings suggest that IL-20 polymorphism have significant role towards the susceptibility of psoriasis in north Indian population. Evaluating the role of IL-20 cytokine in pathogenesis of psoriasis will prove helpful for the development of psoriasis management.

1. Introduction

Psoriasis is a polygenic cutaneous disorder characterized by hyperproliferation, differentiation of keratinocytes, and influx of immune cells into the epidermis [1,2]. The prevalence of psoriasis has recently been inferred as varying from 0.44 to 2.80% in india [3]. IL-20 belongs to the IL-10 cytokine family, which also includes IL-19, IL-22, IL-24, and IL-26 [2,4]. IL-20 is secreted by immune cells and activated epithelial cells like keratinocytes [5]. The function of IL-20 might therefore mediate a crosstalk between epithelial cells and tissue-infiltrating immune cells under inflammatory conditions [6]. IL 20 binds to the receptor expressed on keratinocytes [7]. The exposure of the cells to IL-20 induces STAT3 activation which appears to be the initiator of the signal in the epidermal keratinocytes, leading to the development of psoriatic lesion [6,8]. There is strong evidence that interleukin-20 (IL-20) has a role in the pathogenesis of cutaneous inflammation and in psoriasis [9,10]. Genes encoding for the IL-10, IL-19, IL-20 and IL 24 are found within a 200 kb region of chromosome 1, and all comprise of IL-10 family cytokine cluster [2,10]. Earlier studies have presented evidence for an association between IL-10 SNPs with susceptibility to a numerous autoimmune, infectious and malignant, diseases [11]. Until now, few studies have confirmed that the IL-20 SNPs contribute to the susceptibility towards psoriasis [12–14]. In the view of the above findings, IL-20 appears to be the candidate gene for psoriasis understanding. The present study was designed to investigate whether the IL-20 polymorphism, haplotype analysis and serum levels may be risk factors for the development of psoriasis in north India. To our knowledge no polymorphism study of IL-20 gene has been reported till now in north Indian population.

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2. Materials and methods

2.1. Subject recruitment

This hospital based case-control study was conducted after approval by the ethical committee. The subjects were included only after they willingly decided to become part of the study, and filled the consent form. This study was conducted over the period of fifteen months starting from September 2014 up to November 2015 and includes 200 clinically diagnosed psoriatic patients. The inclusion of psoriasis patients was based on the proper diagnosis which included PASI calculation. Gender, age (±7 years) and geographically matched healthy subjects were included as controls in the study.

2.2. PASI calculation

Psoriasis Area and Severity Index (PASI) is widely used tool for the measurement of severity of psoriasis. PASI score was calculated as described by Langle et al. [15]. The more value of PASI score represents a greater degree of psoriatic severity [16].

2.3. Blood sampling

Five ml of venous blood was taken after taking consent from each subject and was divided into two portions. 2 ml was taken in sterile EDTA coated vials for Genomic DNA Extraction and the remaining was centrifuged at 4000 rpm for 5 min. Serum separated was stored at −80 °C till analysis.

2.4. Genomic DNA extraction

Genomic DNA was isolated from the blood samples by using Phenol-Chloroform method [17] and the isolated DNA was stored at −20 °C for future use.

2.5. Genotyping of IL-20

Novel tetra-primer ARMS-PCR method was applied for genotyping of polymorphisms of IL-20 as prescribed by Kingo et al., [12] Each PCR reaction was carried out in a total volume of 10 μl containing 100 ng of template DNA, 20 pmol of each inner primer, 20 pmol of each outer primer, optimized concentrations of master mix. To increase the specificity of a PCR reaction we applied touchdown cycles: initial denaturation at 95 °C for 2 min followed by 10 cycles of 1 min denaturation at 95 °C, annealing at 10 °C higher than annealing temperature for 1 min (decreasing by 1 °C per cycle) and extension at 72 °C for 1 min.

3. Results

Two hundred confirmed psoriatic cases and an equal number of healthy, age and gender matched controls were recruited in this study. After analyzing the data out of 200 cases recruited in the present study, 130 (65%) were males and 70 (35%) were females. It was found that age ranged from 18 to 70 years with mean 38.61 ± 13.713 in the psoriatic patients while in controls, age ranged from 19 to 65 years with mean value of 36.695 ± 11.4765. Thirty-two (16%) psoriatic patients show the positive family history for psoriasis. Of all the regions majority of cases numbering 57.5% were from rural areas while as 42.5% are from urban areas. Body Mass Index (BMI) of psoriatic patients and controls was 26.94 ± 4.17 Kg/m^2 and 24.80 ± 4.28 kg/m^2 respectively. The mean value of PASI score for clinical assessment in psoriatic patients was (10.654 ± 9.09) (Table 1).

The allele frequencies and genotype frequencies of IL20 1053T/G(rs2981572), IL 20-1380A/G (rs2981573), IL20-1462G/A (rs2232360) and IL 3978T/C(rs1518108) SNPs in patients and controls are summarized in Tables 2–5 respectively. Genotype distributions for the four analyzed IL-20 gene polymorphisms had no deviation from Hardy–Weinberg equilibrium. The minor T allele and TT genotype frequency at position −1053 (rs2981572), was found higher in cases as compared to that of controls (OR = 1.091; 95% CI = 0.816–1.458, adjusted* OR = 1.99; 95% CI = 0.86–4.64 respectively). The difference came out to be statistically non-significant which confirms that −1053TT genotype is not associated with risk of psoriasis. Constructed dominant model do not show any association with the risk of psoriasis. However overdominant (adjusted* OR = 2.52; 95% CI = 1.13–5.63) shows association of genotypes as a risk factor for psoriasis and recessive models (adjusted* OR = 0.57; 95% CI = 0.36–0.91) plays a protective role for psoriasis. Representative gel picture of IL-20-1053 T/G (rs2981572) gene polymorphism by ARMS PCR as shown in Fig. 1. The frequency of minor G allele and GG genotype at position −1380 (rs2981573) was found higher in cases as compared to that of controls (OR = 3.44; 95% CI = 2.26–5.24, adjusted* OR 5.52; 95% CI = 2.43–12.55 respectively) which confirms that −1380A/G polymorphism is associated with increased risk of psoriasis. The dominant (adjusted* OR = 3.43; 95% CI = 1.88–6.28) and recessive (Adjusted* OR = 5.52; (95% CI = 2.31–11.83) models show association of genotypes as a risk factor for psoriasis. However no such association has been seen in case of over dominant model. Representative gel picture of IL-20-1380 A/G (rs2981573) gene polymorphism by ARMS PCR as shown in Fig. 2. The frequency of minor G allele and GG genotype at position −1462 (rs2232360) was found higher in controls as compared to that of cases (OR = 0.681; 95% CI = 0.51–0.90, adjusted* OR = 0.11 95; 95% CI = 0.03–0.34 respectively). The polymorphism of IL-20-1462A/G was found to be in association with decreased risk of psoriasis. The dominant (adjusted* OR = 0.46; 95% CI = 0.24–0.86) and recessive (adjusted*

Table 1
Characteristics of study group.

Characteristics			Cases (%)	Controls (%)
Age: X ± SD			38.61 ± 13.71 Years	36.695 ± 11.47 Year
Sex	Male		130 (65.00%)	130 (65.00%)
	Female		70 (35.00%)	70 (35.00%)
Family History of psoriasis			32(16.00%)	–
Disease duration ± SD			9.88 ± 8.19 Years	
Dwelling		Rural	115 (57.50%)	115 (57.50%)
		Urban	85 (42.50%)	85 (42.50%)
BMI(kg/m^2)X ± SD			26.94 ± 4.17	24.80 ± 4.28
PASI: X ± SD			10.654 ± 9.09	–
PDI: X ± SD			19.11 ± 6.1081	

Table 2
Distribution of genotypes and allele Frequency of IL-20-1053 (rs2981572) Polymorphism in psoriasis cases and controls.

	Genotype	Cases n (%)	Controls n (%)	Un adjusted OR (95% CI)	Adjusted* OR (95% CI)	*P* value
IL 20-1053G/T	G/G	82 (41.00)	75 (37.50)	1	1	
(rs 2981572)	T/G	90 (45.00)	112 (56.00)	0.73 (0.48–1.12)	0.65 (0.40–1.06)	0.18
	T/T	28 (14.00)	13 (6.50)	1.97 (0.95–4.08)	1.99 (0.86–4.64)	0.095
Dominant	G/G	82 (41.00)	75 (37.50)	1.00	1	0.31
	T/G + T/T	118 (59.00)	125 (62.50)	0.86 (0.58–1.29)	0.78 (0.49–1.25)	
Recessive	G/G + T/G	172(86.00)	187 (93.50)	1.00	1.00	**0.02**
	T/T	28 (14.00)	13 (6.50)	2.34 (1.17–4.67)	2.52 (1.13–5.63)	
Overdominant	G/G + T/T	110 (55.00)	88 (44.00)	1.00	1	**0.016**
	T/G	90(45.00)	112 (56.00)	0.64 (0.43–0.95)	0.57 (0.36–0.91)	
Allele	G	254 (63.5)	262 (65.5)	1		0.60
	T	146 (36 0.5)	138 (34.5)	1.091 (0.81–1.46)		

n = Number of Individuals, Statistically Significant p < 0.05.
* Adjusted OR (95% CI) were obtained when OR was adjusted for age and family history.

Table 3
Distribution of genotypes and allele Frequency of IL-20-1380 A/G (rs 2981573) Polymorphism in psoriasis cases and controls.

	Genotype	Cases n (%)	Controls n (%)	Un adjusted OR (95% CI)	Adjusted* OR (95% CI)	*P* value
IL 20-1380A/G	A/A	143 (71.50)	176 (88.00)	1	1	–
(rs 2981573)	A/G	17 (8.50)	14 (7.00)	1.49 (0.71–3.14)	1.92 (0.82–4.46)	0.38
	G/G	40 (20.00)	10 (5.00)	4.92 (2.38–10.19)	5.52 (2.43–12.55)	**0.0001**
Dominant	A/A	143 (71.50)	176 (88.00)	1.00	1	**0.0001**
	A/G + G/G	57 (28.50)	24 (12.00)	2.92 (1.73–4.94)	3.43 (1.88–6.28)	
Recessive	A/A + A/G	160 (80.00)	190 (95.00)	1.00	1	**0.0001**
	G/G	40 (20.00)	10(5.00)	4.75 (2.30–9.80)	5.52 (2.31–11.83)	
Overdominant	A/A + G/G	183 (91.50)	186 (52.50)	1.00	1	0.27
	A/G	17 (8.50)	14 (47.50)	1.23 (0.59–2.58)	1.59 (0.69–3.66)	
Allele	A	303 (75.75)	366 (91.50)	1		**0.0001**
	G	97 (24.25)	34 (8.50)	3.44 (2.26–5.24)		

n = Number of Individuals, Statistically Significant p < 0.05.
* Adjusted OR (95%CI) were obtained when OR was adjusted for age and family history.

Table 4
Distribution of genotypes and allele Frequency of IL-20-1462 (rs2232360) Polymorphism in psoriasis cases and controls.

	Genotype	Cases n (%)	Controls n (%)	Un adjusted OR (95% CI)	Adjusted* OR (95% CI)	P value
IL 20-1462 AG	A/A	42 (21.00)	25 (12.50)	1	1	
(rs2232360)	A/G	150(75.00)	146 (73.00)	0.61 (0.35–1.05)	0. 52 (0.28–0.99)	0.10
	G/G	8(4.00)	29 (14.50)	0.16 (0.07–0.41)	0.11 (0.03–0.34)	**0.0001**
Dominant	A/A	42 (21.00)	25 (12.50)	1.00	1	0.015
	A/G + G/G	158 (79.00)	175 (87.50)	0.54 (0.31–0.92)	0.46 (0.24–0.86)	
Recessive	A/A + A/G	192 (96.00)	171 (85.50)	1.00	1	**0.0001**
	G/G	8 (4.00)	29 (14.50)	0.25 (0.11–0.55)	0.19 (0.07–0.51)	
Overdominant	A/A + G/G	50(25.00)	54 (27.00)	1.00	1.00	0.8
	A/G	150(75.00)	146 (73.00)	1.11 (0.71–1.74)	1.07 (0.63–1.81)	
Allele	A	234 (58 0.50)	196(49.00)	1		**0.0087**
	G	166 (41.5 0)	204 (51.00)	0.681 (0.51–0.90)		

n = Number of Individuals, Statistically Significant p < 0.05.
* Adjusted OR (95%CI) were obtained when OR was adjusted for age and family history.

Table 5
Distribution of genotypes and allele Frequency of IL-20-3978 (rs1518108) Polymorphism in psoriasis cases and controls.

	Genotype	Cases n (%)	Controls n (%)	Un adjusted OR (95% CI)	Adjusted* OR (95% CI)	*P* value
IL 20-3978T/C	T/T	45 (22.50)	46 (23.00)	1	1	
(rs1518108)	T/C	148 (74.00)	153 (76.50)	0.99 (0.62–1.58)	1.11 (0.64–1.95)	0.92
	C/C	7(3.50)	1 (0.50)	7.16 (0.85–60.53)	12.87 (0.97–79.54)	0.076
Dominant	T/T	45 (22.50)	46 (2.00)	1.00	1	0.49
	T/T + C/C	155(77.5)	154 (77.00)	1.03 (0.64–1.64)	1.21 (0.70–2.11)	
Recessive	T/T + T/C	193(96.50)	199 (99.50)	1.00	1	0.076
	C/C	7 (3.50)	1(0.50)	7.22(0.88–59.22)	12.80 (0.95–80.50)	
Overdominant	T/T + C/C	52 (26.00)	47(23.50)	1.00	1	0.84
	T/C	148 (74.00)	153 (76.50)	0.87 (0.55–1.35)	0.95(0.55–1.62)	
Allele	T	238(59.50)	245(61.25)	1		0.66
	C	162(40.50)	155(38.75)	1.07 (0.81–1.42)		

n = Number of Individuals, Statistically Significant p < 0.05.
* Adjusted OR (95% CI) were obtained when OR was adjusted for age and family history.

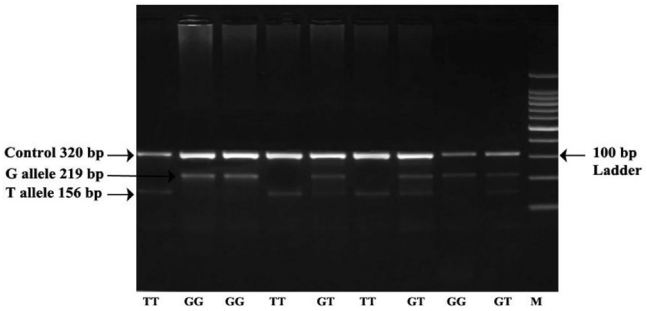

Fig. 1. Representative gel picture of IL-20-1053T/G (rs2981572) gene polymorphism by ARMS PCR.

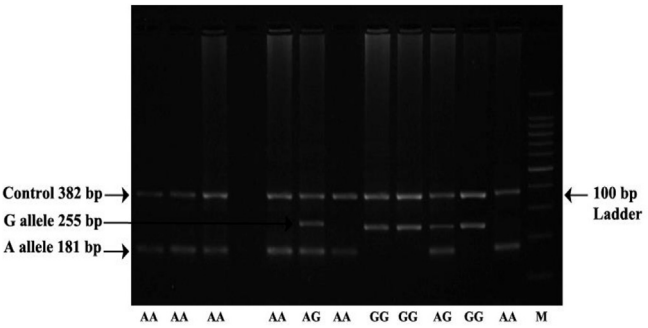

Fig. 2. Representative gel picture of IL-20-1380A/G (rs2981573) gene polymorphism by ARMS PCR.

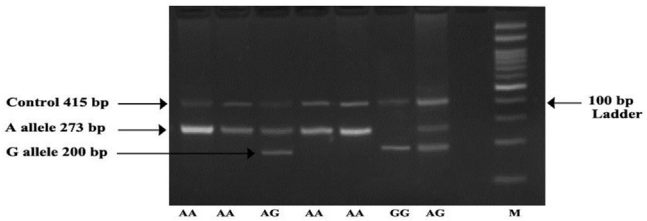

Fig. 3. Representative gel picture of IL-20-1462G/A (rs2232360) gene polymorphism by ARMS PCR.

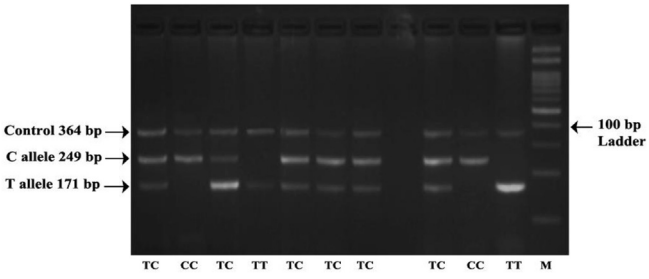

Fig. 4. Representative gel picture of IL-20-3978T/C (rs1518108) gene polymorphism by ARMS PCR.

OR = 0.19; 95% CI = 0.07–0.51) models also show significant association of genotypes with decreased risk of psoriasis. However, overdominant model does not show any association with the risk of psoriasis. Representative gel picture of IL-20-1462G/A (rs2232360) gene polymorphism by ARMS PCR as shown in Fig. 3. The minor C allele and CC genotype frequency at position −3978 (rs1518108) was found higher in cases as compared to that of controls (OR = 1.07; 95% CI = 0.81–1.42, adjusted* OR = 12.87; 95% CI = 0.97–79.54 respectively) but the difference was not statistically significant. The dominant (adjusted* OR = 1.21; 95% CI = 0.70–2.11) overdominant (adjusted* OR = 12.80; 95% CI = 0.95–80.50) and recessive (adjusted* OR = 0.95; 95% CI = 0.55–1.62) models do not show any association of allele as a risk factor for psoriasis. Representative gel picture of IL-20-3978T/C (rs1518108) gene polymorphism by ARMS PCR as shown in Fig. 4.

Haplotype frequencies of psoriasis patients and controls are summarized in Table 6. The pair wise LD Matrix demonstrated that the nearly complete L.D (D > 0 < 1 (D· between 0.30 and 0.50) existed between the polymorphism of position −1053 and 1462 within the IL-20 gene. We excluded SNP 1380 rs2981573 from the haplotype analyses because the frequency of its minor allele was lower than 10%. The presence of four haplotypes with a frequency of ≥1 was estimated. The haplotypes accounted for 95% of all haplotypes in pooled samples. The frequency of HT4 haplotype was increased in controls than cases which reflects the protective role of haplotype HT4 TG. (OR = 0.44; 95% CI = 0.24–0.79) in psoriasis which confirms its association with decreased risk of psoriasis. IL-20 serum level in Psoriatic patients are highly elevated (95 ± 25.51) as compared to controls (44.995 ± 927) respectively (p = 0.005). We observed a non significant correlation between IL-20 serum level and disease severity (p = 0.38) (Table 7).

4. Discussion

The present report is the first demonstration of the association between IL-20 polymorphism and psoriasis in north Indian population. Psoriasis subjects have sharply demarcated, erythematous and elevated skin lesions with marked silvery scales. These clinical features are determined by the thickened epidermis with hyperproliferation and abnormal differentiation of keratinocytes due to increased mitotic activity in the basal layer with the loss of the granular layer. Vascular hyperplasia and a rich immune cell infiltrate in the dermis complete the histological aspect of psoriatic plaques [4,18,19]. The evidence for the role of IL 20 is that the overexpression of IL-20 in transgenic mices induces lesions similar to those seen in psoriatic subjects [10]. Blumberg et al. had seen that IL-20 transgenic mice skin showed hyperkeratosis, thickened epidermis and proliferation in the suprabasal layer resembling human psoriatic abnormalities. Casteligans et al. have observed similar histological changes in human psoriatic skin [20]. These changes in skin appear to be caused by circulating IL-20, because even mice expressing transgene in liver were similarly affected [10]. In psoriasis the IL-20 polymorphism was associated with different form of diseases such as early onset familial and sporadic diseases [12]. The present study investigates four polymorphism within the

Table 6
Possible Haplotype Frequencies of IL 20 gene in cases and controls.

Haplotye	−1053	−1462	Cases (%)	Control (%)	OR 95 CI	P
HT 1	G	A	34.50	34.00	1	
HT 2	G	G	29.00	31.00	0.58 (0.31–1.09)	0.093
HT 3	T	A	24.00	14.00	1.47 (0.72–3.00)	0.29
HT 4	T	G	12.00	20.00	0.44 (0.24–0.79)	**0.0068**

Statistically Significant p **< 0.05**.

Table 7
Correlation between serum levels of Psoriasis patients and control and its relation with severity.

Serum Cytokine Level	Cases (2 0 0)	Controls (2 0 0)	r	p value
IL 20 (pg/m): Mean ± SD	95 ± 25.51	44.995 ± 9. 27	0.23	**0.005**
Range	(70–120)	(30–50)		
Serum level With PASI			0.0208	0.38
IL 20 (pg/m): Mean ± SD	PASI Mean ± SD			
95 ± 25.51	10.65 ± 9.09			

Statistically Significant p **< 0.05**.

IL-20 gene and IL-20 levels in serum. In our study it was found that IL-20 1380A>G polymorphism is associated with the increased risk of psoriasis. Our result substantiate the early findings [12] while as few findings show decreased risk as in palmoplantar psoriasis and Ulcerative colitis [21–23]. On the other hand IL-20 1462A>G is associated with decreased risk of psoriasis while as IL-20 3978T>C does not show any association. Kingo et al. found no association of both IL-20 1462A>G and IL 20 3978T>C with psoriasis [12]. In our study Control group had significantly increased frequency of HT4GA haplotype (OR = 0.4495; 95%CI = 0.24–0.79) which reflects its protective role in psoriasis. However, GAA has been found to be associated with plaque and palmoplantar psoriasis [12,21]. This suggests that IL-20 gene cluster might harbour a common genetic factor for all types of psoriasis. To validate this hypothesis further studies with large subjects should be done. IL-20 serum level in Psoriatic patients are highly elevated in cases as compared to controls. Kunz et al. also confirms that there is increased level of IL-20 in the lesional skin of psoriasis as well as the blood [24] [25]. Wolks et al. correlates IL-20 levels with PASI score of patients with lower significance [26]. We observed a non significant correlation between IL-20 serum level and disease severity which is in line with earlier studies [26,25]. In conclusion IL-20 gene and IL-20 HT GGA haplotype has been found to be associated with increased risk of psoriasis. Serum Level of IL-20 was also significantly increased in psoriatic subjects on comparison to control. It can be concluded that highlighting the role of cytokines in the pathogenesis of psoriasis may play pivotal role for the development of data base, maintenance and resolution of lesions. The outcome of this study provides first evidence regarding IL-20 gene and psoriasis in north Indian population. Further research with large samples should be done in order to determine the exact effects of these cytokine genes in the progression of psoriasis

Conflicts of interest

None.

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