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Study of the genetic polymorphisms of the promoter region of TNF- in Thi-Qar patients affected by psoriasis

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Abstract---Background: The relationship of factor polymorphisms has been portrayed in different investigations of tumor corruption (TNF-) and incendiary pathologies, for example, psoriasis vulgaris and joint pain psoriatic, despite the fact that the outcomes are variable as indicated by the number of inhabitants in birthplace of the example. Objective: To analyze the polymorphisms of the promoter region of the TNF-gene in patients with moderate-severe psoriasis and establish the possible genotypic differences with those found in a group of healthy volunteers. Material and methods: 89 patients with moderate-severe psoriasis and 76 controls were selected no family or personal history of psoriasis. Polymorphisms of the promoter region of the TNF- gene in both groups. Results: We observed a higher prevalence of genotype with both alleles in the wild. in position -238 (GG, 86.5% vs 70.4% respectively) and -1031 (TT, 80.2% vs 45.8% respectively) in the group of patients with psoriasis when compared to the control group. The differences found in position -308 and -857 were not significant. Conclusion: There are differences in polymorphisms at positions -238 and -1031 between patients with moderate-severe psoriasis and healthy volunteers, which supports the importance of the role of TNF- in the physiopathology of this entity.

Keywords---Psoriasis, Genetic polymorphisms, TNF, Thi-Qar.

Introduction

One of the primary issues confronting the clinical pharmacology is the current bury singular changeability in the reaction to drugs, both according to viability most definitely (1). A similar medication can be exceptionally viable in a patient while that in another produces unfriendly impacts that can reach to require the suspension of treatment. This changeability is expected both to hereditary components, which partake in the 20-95% of the fluctuation in the accessibility and impact of a medication two, like non-hereditary variables (2), which not at all like of what as a rule occurs with the past ones differ to what all through life; among them are the physiological elements (age, sex, weight, muscle versus fat), physiopathological (kidney, liver, cardiovascular capacity, related maladies) and natural (tobacco, liquor, medicines concomitants). The extraordinary test of medication today is to distinguish these factors that permit foreseeing the level of reaction to a medication or its poisonous quality in every individual already toward the beginning of treatment. Pharmacogenetics is liable for considering these hereditary qualities and the connection among them and the reaction to a medication, both as sees effectiveness just as unfriendly wonders. Subsequently, the initial step is study these changeabilities entomb singular hereditary qualities. On account of psoriasis a few investigations that have endeavored to connect various polymorphisms hereditary with the vulnerability to endure this illness. The principle qualities that have been dissected have been: the significant histocompatibility complex HLA-Cw * 0602 (3), the quality for tumor necrosis factor alpha (TNF- α) (4-10), different interleukins, for example, IL-1 β , IL-6 and IL-10 (11;12), the p40 subunit regular to IL-12 and IL-23, an of IL-23 receptor subunits (IL23R) (13), IL-13 and IL-15 (14), SNF313 (a quality associated with ubiquitination protein) (15), the tumor development factor (TGF- β) (16) and the advertiser of the interferon gamma quality (IFN- γ) (17). On account of psoriasis, the investigation of polymorphisms of the TNF-quality because of the job that goes about as an objective for most medications organic (18-21). The TNF-quality is found in the arm shy of chromosome 6, near the significant complex Histocompatibility B. This district is polymorphic, up to 44 polymorphisms have been portrayed (22), some of which have been related with various pathologies. Polymorphisms at positions - 238 and - 308 in the advertiser of TNF-quality have been related in certain examinations with reaction to treatment with hostile to TNF natural medications in rheumatological pathologies, for example, rheumatoid joint inflammation and ankylosing spondylitis (22-29). Moreover polymorphisms in position - 857 have additionally been identified with the reaction to other organic medications in joint inflammation patients rheumatoid (30,31). The work done in patients with rheumatoid joint pain distributed by Oregon-Romero et al. indicated that those patients who had a genotype with both wild alleles, both in position - 238 and in position - 308, had higher RNA creation flag-bearer and TNF-than those with any of the alleles in a freak state; anyway these distinctions are not found in solid patients³². In psoriasis the most considered polymorphisms are the substitution of guanine for adenine at positions - 238 and 308(- 238G \rightarrow A, - 308G \rightarrow A), the substitution of cytosine by thymine at position - 857 (- 857C \rightarrow T) and thymine substitution by cytosine at position - 1031 (1031T \rightarrow C). The initial two, Situated in the advertiser locale of the quality, they have been identified with the level of seriousness of psoriasis; the nearness of - 857 T has been related with an expanded danger of joint inflammation psoriatic,

yet not psoriasis. Anyway there are no decisive affiliations in regards to polymorphisms in position - 1031.

Objective

The main objective of this work is to study polymorphisms of the TNF- promoter in patients with psoriasis and control subjects and establish possible differences allelic and genotypic between both groups.

Materials & Methods

Experimental design

This is a planned report in patients with psoriasis. in moderate-serious plaques, characterizing as such a PASI more prominent than or equivalent to 10 and/or BSA more noteworthy than 10% of the surface 32 all out body, with or without psoriatic joint pain. Thi-Qar inception was not a rule of incorporation, albeit 97% of patients they satisfied. For the benchmark group, we utilized sound volunteers from the Clinical Preliminaries Unit of the Pharmacology Administration Center. The incorporation criteria for controls were sound volunteers having a place with the Network of Madrid, non-smokers, of Thi-Qar root and no close to home history or family members of psoriasis in first-degree family members degree. This investigation was endorsed by the Morals Panel of our middle, and in every single sound patient and volunteers the composed educated agree preceding getting of the example. For this investigation, the polymorphisms that have been concentrated more in patients with psoriasis and who are the accompanying: - 238 G → A (rs361525), - 308 G → A (rs1800629),- 857 C → T (rs1799724) and - 1031 T → C (rs1799964).

Sample processing

An sample of 4 was removed from each investigation subject ml of fringe blood that was added to an EDTA tube K3, enlisting and relating to a code. The DNA it was removed with a programmed DNA extractor (MagNa Squashed potatoes® Framework, Roche Applied Science, USA), measuring utilizing spectrophotometry (NanoDrop ND-1000, Wilmington DE, USA). Virtue was dictated by the proportion of 260nm/280nm.

Polymerase chain reaction

Determination of these Single Nucleotide Polymorphisms (SNP) was performed by sequencing using different primers. Primers 308F (5'-TTCTGCATCCTGTCTGGAA-3') and 238R (5'CAGCGGAAAACCTTCCTTGG-3') were used to determine the -308 and -238 polymorphisms, which were studied in the same sequence due to its proximity in the gene. Primers 857F (5'-AGGAATGGGTTACAGGAGAC-3') and 857R (GTCCCCTGTATTCCATACCT) were used to determine the polymorphism -857, and to determine the SNP -1031 primers were used 1031F (5'-TCAGAGAGCTTCAGGGATAT-3') and 1031R (5'-ACATGTGGCCATATCTCCCA-3'). The concentrations of the reaction reagents in polymerase chain (PCR) were: 1X Buffer, 2.5mM MgCl₁, 0.3 M deoxyribonucleotide triphosphate (dNTP) and 1 U / 1 of Ampli Taq Gold two© (Applied Biosystems).

Besides for the study of the nucleotide at position -1031 we add 5% dimethyl sulfoxide (DMSO), since it is a rich region in G and C nitrogenous bases. The PCR product resolved on a 3% agarose gel and said PCR product was purified by GENECLEAN (MP Biomedicals), according to the manufacturer's instructions, to later perform the sequencing of the product amplified.

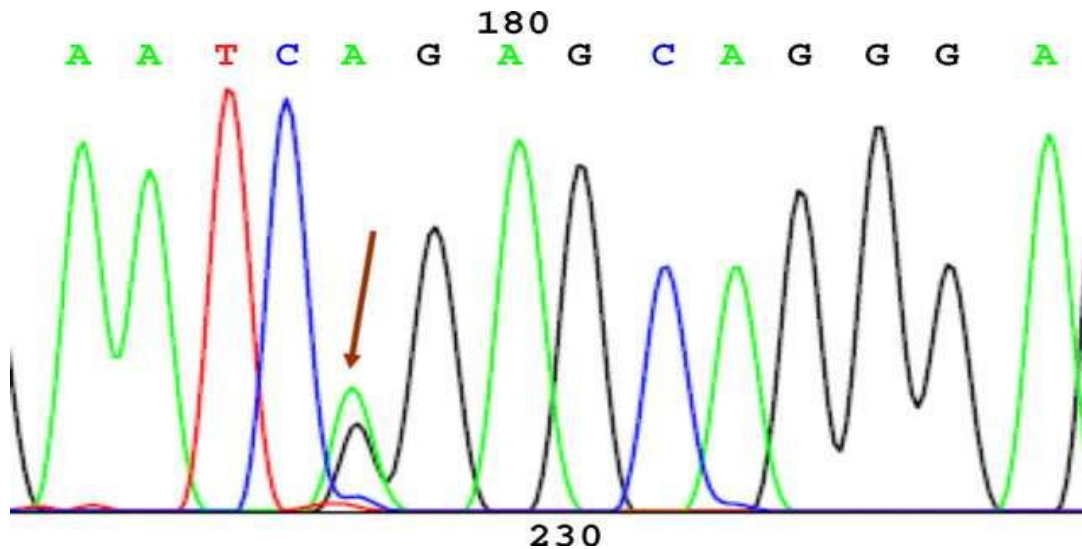


Figure 1 Example of a sequence for the -238 polymorphism (A / G).

Sequencing

Before sequencing, a past PCR was performed with the BigDye® Eliminator v3.1 (Applied Biosystems) in which the main direct groundwork was put on. Followed by this PCR the item was purged again to expel deposits marked dNTP (deoxyribonucleotide triphosphates) with fluorescence, which is the thing that the sequencer records (Applied Biosystems). The consequence of the grouping was examined utilizing Chromas V 1.45 programming. In Figures 1-44 instances of arrangements for polymorphisms are incorporated at position - 238, - 308, - 857 and - 1031.

Analysis of the results

To examine the outcomes acquired, we utilize the program SPSS adaptation 15.0.1, and we apply the Chi test Pearson square for subjective factors, to dissect the distinctions in the genotypic extents of every last one of the 4 polymorphisms that we concentrated in patients with moderate-extreme psoriasis contrasted with the gathering of solid volunteers.

Results

We have investigated the DNA of 89 patients and 76 people sound, whose epidemiological attributes are gathered in table 1. The sequencing of the 4 polymorphisms it was acted in 70 of the cases and 69 of the controls.

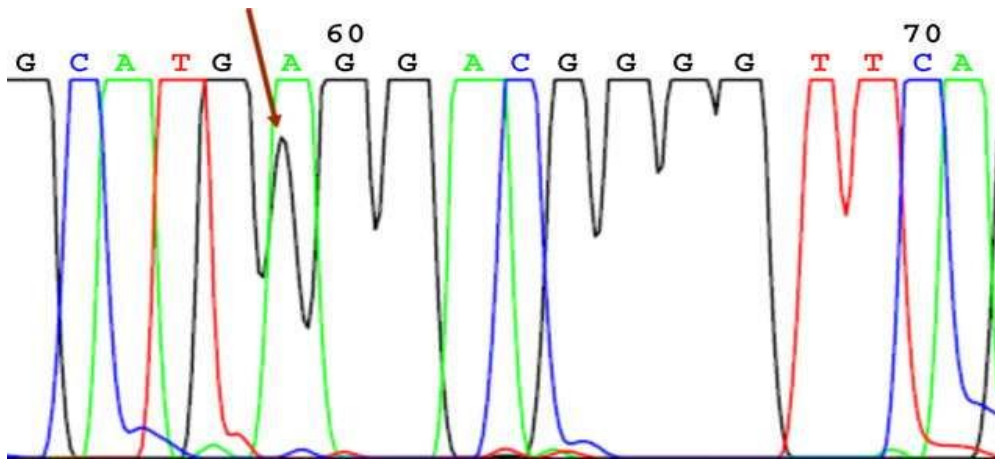


Figure 2 Example of a sequence for the -308 polymorphism(G / A).

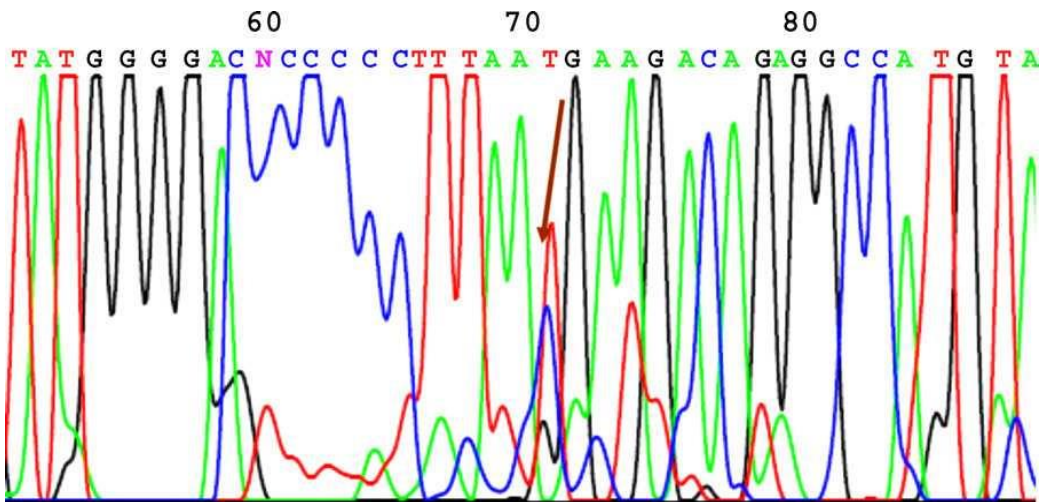


Figure 3 Example of a sequence for the -857 polymorphism (T / C).

Table 1 Population characteristics of cases and controls

	Controls (n=76)	Cases (n=89)
Average age (years) (range)	22,60 (18-31)	48,17 (19-80)
Sex		
Male (%)	46	51.7
Female (%)	54	48.3
Female / male ratio	1.2/1	0.9/1

Inclusion criteria	Healthy volunteers	Moderate-severe psoriasis
	Absence of a family and personal history of psoriasis	
	Non smoking	

Table 2 Allelic and genotypic frequencies obtained in our study, comparing those observed in cases and controls

SNP (n° patients)	Controls		Cases		P value of statistical significance (genotypic frequencies)
	Frequencies allelic	Frequencies genotypic	Frequencies allelic	Frequencies genotypic	
-238 G→A	G 92,6% A 7,4%	G/G 70/81 (86,5%) A/G 10/81 (12,3%) A/A 1/81 (1,2%)	G 83,1% A 16,9%	G/G 50/71 (70,4%) A/G 18/71 (25,4%) A/A 3/71 (4,2%)	p= 0,050
-308 G→A	G 91,7% A 8,3%	G/G 70/84 (83,3%) A/G 14/84 (16,7%) A/A 0	G 89,5% A 10,5%	G/G 60/76 (78,9%) A/G 16/76 (21,1%) A/A 0	p= 0,478
-857 C→T	C 87% T 13%	C/C 58/77 (75,3%) C/T 18/77 (23,4%) T/T 1/77 (1,3%)	C 92,1% T 7,9%	C/C 65/76 (85,5%) C/T 10/76 (13,2%) T/T 1/76 (1,3%)	p= 0,262
-1031 T→C	T 80,2% C 19,8%	T/T 55/86 (69,4%) T/C 28/86 (28,6%) C/C 3/86 (2,0%)	T 66,7% C 33,3%	T/T 33/72 (45,8%) T/C 30/72 (41,7%) C/C 9/72 (12,5%)	p= 0,025

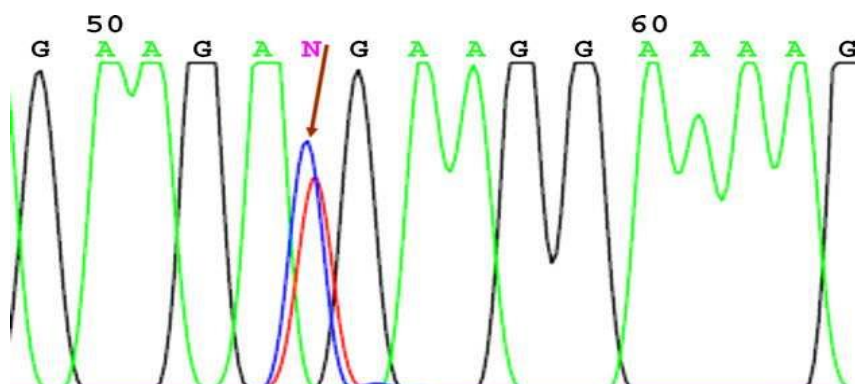


Figure 4 Example of a sequence for the polymorphism-1031 (T / C).

The dissemination of allelic and genotypic frequencies found so far are appeared in Table 2. The sequencing of the - 238 polymorphism indicated a higher recurrence of the wild allele G, just as a higher recurrence of genotype with both wild alleles (GG), in patients with psoriasis than in the gathering of solid volunteers (86.5 and 70.4% individually), bringing about these distinctions measurably huge ($p = 0.050$). We watched a higher recurrence of - 308GG in patients than in controls, despite the fact that the distinctions were not huge (83.3% versus 78.9%, $p = 0.478$). In position - 857 the nearness of a genotype with both wild alleles (CC) had a higher recurrence in controls (85.5%) than in patients (75.3%), albeit neither did these distinctions they were noteworthy ($p = 0.262$). In the investigation of the sequencing of the polymorphism - 1031 we found a higher recurrence of the wild allele T in psoriasis patients (80.2% versus 66.7%); 69.4% of the patients gave a genotype both wild alleles (TT), while this was just present in a 45.8% of the controls, the distinctions being likewise critical from the factual perspective ($p = 0.025$).

Discussion

TNF- α is a genius provocative cytokine associated with the pathophysiology of psoriasis, just as different maladies fiery, for example, rheumatoid joint inflammation and Crohn's sickness. Different polymorphisms have been portrayed related with psoriasis. We have discovered a relationship between certain polymorphisms TNF- α and weakness to psoriasis. We have additionally discovered contrasts in hereditary successions of the TNF - 238 and TNF advertiser polymorphisms-1031 when contrasting a populace with moderate with serious psoriasis with a populace of solid volunteers. This we drives one to believe that these polymorphic contrasts must assume a significant job in the pathophysiology of psoriasis. The nearness of a higher recurrence of - 238GG and-308GG in patients with psoriasis contrasted with controls could clarify by the way that in these subjects there is expanded creation of TNF- α , as demonstrated delegate RNA considers did in different pathologies in which there is an expansion in the degrees of TNF- α . In regards to the most elevated extent of - 1031TT in patients with psoriasis, could have a similar significance, in spite of the fact that reviews on the recurrence of this polymorphism in patients with psoriasis they are not many and discover no distinctions; moreover, there are no information of importance in vitro for this polymorphism. We have seen that the wild TNF - 238G allele is progressively visit in patients with psoriasis (92.6%) than in the benchmark group (83.1%), just as the GG genotype (86.5%vs. 70.4%). The vast majority of the works distributed by others creators find higher extent of freak allele TNF - 238A among patients with psoriasis, just as a danger of expanded psoriasis in relationship with genotypes with any of the freak alleles (GA/AA) (4-6,9,33). In any case, An as of late distributed examination presumes that it is more The - 238GG genotype wins among those people with increasingly serious types of psoriasis 3. 4, as would be our case. A few examinations have discovered these distinctions just in patients with beginning stage psoriasis (5,6), or just in male patients (6). Studies did on the eastern populace they have not recognized contrasts in the conveyance of these polymorphisms (7,35,36). We have not discovered huge contrasts in dissemination of the TNF - 308 genotype, similar to others creators (4,7,9,10,35,36). Be that as it may, a few investigations have discovered a higher recurrence of TNF-308GG genotype in instances of moderate-

serious psoriasis (37), or higher recurrence of bearers of the TNF - 308G allele in patients with beginning stage psoriasis (5,8,33,38). In a distributed meta-investigation by Li et al. in 2007, remembering reads for the TNF-polymorphisms at position - 238 and - 308 to date, they reasoned that the nearness of the wild allele G appeared to assume a defensive job in psoriasis. The TNF-polymorphisms at position - 857 additionally they introduced appropriation contrasts in our work. Comparative investigations led in different populaces have not discovered contrasts in psoriasis (9), in spite of the fact that in joint inflammation psoriatic a higher allele recurrence has been watched TNF - 857 T freak in patients contrasted with volunteers solid (9,40). We have discovered contrasts in the genotypic dissemination. tangles of TNF - 1031 among patients and controls, existing a higher recurrence of wild TT genotype among patients. Supposedly, the main gathering that has contemplated this polymorphism has not discovered huge contrasts. We need to consider that these distinctions found in polymorphisms of the TNF-quality between distributed works might be expected to between populace contrasts and interracial (41). In completing our work we need to call attention to certain confinements. Among them is, first rather, the restricted example size in the two patients and in controls. Likewise there is a significant distinction old enough and not all that significant of sex among cases and controls. Nonetheless, we don't accept that the significance of these realities is significant, since the genotype essentially it stays stable all through life. Then again, the that we just esteemed those patients with moderate-serious psoriasis, or that we have not balanced for nearness or not of psoriatic joint pain, has had the option to present a predisposition considering distributed articles. At last, so it would be a similar report must be completed with tests from different districts to decide whether these outcomes are extrapolated to the whole Thi-Qar populace. To complete this work, a base of hereditary material that has permitted us to begin the investigation of polymorphisms of TNF-. This is significant, since so far we have no record that there is a polymorphism database in our nation of the TNF-receptor in psoriatic patients and controls, and there is likewise small existing writing right now. The genotyping of these polymorphisms of the TNF-is the initial step to concentrate later on new polymorphisms of both TNF-and p40 protein and different proteins associated with pathophysiology and treatment of psoriasis. Besides, this hereditary investigation related with assessing the security and viability of medications The examination permits us to consider the potential contrasts Hereditary qualities among patients as indicated by the reaction of every one to specific medications. Set the distinctions between singular hereditary qualities, and subsequently streamline treatment of the pathologies in every patient, acquiring a treatment more secure for the patient, is the essential goal of pharmacogenetics. This would maintain a strategic distance from delays in overseeing compelling treatment and keeping away from dangers for the patient, notwithstanding killing superfluous costs in medicines that are not successful. We should believe that not just the hereditary blessing impacts in the advancement of a specific infection, yet in addition the manner in which those qualities are communicated 41, with the goal that articulation investigation is intriguing for future examinations quality utilizing strategies like DNA microarrays, which would give a subjective investigation, yet in addition quantitative (42). With this examination we have attempted to go above and beyond in the field of pharmacogenetics.

Conclusion

In our examination we need to feature that:

1. We discovered noteworthy contrasts in the polymorphism - 1031 in psoriatic patients regarding the benchmark group, which implies that it could assume a functioning job in the pathophysiology of this malady.
This finding has not been recently portrayed in any Hereditary investigation of patients with moderate to serious psoriasis.
2. We likewise discovered pertinent contrasts in polymorphism-238, so this one could likewise take an interest of the beginning of this pathology. This finding has not recently portrayed in patients with psoriasis moderate-serious of the Thi-Qar populace.
3. The assurance of these polymorphisms has a momentous functional application, as it can permit present or future investigations:
 - a. make a library of patients with psoriasis in plates with blood tests got.
 - b. develop the information on the systems pathogenic hidden psoriasis.
 - c. distinguish other conceivable restorative targets.
 - d. associate these outcomes with reaction to treatment and poisonous quality, with what we accomplish:
 - increase information about the component of activity at the atomic degree of medications to consider.
 - determine from the earlier the medication of decision (medication individualized).

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