Republic of Iraq
Ministry of Higher Education
and Scientific Research
University of Al-Qadisiyah
College of Medicine

Genotyping of Specific HLA-C Loci and Some Pro-Inflammatory Cytokines Gene Polymorphism in Type I Psoriasis

A Thesis
Submitted to the Council of the
College of Medicine / University of Al-Qadisiyah
In Partial Fulfillment of the Requirements for
The Degree of Philosophy Doctorate
Medical Microbiology

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2018 A.D 1439 H

بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

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صَدَقَ اللَّهُ العَظِيمُ

(سورة مريم : (١)

DEDICATION

To my family

Who brought me up in milieu of goodness and inspired my determination.

Everything I do, and all the success I've got or will get is because of them and for them ….

ACKNOWLEDGEMENTS

Praising to **Allah** who gave me health, strength and facilitated the ways for me to accomplish this work.

Sincerely I feel a great urge to present my deepest affection and gratitude to Prof. **Dr. Manal M. Kadhim,** under here supervision this work was done, for her excellent supervision, scientific guidance, kind advice, suggestions, comments and encouragement throughout the duration of this work.

I offer my deep thanks to Deanship**,** and special thanks for department head**,** all Professors, teachers, and all staff members of the Collage of medicine for their cooperation and all that they teach me, my sincere thanks to them, and I will be always grateful to each one of them.

My appreciation is extended to the staff of Al-Zahra teaching hospital, especially dermatologists and laboratory staff for all the help and support they provided during the practical part of this research.

Certification

I certify that this thesis entitled (**Genotyping of Specific HLA-C Loci and Some Pro-Inflammatory Cytokines Gene Polymorphism in Type I Psoriasis**) by "Alaa Irhayyim Ali" has been prepared under my Supervision at the Medical Microbiology Department, College of Medicine/ University of Al-Qadisiyah in partial fulfillment of the requirements for the degree of Philosophy Doctorate Medical Microbiology

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Recommendation of Head of Medical Microbiology Department

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Certification of Examining Committee

We, the members of examining committee, certify after reading this thesis entitled (**Genotyping of Specific HLA-C Loci and Some Pro-Inflammatory Cytokines Gene Polymorphism in Type I Psoriasis**) and after examining the student in its contents, it was found adequate for the degree of PhD philosophy of medical microbiology with an excellent degree.

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Summary

Psoriasis is a chronic, autoimmune, inflammatory disease of human skin. It can occur in various phenotypes, though, plaque phenotype is more frequent. The etiology is obscure till now, but several genetic, immunologic and environmental factors identified. It can affect both sex and show no ethnic differences, type I (early onset) show high genetic predisposition. Psoriasis also characterized by elevation of pro-inflammatory cytokines like IL1, IL6 and TNF. This study aims to determine if *IL1β, IL6* and *TNF- α* gene polymorphism is associated with *HLA-C* genotypes, and its impact on type I psoriasis presentation in Iraq population

Current study includes 163 participants, classified into two groups. Psoriatic group (type I) involve 76 patients and a match apparently healthy group comprise 87 persons as control subdivided into 36 relatives and 51 neither psoriatic nor have a family history of psoriasis. A 2 ml venous blood sample toke from each participant in K3-EDTA anticoagulated tube and stored at -20c°, then subjected to a DNA extraction procedure and polymerase chain reaction amplification and detection of HLA (CW6, CW7 and CW17) and for SNPs detection at (IL1β, IL6 and TNFα) gene promoters.

The mean age for patients is 26.2 years, the incidence is more frequent in more than 30 years' age group. There are no gender differences and more than three quarter of them (84.2%) resident in an urban location. There is also a low frequency of patients found to be smoker (15.8%) and more than half of the patients (53%) presented with a positive family history. The higher percent of patients (47.3%) were found to suffer from a mild form of disease.

Summary

Results show a significant association of CW6 (p-value 0.002) and CW7 (p-value 0.002) with type I psoriasis. There is also a significant association of type I psoriasis with IL1β -511 T allele (p-value 0.006), IL6 -174 C allele (p-value 0.000), CC (p-value 0.01) and GC genotypes (p-value 0.001), TNFα -308 A allele (p-value 0.01) and GA genotypes (p-value 0.04). From these markers, CW7 allele associate with earliest age of first attach (mean 17 years) while IL6 -174 G\C polymorphism associate with latest age (mean 20 years). While none of the selected HLA types associate with family history, IL6 -174 C allele and TNFα A\G genotype significantly associated with those positive for family history (p-value 0.05 for each). With regard to severity, only the C allele of IL6 significantly increase in frequency in mild cases (p-value 0.05).

Results also show significant association of CW17 with A allele of TNFα (p-value 0.01) that increase relative risk about three folds (OR 3.6). CW7 on the other hands, show a significant association with GG genotype of TNFα (p-value 0.005) and also with G allele (p-value 0.004) that increase risk of psoriasis. CW6 significantly associated with GG genotype of IL6 (p-value 0.02) that increase relative risk about eight folds (OR 8.2) and with G allele (p-value 0.005) that increase relative risk to about nine times (OR 9.4).

In conclusion, a significant association of CW6 with G allele and GG genotype of IL6 increase the risk of psoriasis, this is also true for CW7 with G allele and GG genotype of TNFα. Psoriasis risk also increased by significant association of CW17 with A allele of TNFα.

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List of Abbreviations

Abbreviation	Meaning
AMPs	Anti-Microbial Peptides
BSA	Body Surface Area
CARD	Caspase Recruitment Domain
CDs	Clusters Of Differentiation
DCs	Dendritic Cells
DNA	Deoxyribose Nucleic Acid
dNTPs	Deoxyribose Nucleotide Tri Phosphates
EDC	Epidermal Differentiation Complex
EDTA	Ethylene Diamine Tetra Acetic Acid
GAPDH	Glycer Aldehyde 3-Phosphate Dehydrogenase
GMCSF	Granulocyte Monocyte Colony Stimulating Factors
GWAS	Genome Wide Association Scan
HLA	Human Leukocyte Antigens
IFN	Interferon
IL	Interleukin
IL1β	Interleukin 1 Beta
KCs	Keratinocytes
KIR	Killer Inhibitory Receptor
MDCs	Myeloid Dendritic Cells
MHC	Major Histocompatibility Complex
NFKB	Nuclear Factors Kappa B

List of Abbreviations

NK	Natural Killer Cell
NKT	Natural Killer T Cell
PASI	Psoriasis Area Severity Index
PCR	Polymerase Chain Reaction
PDCs	Plasmacytoid Dendritic Cells
PRRs	Pathogen Recognition Receptors
PSO	Psoriasis
PSORS	Psoriasis Susceptibility
PSV	Psoriasis Vulgaris
RNA	Ribo Nucleic Acid
SNP	Single Nucleotide Polymorphism
SSP	Sequence Specific Primer
Ta	Annealing Temperature
TBE	Tris-Borate-EDTA
TGF	Transforming Growth Factors
Th	T-Helper Cell
TLRs	Toll Like Receptors
Tm	Melting Temperature
TNFα	Tumor Necrotic Factor Alpha
UC	Ulcerative Colitis
UV	Ultra Violate

1.1. Introduction.

Psoriasis (PSO) defined as a common, chronic, relapsing disease, with a genetic background, it is an inflammatory and proliferative disease of the human skin (Al-Hamdi et al., 2006). Although PSO has several phenotypes, about 90% of patients suffer from plaque PSO (Sami., 2015). Typically, PSO lesions characterized by erythematous papules which develop to form plaques that characterized by sharp borders and increased scaling (Estabraq et al., 2011). It has a complex, multifactorial nature that influenced by genetic, environmental factors and immune components, with a worldwide prevalence of approximately 1 to 3% (Mohammad et al., 2015). PSO can occur at any time in the lifespan and affects both genders equally (Muhsin et al., 2016). According to age of onset, PSO characterized by bimodal distribution. Type I or early onset PSO and Type II or late onset PSO (Fadhil et al., 2013). Other authors, identify type I PSO as inherited and associated with CW6, while type II PSO occurs sporadically (Ahmed., 2016).

Several susceptibility loci have been identified, among them, PSORS1 (6p21.3) is a well-confirmed, in which HLA-Cw6 is the main marker allele, and have been notified in a number of studies (Khalda et al., 2010). Susceptibility to PSO is associated with different HLA alleles in different ethnic groups (Ahmed., 2016). PSO characterized by increase secretion of pro inflammatory cytokines, that create a “cytokine storm” (Mezentsev et al., 2014). Dysregulated immunity contributes to the construction of PSO by inducing the over-production of pro-inflammatory cytokines by keratinocytes (KCs) (Satveer et al., 2016).

There is over production and persistent secretion of IL- 1, IL-6 and TNF- α in type I PSO, (Audrey et al., 2016). IL-1 family altered their expression in non-lesional and lesional psoriatic skin compared to healthy skin (Johnston., 2011). Three polymorphisms in IL-1β gene have been reported, all representing di-allelic C–T base transitions, of these, the -511 C–T polymorphism is considered the most important (Nikhil et al., 2015). IL6 involved at different key points in the immune pathogenesis of PSO (Andreea et al., 2013). About 50 single nucleotide polymorphism (SNP) in the promoter region of the IL-6 gene have been identified, but the most studied SNP is that at position -174 (IL-6 -174G/C) which can modify transcription and cytokine levels (Nie et al., 2016). TNF have been shown to play pivotal roles in the pathogenesis of PSO (Fadhil et al., 2013). TNF-α gene is highly polymorphic, up to 44 SNPs reported. Of these, SNPs at positions -238 and -308 of the TNF-α promoter have been associated with response to anti-TNF-α biologics, levels of messenger RNA and protein production and have been associated with the severity of PSO (Gallo et al., 2012).

Till now, there is no single genetic factor that has been associated with all PSO cases, so that PSO can be considered as a heterogeneous group according to genes involved, which result in similar cutaneous pathological process outcome. Knowing the genes involved in early onset PSO have a significant consequence on understanding of PSO initiation and maintenance as well as therapeutic intervention tailoring according to individual genetic profile.

This study aim to determine the possible role of IL1β, IL6 and TNF- α gene polymorphism in association with HLA-C genotypes, and its impact on psoriasis disease presentation in Iraq population. Through the following experimental setting:

1. Grouping patients according to HLA-C status (cw6, cw7 and cw17) to elucidate the associations with IL1β, IL6 and TNF- α alleles and genotypes by taking blood sample from each participant and employing sequence specific priming-polymerase chain reaction (SSP-PCR) technique.
2. Focusing attention into the combined effect if any of two of these allele groups in causation of clinical presentation of psoriasis by comparison between patients and control group.
3. Investigating the hypothesis that some allelic variants are sufficient to induce clinical expression of psoriasis by comparison between patients and first degree relative.
4. Identifying allele or genotype that offer the opportunity to construct psoriasis within family members by make a comparison between patients with positive family history and negative family history.

1.2. Literature Review.

1.2.1. Overview of Psoriasis.

The first use of the term psoriasis was as an explanation of disease, which indicated its major symptoms i.e. itching. Psora in Greek mean “to itch” (Roberson and Bowcock., 2010). It has been taken time until its proved to be an autoimmune disease (Mattozzi et al., 2016). Advanced genetic incriminate the innate immunity in PSO, as it is found to be unusually hyper activated (Tsoi et al., 2012). Despite the significant advances in revealing the genetic basis and inflammatory pathway in disease pathogenesis, there is still a deficit in understanding of PSO. Necessitating further research in this field (Caitriona et al., 2014).

Psoriasis is a chronic, disfiguring, disabling and non-communicable disease, without a single typical clinical presentation, and for which there is no cure (Abuabara et al., 2010). The most significant feature of PSO is KCs and dermal vascular endothelial cells hyper proliferation and cellular infiltration with subsequent vascular changes and inflammation. About five subtypes of PSO have been found, include vulgaris (plaque) (PSV), guttate, pustular, inverse, and erythrodermic. With a plaque PSO affects approximately 85%–90% of psoriatic patients (Nilmarie et al., 2016). The lesion may appear anywhere on the skin but spared the mucosa, characterized by well demarcated erythematous plaque with silvery scale that easily detach, and may be aggravate by irritation, trauma, infection, some drugs, seasonality and stress (King-man., 2010).

It has a bi modally distribution with one peak at 20-30 years and other at 50-60 years, with approximately 0.5-1% children affected compared to 2-3% of adults (Cameron and Voorhees., 2014).

1.2.2. Classification of Psoriasis.

Clinical phenotypes classification of PSO depends on several characteristic including distribution of the psoriatic lesions, thickness and size of lesion and anatomical sites (Raychaudhuri et al., 2014). Plaque PSO (PSV) is the most common phenotype, account about 90% of psoriatic patients (Boehncke and Schon., 2015). PSV characterized by defined contour plaques, covered by whitish scaly skin and most commonly found on elbows, knees and scalp (seborrheic psoriasis) (Audrey et al., 2016).

Guttate psoriasis frequently seen in childhood, generally after strep throat with general lesion resolve after infection regression. It is most frequently associated with PSORS1. This form of PSO characterized by small drops of PSO over the body but no plaque. Though some cases subsequently develop chronic PSV (Raychaudhuri., 2014).

Erythrodermic psoriasis can be widespread over the body, accompanied by sever itching, swelling and pain. Its development occurs due to either poor control of existing PSO or abrupt withdrawal of systemic drugs. It can be accompanied by hypothermia, anemia, acute respiratory distress Syndrome and risk of heart failure (Audrey et al., 2016).

Pustular psoriasis can occur either on the palms and soles only (palmoplantar) or anywhere on the body. Although frequently seen in young individuals, it can develop either independently or due to abrupt withdrawal of systemic steroid treatment of PSV. (Gulbahar et al., 2016).

Inverse psoriasis is more frequently seen in obese individuals; it is localized in skinfolds also termed flexural. due to friction and moisture in skin folds the Squamous lesions do not form (Gulbahar et al., 2016). General phenotypes of PSO presented in figure (1-1).

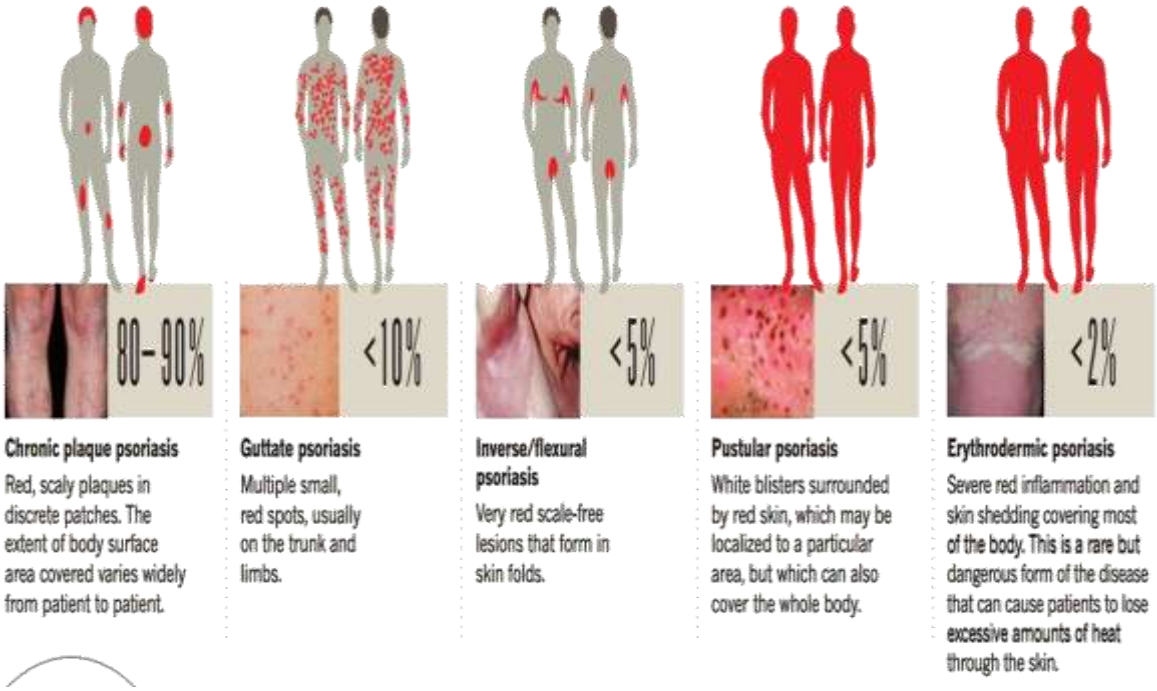


Figure 1-1: psoriasis phenotypes (James., 2012**).**

1.2.3. Epidemiology of Psoriasis.

Several studies found out a great variation in the prevalence of PSO over the globe (Parisi et al., 2013). This variation is likely influenced by geographic location, being increased proportionally with distance from the equator (Michalek et al., 2017). It occurs most commonly in populations of northern Europe than populations of eastern Asia (Kubota et al., 2015). PSO can occur in all age with no gender or ethnic spared. Although several studies published about PSO prevalence around 0.09% in some countries, other studies register an increase in prevalence to 11.4% (Danielsen et al., 2013). The prevalence of PSO in Iraq range from 0.7% (Al-Rubiay., 2006) to 1.5% (Al-Hamdi et al., 2006). The global prevalence shown in figure (1-2).

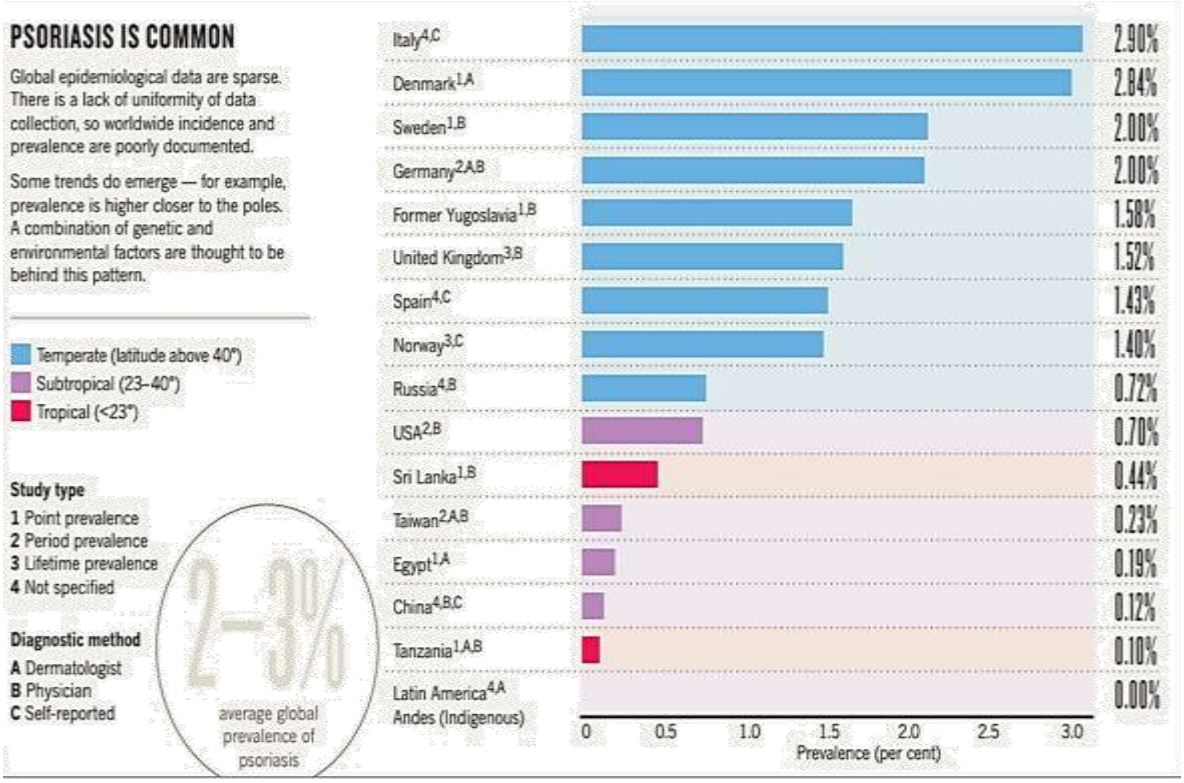


Figure 1-2: Global epidemiological data of psoriasis (James., 2012**).**

1.2.4. Risk Factors of Psoriasis.

Despite the multifactorial nature of PSO, several risk factors have been identified. Including those associated with genetic predisposition, immunological dysregulation and environmental risk factors (Oka et al., 2012). Regarding genetic predisposition, different numbers of genes associated with PSO are denoted by different studies. Genome-wide association studies implicate 36 susceptibility genetic loci in the pathogenesis of PSO (Tsoi et al., 2012). Though high number of heritability still unexplained, which may be hidden in genome with large number of variants that have small effects (Oka et al., 2012).

Various single nucleotide polymorphisms (SNPs) have been associated with PSO. A number of these SNPs have been associated with increased risk of PSO, while other confer protection. Other studies have not detected any association of these SNPs with PSO. (Alejandra et al., 2016) ascribe these discrepancies to genetic variations in the populations studied. So it is not surprising when Tsoi et al., 2017 identify 63 unique susceptibility loci in patients of European descent with PSO, though these loci only explain approximately 50% of PSO inheritances. loci of susceptibility to PSO denoted (PSORs) from PSORs-1 to PSORs-13. Some are well characterized, including PSORs-1 which located on chromosome 6p21, including among others HLA-CW0602 allele, and implicated in about 50% of early onset PSO cases (Puig et al., 2014).

The immune bases of PSO established by early observations that skin lesions contain increased numbers of inflammatory cellular infiltrates. Additionally, patients with PSO undergoing bone marrow transplantations or treatment with immunosuppressive agents experienced dramatic improvements in their inflammatory skin lesions (Jason et al., 2017). The immune-mediated mechanism of PSO has been extensively studied, Th1 cell differentiation up-regulated and impaired Th1/Th2 ratio, result in Th1-delivered cytokines IL-1, IL-2, IL-6, IL-8, TNF-α, TGF and GMCSF are upregulated, Th2-delivered cytokines IL-4, IL-5, and IL-10 are downregulated (Hız et al., 2017). A KCs derived anti-microbial peptide catheliciden (LL37) which act as auto antigen for T-cell restricted by HLA-C∗ 06:02, establish PSO as an auto immune disease (Lande et al., 2014).

Several environmental conditions that either predispose or exacerbate PSO have been suggested as risk factors, including among others stress, smoking, alcoholism and obesity. Stress including anxiety and depression has been linked with the risk of incident of PSO. Depression associated with an increased risk of incident PSO (Luigi., 2013), while other study by Remrod et al., 2015 denote that in patients with PSO, increased risk of anxiety and depression is associated with intensive pruritus, and there is unwillingness to undergo regular treatment of PSO. Stressed PSO patients have elevated levels of TNF- α and IL-6, though an improvement in depression scores when treated with TNF-α inhibitors (Rebecca and Kathryn., 2016).

Smoking is an independent risk factor for PSO. and the risk for PSO increased with amount and duration of smoking (Kelsey et al., 2017). Excessive alcoholism exacerbates PSO as a result of immune dysfunction and increase production of inflammatory cytokines (Rahul., 2013). Obesity have a bidirectional relation to PSO, in that obesity predispose to PSO while PSO favoring obesity (Luigi et al., 2016).

1.2.5. Etiology of Psoriasis.

Although the exact cause of PSO is still uncovered, it is believed to be a multifactorial in nature, with several key players include genetic susceptibility, skin barrier disruption, immune dysfunction and environmental triggers (Raychaudhuri et al., 2014). In this context the immune and genetic factors are the most important, with about 33% of psoriatic patients have an affected first degree relative (Weigle and Mcbane., 2013). According to British Skin Foundation 2016, PSO considered as a complex trait, many genes involve and it's difficult to incriminate a single allele in causation of PSO. Furthermore, even if right combination of genes has been inherited, PSO may not initiate. Gupta et al., 2014 make a linkage between PSO and different chromosomal loci.

Certain interleukins including among others IL1, IL6 and TNF are raised, with increases in cellular expression of the adhesion molecules that signifies an inflammatory response (Lowes et al 2014).

Several environmental factors involve in PSO initiation include mechanical and chemical injury, UV radiation, certain drugs and various infection. In additions to smoking and psychological stress (Prieto-Perez et al., 2013).

Although stress consider as an important player, several studies presume that several dermatological disorders are immunogenic and psychosomatic in nature (Sing et al., 2014). Trauma resulting for example from needle puncture can cause Koebner's phenomenon and subsequent psoriatic flare (Jashin and Caroline., 2013). With regard to infection, altered microbial profile and upregulation of antimicrobial peptides support the role of microbes in PSO etiology (Morizane and Gallo., 2012).

1.2.6. Pathogenesis of Psoriasis.

Eruption of PSO associated with immune cells infiltration into the epidermis with subsequent secretion of pro inflammatory cytokines and chemokines (cytokines storms) accompanied by dilation of blood vessels in the dermis. There is an increased turnover of KCs with altered differentiation (Mezentsev et al., 2014). Histopathological changes include thickening of epidermis (acanthosis) as a result of increased KCs turnover, with retention of nuclei in stratum corneum due to altered differentiation (parakeratosis) (Satveer et al., 2016).

Although the exact mechanism of PSO induction is not fully understood yet, several factors include physical injury, infection and some drugs may involve in initiation of PSO. Some of these insult cause release of anti-microbial peptide LL37 (cathlecidin) from KCs. LL37 either bind to foreign or self DNA released from stressed cell, these complex activate TLR9 on PDCs. This events result in breakdown of tolerance to self-nucleic acids, directly activate auto-reactive circulating T cells (Lande et al., 2014).

The LL37 can also bind to self RNA lead to activation of PDCs through TLR7,8 (Ganguly et al., 2009). IL26 from Th17 can form complex with foreign or self DNA then activate PDCs through TLR9 (Meller et al., 2015). PDCs release IL1, IL6, TNF and IFNα that activate MDCs which in turn migrate to regional draining lymph node and release IL12 and IL23 that drive T-cell differentiation into Th1 and TH17 respectively (Lowes et al., 2014). Epidermal hyperplasia, a hallmark of PSO, caused by activation of KCs by Th17 cytokines include IL17 A, F and IL22. And by IFNα and TNFα from Th1. In contrast KCs proliferate and produce pro inflammatory cytokine IL1, IL6 and TNFα plus chemokines and AMPs that form a positive feedback to innate and adaptive immune cell (Alwan and Nestle., 2015). The general outline of PSO pathogenesis illustrated in (figure 1-3).

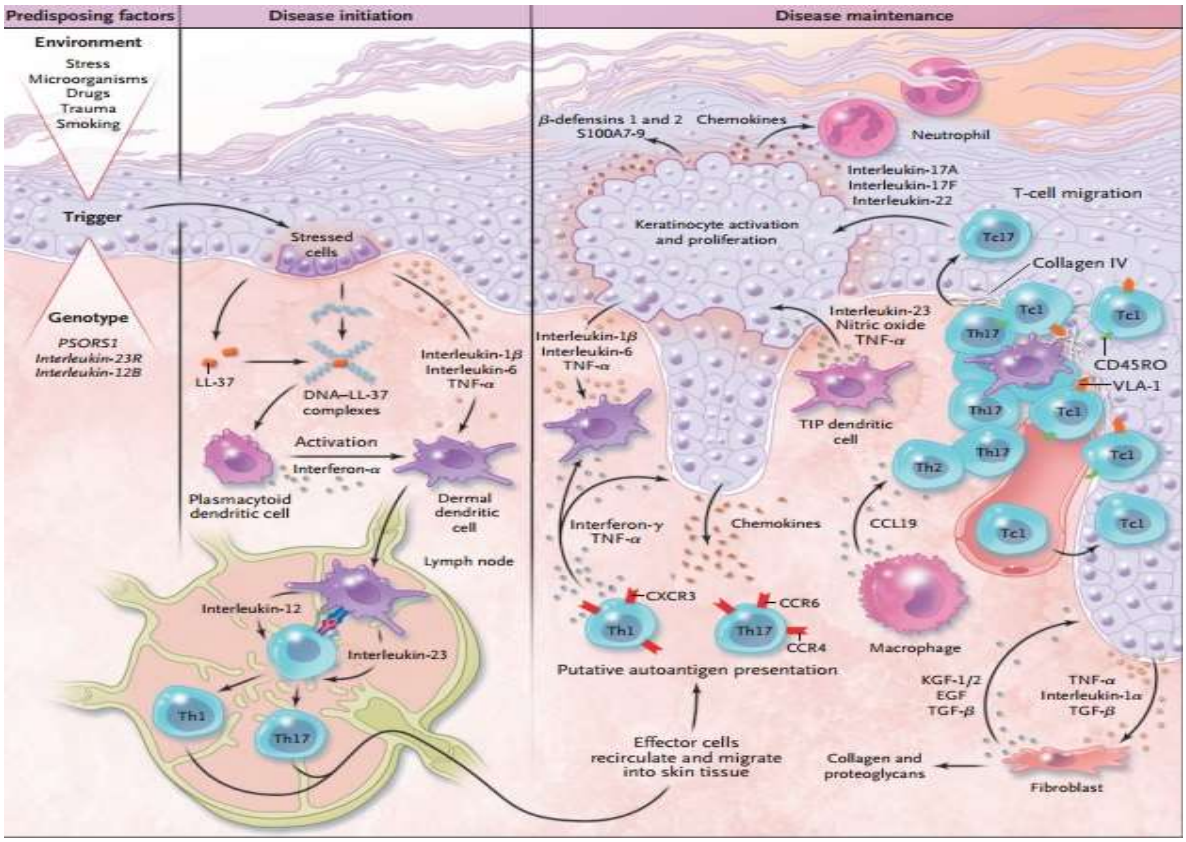


Figure 1-3: psoriasis pathogenesis outline (Frank et al., 2009).

1.2.7. Genetic of Psoriasis.

The increased incidence of PSO observed in 1st and 2nd degree relatives, beside two to three folds increased risk in monozygotic over dizygotic twins established the genetic basis of the disease (Alwan and Nestle., 2015).

Regarding the twin's studies, PSO incidence never reach 100% in monozygotic, indicating that other factors having role including environmental factors (Lonnberg et al., 2013). linkage analyses found important genes conferring susceptibility to PSO (Alshobaili et al., 2010). (PSORS1-(6p21.3), PSORS2-(17q25), PSORS3-(4q34), PSORS4-(1q), PSORS5-(3q21), PSORS6-(19p13), PSORS7-(1p) PSORS8-(16q12-13), PSORS11-(5q31.1-q33.1), PSORS12-(20q13), and PSORS13-(6q21)) (Hız et al., 2017). Only PSORS1 and PSORS2 has been reported to promote susceptibility to PSO. while, for most of the other loci, the evidence is doubtful (Aparajita and Saumya., 2017). Within PSORS1 locus there are three gene associated with PSO: HLA- Cw6, CCHCR1 and CDSN (Tsoi et al., 2012).

Regarding the HLA, Cw6 show strongest association with PSO, followed by B57, A1, B47 and B13. Families inspection indicate that all family member affected have Cw6 allele due to presence of this allele on more than one haplotype in a family. Although Cw6 associated with more severe and early onset PSO, the nature of the contribution of the HLA region to PSO is unexplained (Alshobaili et al., 2010).

Although CCHCR1 and CDSN have been proposed as contenders to HLA in PSOR1, a consensus is now beginning to emerge that excluding them, a gain of function mutation in CARD14 on PSOR2 locus may cause PSO through increased induction of NF-kβ, which leads to enhanced expression of key psoriatic chemokines (Jordan et al., 2012). Mapping of the PSORS4 susceptibility locus reveal that it is included within the Epidermal Differentiation Complex (EDC), a cluster of 27 genes expressed during the epidermal differentiation (Aditi et al., 2016).

Single nucleotide polymorphism (SNP) are substitutions of one base pair for another in >1% of the population, most commonly found in noncoding regions of the genome. Genome-wide association studies (GWAS) aim to identify SNPs by comparing the allele frequency of each SNP between individuals with disease (cases) versus participants without disease (controls) (Michelle et al., 2014). (GWAS) demonstrates that SNPs in the MHC region are strongly associated with PSO in different populations. Though, it is still unknown how many independent SNPs located within the MHC region contribute to the risk of PSO (Zhu et al., 2011).

Various (SNPs) associated with an increased risk of developing PSO. These SNPs are involved in various processes, including: Skin barrier functions, interleukin (IL)-23 signaling, nuclear factor- κB (Alejandra et al., 2016). SNP located in the 3’ terminal region of the IL12B gene encodes the p40 subunit common to IL-12 and IL-23, was the first locus clearly and reproducibly associated with PSO risk and was independent of MHC (Puig et al., 2014).

1.2.8. Immunology of Psoriasis.

During the initial phase of PSO there is a hyper activation of innate immune cells: KCs, dermal Dendritic Cells (DC) and macrophages. Through Pathogen Recognition Receptors – PRR (Yaxiong et al., 2016). As it is shown in figure (1-4).

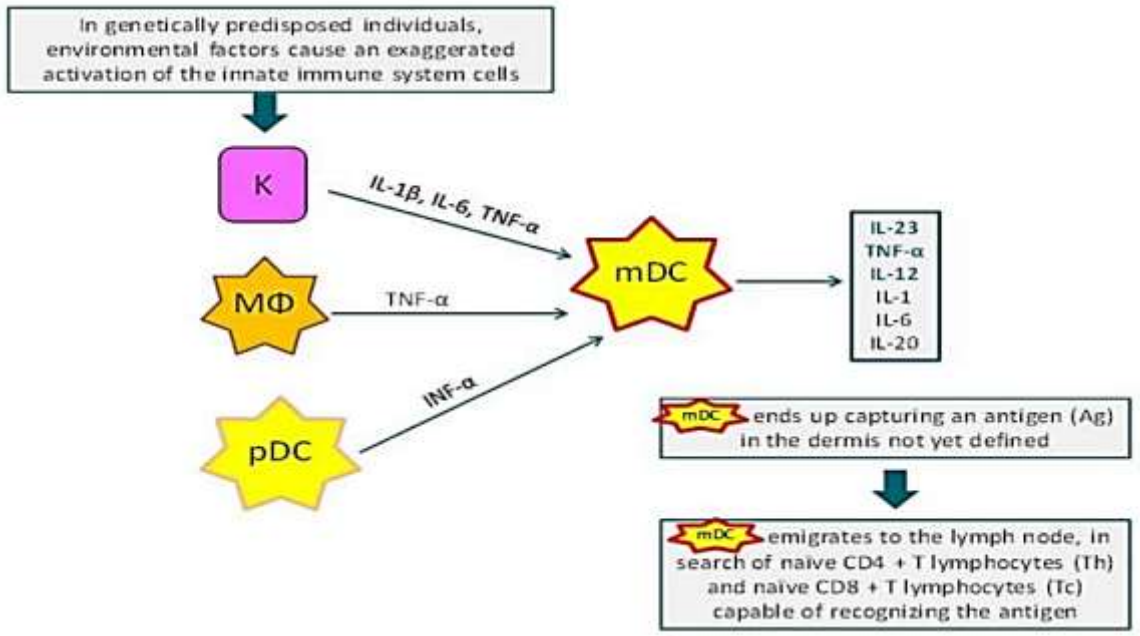


Figure 1-4: Innate immune cells involved in the initiation of psoriasis (Ana., 2017).

When the mDCs migrate to the lymph node, in search of naïve CD4 + Th and naïve CD8 + Tc capable of recognizing the antigen. mDCs produce IL-23, TNF-α and IL-12. In the lymph node, these cytokines drive naïve Th0 to differentiate preferably in Th17, Th22 and Th1 (Lynde et al., 2014).

Several studies attempt to identify the PSO auto antigens. Lande et al., 2014 have been found autoreactive CD4+ or CD8+ T cells against LL-37 produced by KCs in 75% of patients with moderate-to-severe PSO. Another potential PSO autoantigen, a disintegrin like and metalloprotease domain containing thrombospondin type1 motif-like 5 (ADAMTSL5) identified by Arakawa et al., 2015. This autoantigen presentation and the subsequent activation of IL-17–producing T cells in psoriatic skin involve melanocytes, KCs and DCs. phospholipase A2 group IVD (PLA2G4D) was reported as a possible PSO autoantigen found to be upregulated in psoriatic plaques. PLA2G4D expression increase in psoriatic KCs and mast cells (Cheung et al., 2016). With regard to Ag presentation, HLA cw6 is the most implicated in PSO. It may act via the adaptive immune system by its antigen presenting capacity. Or through an innate immune response via its interaction with KIRs expressed on NK and NKT cells. As it is shown in figure (1-5), (Mak et al., 2009).

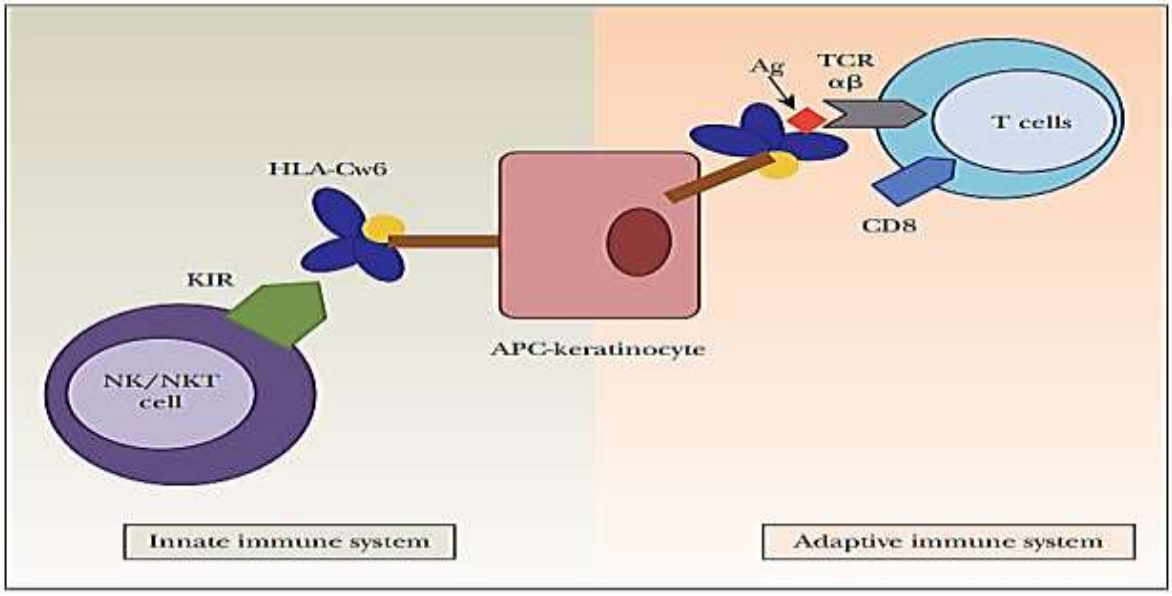


Figure 1-5: HLA-Cw6 regulate adaptive as well as innate immune responses (Mak et al., 2009).

A nonamer peptides predominantly presents by HLA-C*06 with dominant arginine anchors at the P2 and P7 positions and a preference for small hydrophobic residues at P9. HLA- C*07 have the closest related peptide motif with P2- Arg and P9 hydrophobic anchor residues. HLA-C in general lack the negatively charged Asp9 that attracts positively charged P2 anchor residues and have positively charged peptide- binding grooves (Jesse et al., 2017). Indeed, only HLA-Cw6 and HLA- Cw7 that display negative charges across the entire peptide binding groove and have a Asp9, similarly been shown to present peptides with P2- Arg. It can be seen that other HLA- C have Arg preferences at P2 or P7, but only HLA-Cw6 has both. For example, the HLA- Cw7 group has preference for P2- Arg containing peptides (Jesse et al., 2017). HLA-C have either Asparagine (Cw7 termed C1 epitope) or Lysine (Cw6, Cw17 termed C2 epitope) at position 80, located in the peptide binding groove (Ralph et al., 2016).

Activated T cells leave the lymph node, expressing adhesion molecule fit to that expressed by activated endothelial cells on the skin, The Tc migrate to the epidermis and the Th concentrate in the dermis (Sanchez., 2010). The ADAMTSL5 recognition is restricted to epidermal CD8+ T cells and a HLA-C*06. Stimulation of these cells results in IL-17A production (Arakawa et al., 2015). epidermal CD8+ T reside in the skin even after successful treatment and retain their capability of production of IL-17A. this can explain even partially why the same body sites can develop psoriatic plaques, even after long periods of remission (Cheuk et al., 2014).

For long time, PSO considered to be a Th1-mediated disease; however, recent studies have shown the important role of other T cell subsets, including Th17, Th22, Th9 and Treg cells in PSO (Jacek et al., 2016). Th1 produce IFNγ, which in turn induce MDCs to produce CCR6 ligand (CCL20) and secrete IL23 that recruit IL17 producing cells. IFNγ also has effect on KCs by up regulation of CXCL9, 10 and 11 genes. Recent study demonstrates CCR5+ IFNγ producing Th cells in advance PSO stages (Sgambelluri et al., 2016). Th17 characterized by the expression of IL-17A. IL-17F, IL-21, IL-22, TNF, GM-CSF.

Th17 seems to be the central player orchestrating PSO pathogenesis. They interact with KCs and endothelial cells and with various immune cells. The reactivation of memory Th17 cells is presumably responsible for the chronic course of PSO (Franziska et al., 2016). IL-17-induced KCs to produce AMPs, cytokines and various chemokines that create a positive feedback loop around the IL-23/Th17 axis and play role in amplifying the immune response in PSO (Lowes et al., 2013). IL-22 receptor complex expression observe in KCs and was upregulated by IFNγ, elevation of IL-22 levels has been seen in PSO, IL-22 associated with KCs activation and to the formation of acanthosis. IL-22 produce by Th22 in the absence of IL-17 (Marco et al., 2016). Th9 cells upon activation produce IL-9, which exerts an autocrine effect by inducing IL-9 production, and a paracrine effect by inducing IFNγ, IL-13, and IL-17 production by Th1, Th2, and Th17 cells (Schlapbach et al., 2014).

Failure of Treg to constrain the activation and proliferation of T cells seen in PSO. One of the treatment strategies goal is to correct Treg function or increase the Treg: pathogenic T cell ratio as seen with phototherapy (Mak et al., 2009).

Insult to the skin cause the release AMPs, such as LL37, S100 proteins and β-defensins by KCs. KCs also release IL-1 family cytokines including IL-1β and IL-18 that initiate the cutaneous inflammatory response to injury and involved in the differentiation of Th1 cells and Th17. IL-1β has several paracrine effects including the production of TNFα by local KCs and upregulation of selectins, which promote the skin infiltration and activation of T cells (Satveer et al., 2016).

The IL1β is a key inflammatory cytokine implicated in the pathogenesis of many inflammatory diseases. In PSO, IL-1β regulates chemokine expression and contributes to T-cell extravasation (Giulia et al., 2016). The role of IL1 in the pathogenesis of PSO suggested after it has been shown to be markedly increased in skin lesions of psoriatic patients, and effective treatment of PSO led to a significant decrease in epidermal IL-1β expression (Yelin et al., 2014). Most members of IL-1 family have been reported to be constitutively expressed by KCs and to be highly expressed in the psoriatic skin (Balato et al., 2013). Three polymorphisms in IL-1β have been reported, all representing di-allelic C–T base transitions, of these, the -511 C–T transition is considered the most important (Nikhil et al., 2015).

The IL-6 is produced by a wide range of cell types in psoriatic lesion (ex. KCs) in response to several stimuli, such as IL-1, TNFα, furthermore, KCs stimulated by IL-17 or IL-36 serve as a significant source of IL-6 (Andrea et al., 2014). IL6 is a pleiotropic cytokine that has a wide range of biological activities, including immune regulation, inflammation and it appears to be involved at different key points in the immune pathogenesis of PSO (Andreea et al., 2013). About 50 SNPs in the promoter region of the IL-6 gene have been identified, but the most studied SNP is that at position -174 (IL-6 -174G/C) which can modify transcription and cytokine levels (Nie et al., 2016).

The TNFα is produced by a variety of cells, including lymphocytes and KCs in the skin (Suzan., 2017). It is a pleiotropic cytokine, has multiple proinflammatory and costimulatory effects on a broad range of cell types, and have been shown to play pivotal roles in the pathogenesis of PSO (Fadhil et al., 2013). TNF-α gene is highly polymorphic, up to 44 SNPs reported. Of these, SNPs at positions -238 and -308 of the TNF-α promoter have been associated with response to anti-TNF-α biologics, levels of messenger RNA and protein production and have been associated with the severity of PSO (Gallo., 2012). The cells and mediators that participate in PSO as well as the interplay between innate and adaptive immune system are summarized in figures (1-6,7).

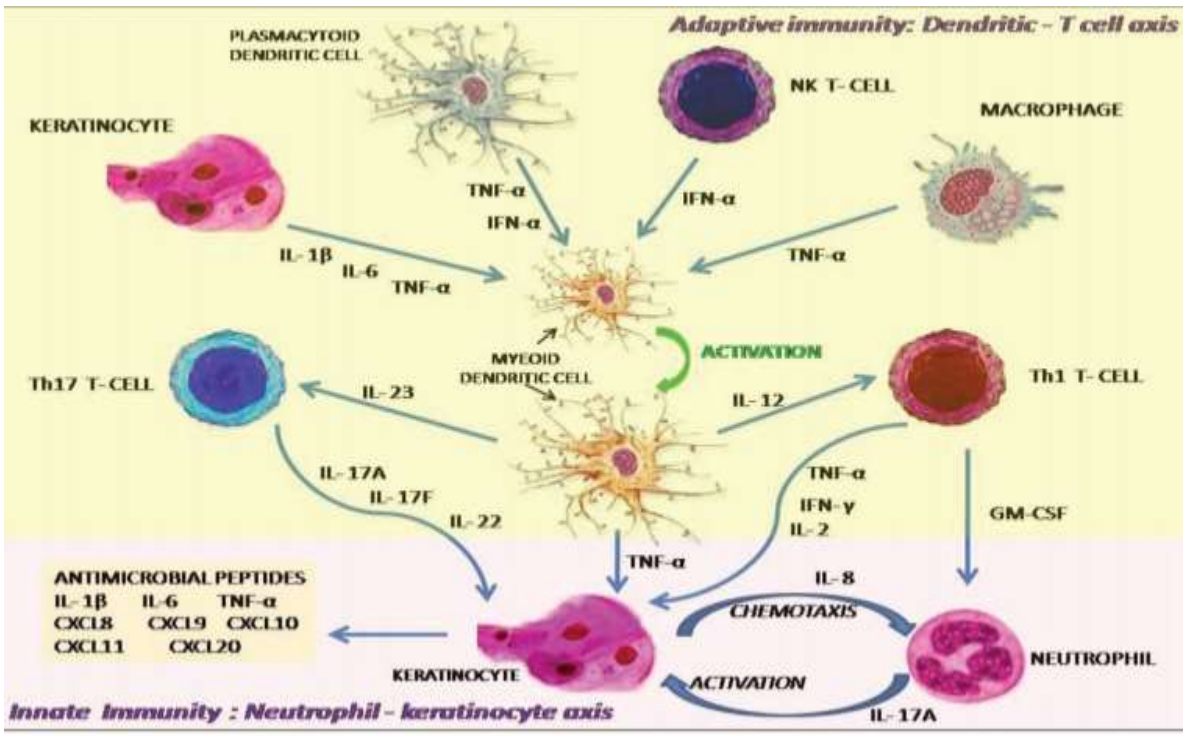


Figure 1-6: cells and mediators involved in Psoriasis (Aparajita and Saumya., 2017**).**

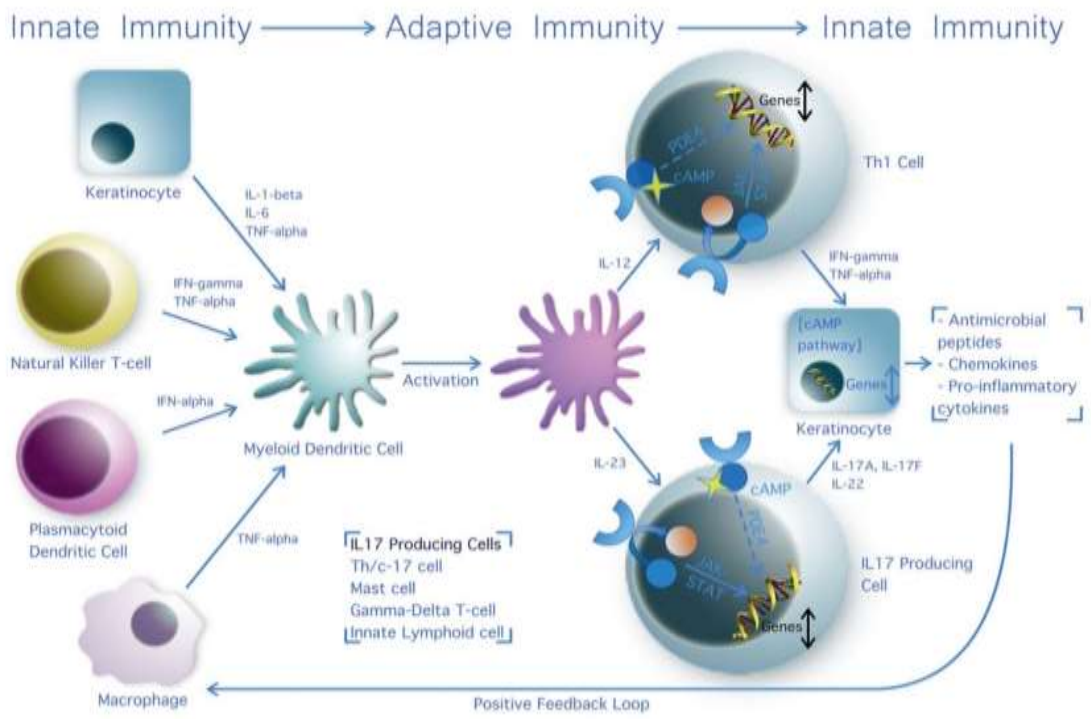


Figure 1-7: interplay between innate and adaptive immune system (Alwan and Nestle., 2015**).**

1.2.9. Diagnosis.

PSO diagnosis can be made clinically. Based on signs and symptoms. Though in cases with atypical clinical picture, a skin biopsy is necessary to performed (Zeljko et al., 2016). The diagnosis is depending on morphology, configuration and distribution of skin lesions (Shan., 2016). According to the Canadian PSO Guidelines Committee 2009, children's lesions are often smaller, thinner, and less scaly, compared to those in adults, which can make diagnosis more difficult.

1.2.10. Prognosis and Complication.

Psoriasis is a benign condition yet it is a lifelong illness with remissions and exacerbations, sometimes refractory to treatment. Although mild cases do not associate with increased risk of death, both men and women died earlier than their counterparts. several evidence indicate that PSO is associated with important systemic manifestations and comorbidities, the concept of "psoriatic march" has been introduced as an explanation to the systemic manifestation of the diseases (Boehncke et al., 2011).

The presence of the pro- inflammatory cytokines can contribute to initiation of other diseases by the deregulated trafficking of the immune cells, or due to secretion into the systemic circulation that modifying the function of the cells in different organs (Audrey et al., 2016). PSO comorbidity illustrated in figure (1-8).

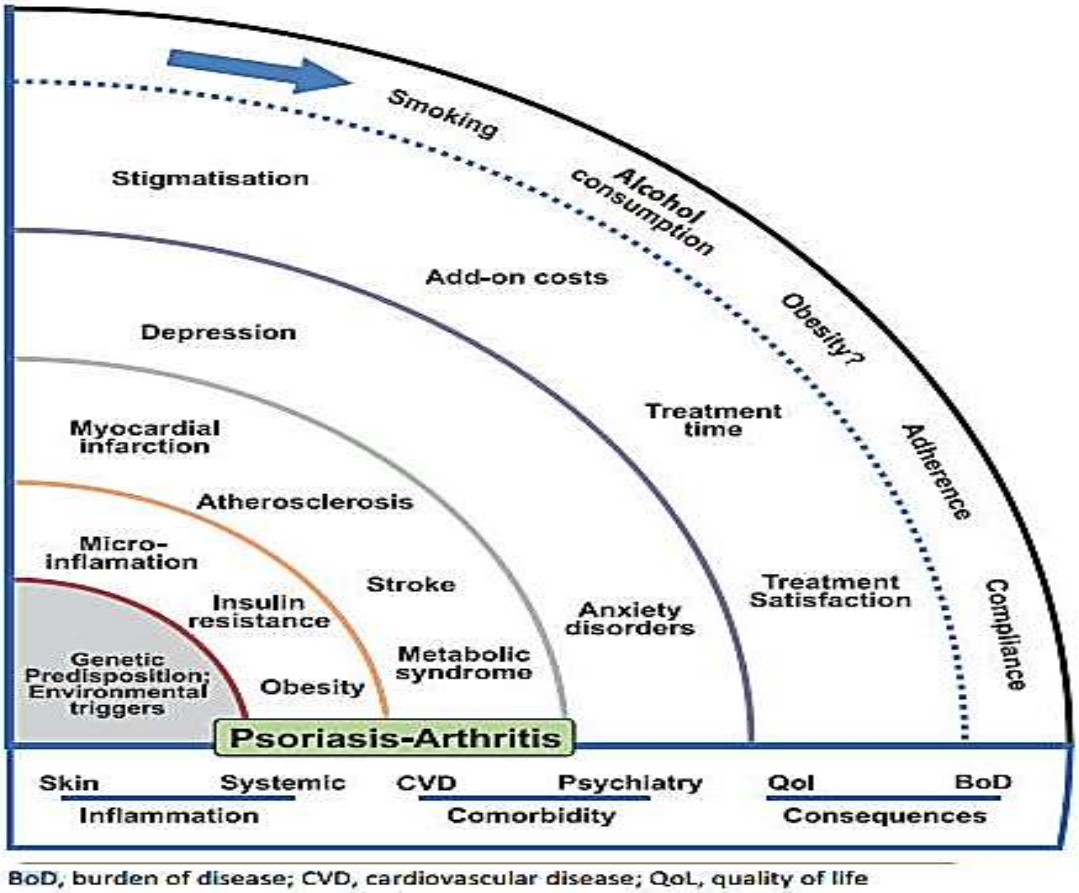


Figure 1-8: comorbidity of psoriasis (Mrowietz et al., 2014**).**

2.1. Materials.

2.1.1. Equipment and Instruments.

The equipment and instruments used in the current study have been summarized in the tables below (table 2-1,2,3).

Table 2-1: Equipment used in this study with their remarks.

No.	Equipment	Manufacturer
1	Disposable syringe (3ml)	AA-china
2	EDTA tube (K3)	AFCO-Jordan
3	Eppendorf tube	Sterilin-UK
4	Glass ware	
5	Gloves	Broche-Malaysia
6	Micropipette	Eppendorf -Germany
7	Tip	Sterilin-UK

Table 2-2: Chemicals used in this study with their remarks.

No.	Chemicals	Manufacturer
1	Agarose	Bromega-USA
2	DNA ladder-100 bp	Biolabs-NEW England
3	Ethanol	England
4	Ethidium bromide	Bromega-USA
5	Loading dye	Bromega-USA
6	TBE-buffer	Bromega-USA
7	Nuclease-free water	Biolabs-NEW England

Table 2-3: Instruments used in this study with their remarks.

No.	Instruments	Manufacturer
1	Deep freezer	GFL-Germany
2	Electrical balance	Sartorius-Germany
3	Gel electrophoresis	Consort-Belgium
4	Gel-documentation	Vision-UK
5	Micro centrifuge	Lab tech-Korea
6	PCR-work station	SCIE-PLAS-USA
7	Thermocycler	Sure cycler 8800-agilent tech
8	UV-spectrophotometer	APEL-Japan
9	Vortex	Stuart-UK
10	Water bath	Kottermann-Germany

2.1.2. DNA Extraction Kit.

A spin column kit from favorgen\Taiwan (favor prep genomic DNA mini kit) have been used in the current study. Kit contents listed in table (2-4).

Table 2-4: DNA Extraction Kit Contents.

No.	Contents
1	collection tube (2ml)
2	Elution buffer
3	FABG buffer
4	FABG column
5	FATG buffer
6	Proteinase K (provided)
7	RBC lysis buffer
8	W1 buffer
9	Wash buffer

The principle of SSP-PCR is that the perfectly match primer at its 3' end will be more efficient than primer with mismatch at 3' end in PCR reaction *(Khalda et al., 2010).* In case of HLA investigation by using PCR and in order to check for false negative, a positive internal control primer with a known amplicon size was run with each sample *(Aditi et al., 2016).* The negative control tube which contain all contents except target DNA were included in each run to check for false positive.

2.1.3. Polymerase Chain Reaction Primers.

Sequence specific primers (SSP-PCR) for polymorphic alleles of selected target prepared according to manufacturer and aliquot as a stock and working conc. The sequence for each primer listed in table (2-5).

Table 2-5: Primer Sequence with their product size and references.

No.	Target	Sequence 5'-3'	Tm (c°)	Product size	References
1	HLA-cw6 F	GGATCAGGACGAAGTCCCAG	59.5	170 bp	NCBI/ primer-BLAST
2	HLA-cw6 R	GGGGACGCGTCATGAGTATT	59.9		
3	HLA-cw7 F	TTA CAT CGC CCT GAA CGA GG	59.8	237 bp	NCBI/ primer-BLAST
4	HLA-cw7 R	GGC CAT CCC GGG AGA TCT AT	60.6		
5	HLA-cw17 F	GGA TGA GGG GTC ATG TGT CT	59.9	400 bp	NCBI/ primer-BLAST
6	HLA-cw17 R	AGT AAG TGC TGG CAC ACA GG	59.9		
7	IL1β F	CTC ATC TGG CAT TGA TCT GG	57.8	215 bp	HUNT et al., 2000
8	IL1β R1	GGT GCT GTT CTC TGC CTC G	61.9		
9	IL1β R2	GGT GCT GTT CTC TGC CTC A	59.7		
10	IL6 F	GAG CTT CTC TTT CGT TCC	55.0	234 bp	Ahmad et al., 2015
11	IL6 R1	CCT AGT TGT GTC TTG CC	54.6		
12	IL6 R2	CCC TAG TTG TGT CTT GCG	57.3		
13	TNFα F	CTG CAT CCC CGT CTT TCT CC	61.9	863 bp	Ahmad et al., 2015
14	TNFα R1	ATA GGT TTT GAG GGG CAT CG	57.8		
15	TNFαR2	ATA GGT TTT GAG GGG CAT CA	55.8		
16	GAPDH F	AGA CCA CAG TCC ATG CCA TC	59.9	498 bp	NCBI/ primer-BLAST
17	GAPDH R	CAG GGC CCT TTT TCT GAG CC	61.9		

During the current study a primer with specific sequence for glyceraldehyde 3 phosphate dehydrogenase was use as a control primer, as the GAPDH is a wildly-used housekeeping gene (*Emanuela et al., 2013).*

For primer sequence from NCBI/ primer-BLAST, several criteria have been taking into account before picking-up the primer pair including GC content, nearly closed TM, unique amplicon size, and finally under the heading of primer specificity "Primer pairs are specific to input template as no other targets were found in selected database"

2.1.4. Master Mix Kit.

A premixed ready to use (GOTaq G2 green master 2X) promega\USA master mix employed in this work, with its contents illustrated in table (2-6).

Table 2-6: Master Mix Kit Contents

No.	Ingredients
1	dNTP 400 µm
2	GOTaq G2 DNA polymerase
3	Green GOTaq G2 reaction buffer
4	$Mgcl_2$ 3 mM

2.1.5. Molecular Size Marker.

A quick-load 100 bp (ready to use, loading dye incorporated) DNA ladder used to validate the specific molecular size target in tested sample. It consists of 12 different DNA molecule with different sizes that give 12 bands to cover a range of molecular size from 100 bp to 1500 bp. For easy identification, the manufacturer makes the 500 bp and 1000 bp band brighter than others.

2.2. Methods.

2.2.1. Study Design.

According to the statistical formula for calculation of minimum sample size {sample size = $Z^2*p(1-p)/d^2$} where Z (level of confidence=1.96), p(prevalence) and d (margin of error= 0.05). and by depending 2% as general prevalence of psoriasis, minimal sample size equal to 30. Only type I psoriasis patients were involve with a psoriasis free first degree relative if possible.

A questioner for each participant after formal and informal consent have been filled according to several parameters (age, gender, habitat, and smoking) while (age of first attach, number of family member affected, severity) specially for patients. All the non-relative controls in current study were neither had a psoriasis nor had a family history of psoriasis.

2.2.2. Inclusion and Exclusion Criteria.

The patients that has been firstly diagnosed by a dermatologist as suffering from plaque type psoriasis before 40 years' old, psoriasis free first degree relative to type I psoriasis patients and psoriasis free, family history free apparently healthy control are included in this study.

Any patient with other psoriasis phenotypes, first degree relative to patients with psoriasis phenotypes other than plaque type and apparently healthy control with positive family history for any type of psoriasis are excluded from this study.

2.2.3. Sample Setting.

This is a prospective case control study comprised seventy-six patients diagnosed by dermatologist, selected from those visited the dermatology clinic in Al-Zahra teaching hospital in Al-Kut city from February to august 2017, based on the age of first attach (been less than 40 years) of chronic plaque psoriasis. And a match eighty-seven apparently healthy persons as a control, from whom about thirty-six been first degree relative to those patients.

A venous blood sample (2 ml) toke from each patients and controls in K3-EDTA anticoagulated tube and stored at -20c°, until a batch of these samples subjected to a DNA extraction procedure. After that, the extracted DNA that fulfil the required purity and concentration aliquot and stored at -20c° for polymerase chain reaction amplification and detection.

2.2.4. Preparation of Solution.

- TBE buffer: one Litter of (10x) TBE buffer provided by the manufacturer, 100 ml working solution prepare by adding 90 ml deionized DW to 10 ml stock solution.

- DNA stain: ten ml of ready to used ethidium bromide solution provided by the manufacturer. 5 µl of ethidium bromide added to the dissolved gel before pouring into gel tray.

- Loading dye: ready to used loading dye provided by the manufacturer, 5 µl extracted DNA added to 1 µl loading dye, mixing by pipetting, then 5 µl of mixture loaded into the well in the gel.

2.2.5. preparation of primers.

The primers provided in lyophilized form. Each primer dissolve in specific volume of deionized DW designated by the manufacturer to prepare stock solution at conc. 100 pmol/µl. Then working solution at conc. 10 pmol/µl prepared in volume calculated according to number of sample being tested.

2.2.6. DNA extraction.

The extraction protocol (for frozen blood) has been done according to the manufacturer's instruction (favorgen) genomic DNA mini kit.

Special protocol (for frozen blood):

Step 1-Sample preparation

1-up to 200µl blood in 1.5 ml micro-centrifuge tube.

2-add 30µl proteinase K (10 mg/ml). incubate for 15 min at 60c◦.

Step 2-cell lysis

1-add 200µl FABG buffer, vortex.

2- incubate at 70c◦ water bath for 15 min, invert every 3 min.

Step 3-binding

1- add 200µl ethanol (96%), vortex for 10 sec.

2-place FABG column into 2 ml collection tube, transfer the mixture, centrifuge at full speed for 5 min. discard the collection tube. Then place the FABG column in new collection tube.

Step 4-washing

1- wash by 400µl W1 buffer, centrifuge at full speed for 30 sec.

2-place FABG column in new collection tube, wash by 600µl wash buffer, centrifuge at full speed for 30 sec.

3- use new collection tube, centrifuge at full speed for 3 min.

Step 5-elution

1- place the dry FABG column in 1.5 micro-centrifuge

2- add 100µl preheated elution buffer, stand for 3-5 min

3- centrifuge at full speed for 30 sec.

Store the DNA fragment at 4◦c or -20◦c.

Then the following steps followed to ensure the quality and quantity of the extracted DNA.

I. 5µl of extracted DNA mixed with 1µl of loading dye and then 5µl of mixture loaded to 2% agarose gel with ethidium bromide, undergo electrophoresis (60 volts for 1hr) to indicate The presence of DNA.

II. Measuring the DNA conc. By using UV spectrophotometer according to the following formula (DNA conc. $=A_{260}$ *DF*50). The average conc. was 72 µg/ml. while the DNA purity calculated as follow (A_{260}/A_{280}) with an average 1.6.

2.2.7. Polymerase Chain Reaction.

A 25 µl reaction volume mix prepared according to the premixed kit leaflet with some differences between reaction that involve control primer and that without. As shown in table (2-7,8).

Table 2-7: Reaction Mix Contents in Reaction with Control Primer.

No.	Components	Volume
1	GOTaq G2 green master mix 1x	12.5 µl
2	Primer F (control)	1.0 µl
3	Primer R (control)	1.0 µl
4	Primer F (target)	1.25 µl
5	Primer R (target)	1.25 µl
6	DNA templet	2.5 µl
7	Nuclease-free water	5.5 µl

Table 2-8: Reaction Mix Contents in Reaction Without Control Primer.

No.	Components	Volume
1	GOTaq G2 green master mix 1x	12.5 µl
2	Primer F (target)	1.25 µl
3	Primer R (target)	1.25 µl
4	DNA templet	2.5 µl
5	Nuclease-free water	7.5 µl

2.2.7.1. Thermocycling.

A plenty of authors declare that each lab has to have its own thermocycler condition because the efficiency of each thermocycler will be effected by time. In this study several optimizations have been done until a sharp band on gel gained. One of these optimization is the touchdown PCR *(Darren and John., 2008).* based on the "rule of thumb" of *don et al.,1991* started with high Ta, reduced by 1c°every 2cycle for first cycles, then completed with appropriate Ta for the last cycles. So in current study the first 14 cycles start with (Ta+7). while the last 19 cycles with the exact Ta. A negative control tube included in all protocol in which all contents are present except target DNA.

PCR protocols (based on online optimase protocol writer-edited-).

HLA- CW6: (locally prepared)

Step 1: 95 c°- 2 min
Step 2: 95 c°- 30 sec
Step 3: 65.3 to 58.3 c°- 30 sec
Step 4: 72 c°- 30 sec (14 cycles)
Step 5: 95 c°- 30 sec
Step 6: 58.3 c°- 30 sec
Step 7: 72 c°- 30 sec (19 cycles)
Step 8: 72 c°- 5 min
Step 9: 4 c° forever

HLA- CW7: (locally prepared)

Step 1: 95 c°- 2 min
Step 2: 95 c°- 30 sec
Step 3: 67.3-60.3 c°- 30 sec
Step 4: 72 c°- 30 sec (14 cycles)
Step 5: 95 c°- 30 sec
Step 6: 60.3 c°- 30 sec
Step 7: 72 c°- 30 sec (19 cycles)
Step 8: 72 c°- 5 min
Step 9: 4 c° forever

HLA- CW17: (locally prepared)

Step 1: 95 c°- 2 min
Step 2: 95 c°- 30 sec
Step 3: 66.3-59.3 c°- 30 sec
Step 4: 72 c°- 30 sec (14 cycles)
Step 5: 95 c°- 30 sec
Step 6: 59.3 c°- 30 sec
Step 7: 72 c°- 30 sec (19 cycles)
Step 8: 72 c°- 5 min
Step 9: 4 c° forever

PCR protocol for IL1β: **(locally prepared)**

Step 1: 96 c°- 2 min
Step 2: 96 c°- 30 sec
Step 3: 63.1-56.1 c°- 30 sec
Step 4: 72 c°- 30 sec (14 cycles)
Step 5: 95 c°- 30 sec
Step 6: 56.1 c°- 30 sec
Step 7: 72 c°- 30 sec (19 cycles)
Step 8: 72 c°- 5 min
Step 9: 4 c° forever

PCR protocol for IL6 (***Ahmad et al., 2015)***

Step 1: 96 c°- 3 min
Step 2: 95 c°- 30 sec
Step 3: 54 c°- 60 sec
Step 4: 72 c°- 60 sec (30 cycles)
Step 5: 72 c°- 7 min
Step 6: 4 c° forever

PCR protocol for TNFα (*Ahmad et al., 2015)*

Step 1: 96 c°- 3 min
Step 2: 96 c°- 45 sec
Step 3: 55 c°- 80 sec
Step 4: 72 c°- 2 min (30 cycles)
Step 5: 72 c°- 3 min
Step 6: 4 c° forever

2.2.7.2. Interpretation of Results.

Gel electrophoresis technique used to detect the PCR product, any band corresponding to the desired molecular size of target considered positive result. A 2% agarose gel have been prepared as follow

1) A gel-casting tray placed onto a gel-casting base, inserting a comb and level the base.
2) Preparing 2% agarose by weighting out 1 g of agarose powder and dissolving it in 50ml of 1x TBE buffer. then dissolved by heating in microwave oven.
3) Cooled the melted agar to about 60 °C, and then adding 5 µl of ethidium bromide.
4) Pouring the melted agarose into the gel-casting tray& allow the gel to solidify at room temperature.
5) Removing the comb from the frame.

6) Then the tray placed into the electrophoresis chamber with the wells at the cathode side.
7) The chamber filled with buffer at a level that can cover the top of the gel.

2.2.7.3. Electrophoresis Procedure.

1) loaded molecular size marker to the first well of the agarose gel.
2) Pipetting 5µl of the PCR product to the well.
3) The last well receive the negative control (target DNA omitted).
4) Close the lid on chamber and attach the electrodes. running the gel at 60V for 60 min.
5) Visualizing presence of marker and PCR product bands and document gel picture with a Gel-documentation.

2.3. Statistical Analysis.

All data are normally distributed and recorded in a Microsoft excel spreadsheet, Statistical analysis carried out with the SPSS v 0.17 software (chi-square) after translated data into codes. Suitable statistical methods used in order to analyze and assess the results. The level of significance considered when P value less than 0.05 (≤0.05).

3.1. Study Groups.

Current case-control study includes 163 participants, classified into two groups. Psoriatic group involve 76 patients and a match apparently healthy group comprise 87 persons as control. The control group subdivided into 36 psoriatic free relatives to psoriatic patients and 51 neither psoriatic nor have a family history of PSO. As shown in figures (3-1)

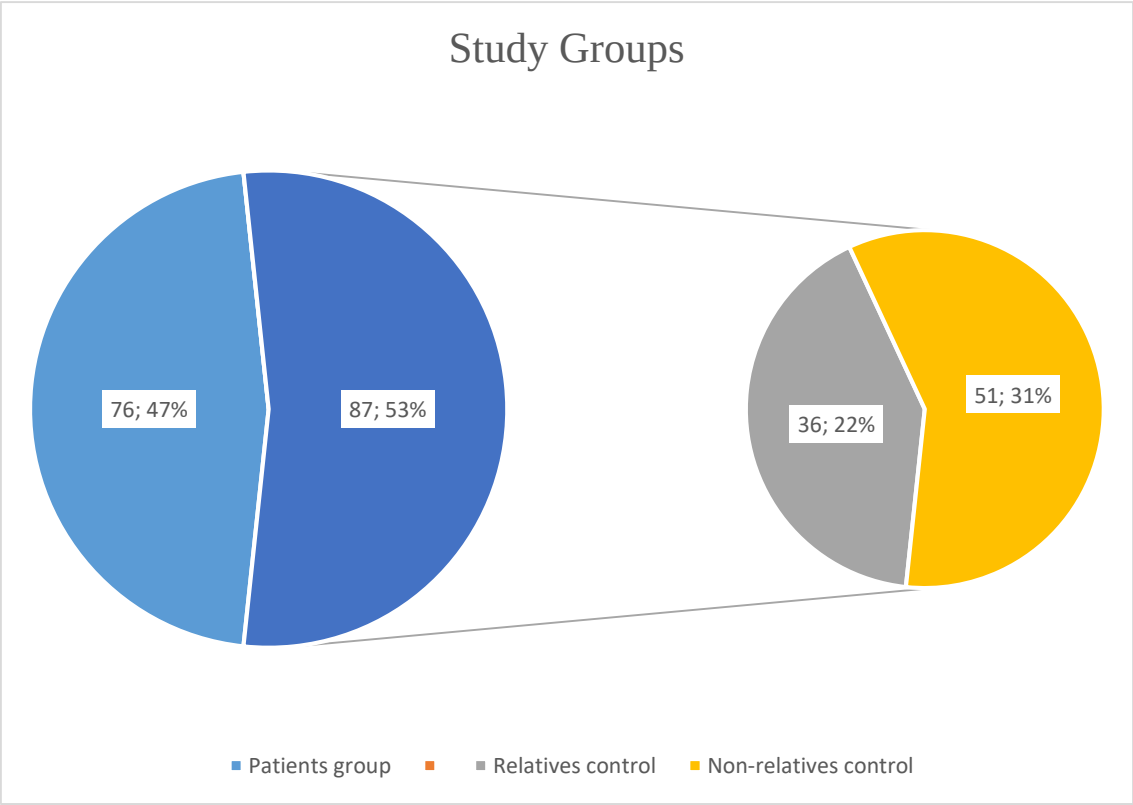


Figure 3-1: Frequency of participants (patients and control).

3.1.1. Distribution of Type I Psoriatic Patients and Control According to Some Demographic Traits.

According to age, all patients included in this study have to have first attack of PSO before 40 years old (Type I). The mean age for patients is 26.2 years. Compared to 29.7 and 33.6 years of non-relatives and relatives respectively. The male and female frequencies not highly differ in psoriatic patients, accounting about 47.4%, 52.6%, while accounting 45.1%, 54.9% in non-relatives group and 55.6%, 44.4% in relatives. About 84.2% of psoriatic patients' resident in an urban location while only 15.8% with rural residency. All data about demographic traits of participant shown in table (3-1).

Table 3-1: Description of Patients with Type I Psoriasis and Control According to Age, Gender and Residency.

Variables		Control group		
	Patients n=76	Relatives n=36	Non relatives n=51	*p-value
Age yrs. (mean)	26.2	33.6	29.7	
Gender (NO.)%				
Males	(36) 47.4	(20) 55.6	(23) 45.1	0.4
Females	(40) 52.6	(16) 44.4	(28) 54.9	
Residence (NO.)%				
Urban	(64) 84.2	(35) 97.2	(46) 90.2	0.06
Rural	(12) 15.8	(1) 2.8	(5) 9.8	

*Chi-square test, p-value

3.1.2. Distribution of Type I Psoriatic Patients According Age Groups.

The results indicated that the age group >30 were more susceptible to type I psoriasis than other group, it account (39%) of patients, followed by (23.7%) and (22.4%) in 21-30 and 11-20 age group respectively, while age group <10 account only (14.5%). As shown in table (3-2).

Table 3-2: Age Groups of Patient with Type I Psoriasis.

Age groups	(NO.) %
< 10 years	**(11) 14.5**
11-20 years	**(17) 22.4**
21-30 years	**(18) 23.7**
> 30 years	**(30) 39.4**
Total	**(76) 100**

Mean age 26.20 years. (SD: 13.8, SE: 1.58).

3.1.3. The Riske of Smoking Among Type I Psoriatic Patients and Control.

About 15% of patients found to be smoker and about 41% of relatives to some psoriatic patients also smoke. In compare to 25% smoker in non-relative group. A statistical significance differences was found between patients and relative groups (p-value < 0.05). As shown in table (3-3).

Table 3-3: Distribution of Patients with type I psoriasis and Control Group According to Smoking Behavior.

Sample	Smoking behavior			
	Smoker (no.)	Nonsmoker	*OR	**Sig.
Patients(Pts.)	(12) 15.8	(64) 84.2	Pts. vs. NR 0.5	0.1
Relatives(Rel.)	(15) 41.7	(21) 58.3	Pts. vs. Rel 0.2	0.003
Nonrelatives(NR.)	(13) 25.5	(38) 74.5		
Total n=163				
* Odds Ratio, **Chi-square test, p-value				

OR=ad/bc. where a for positive patients, b for negative patients, c for control positive and d for control negative.

3.1.4. Distribution of Type I Psoriatic Patients According to Family History.

Psoriatic patient classification according to family history reveal that 40 patients (53%) present with positive family history and 36 patients (47%) with psoriatic free family history. As shown in figure (3-).

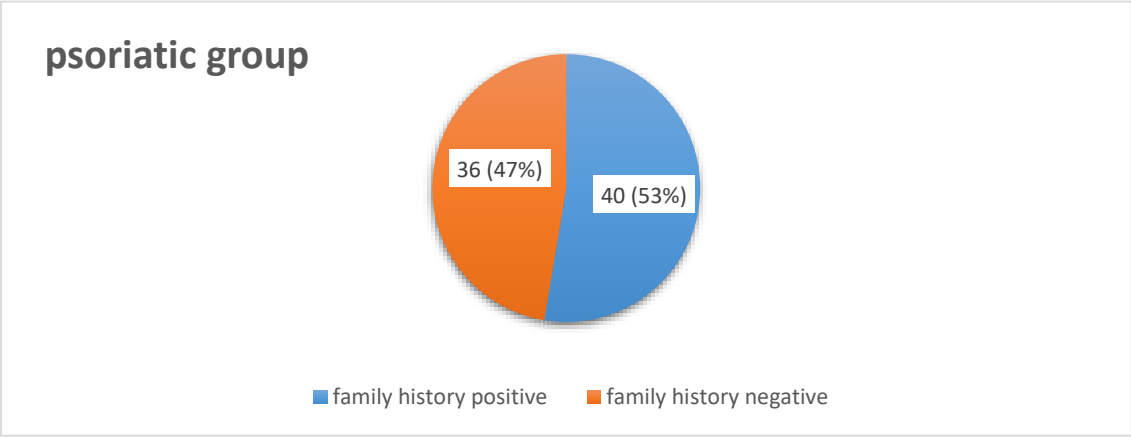


Figure 3-2: Classification of Patients According to Family History.

3.1.5. Distribution of Type I Psoriatic Patients According to Severity.

Psoriatic patients stratified into three group based on body surface area affected that has been evaluated by dermatologist and design as mild, moderate and sever. As it shown in table (3-4).

Table 3-4: Classification of type I Psoriatic Patients According to Severity.

Severity	Body surface area (BSA)	(no.)%
Mild	< 3%	(36) 47.3
Moderate	3%-10%	(16) 21.0
Sever	>10%	(24) 31.5
Total		(76) 100

3.2. HLA Typing in Type I Psoriatic Patients and Control.

A low resolution SSP-PCR techniques used in current study, in order to stratified the participants into positive or negative regarding to *CW6*, *CW7* and *CW17*. While negative patients haven't neither CW6, CW7 nor CW17 alleles. Positive patients have at least one allele, as the technique cannot distinguish between homogenous and heterogonous state. Agarose gel detection of PCR products for selected HLA alleles shown in figure (3-4).

3.2.1. *HLA-CW6* Allele Detection.

About 18% of psoriatic patients show the presence of *CW6* allele. In compared to about 8% and 2% in relatives and non-relatives respectively. A statistical significance differences found between patient and non-relatives (p-value < 0.05). According to our results, *CW6* increase the risk of PSO eleven times (OR 11.3). As shown in table (3-5).

Table 3-5: Distribution of *CW6* Allele Among Type I Psoriatic Patients and Control.

Samples	*Cw6+* (no.)%	*Cw6-* (no.)%	*OR	**Sig
Patients n=76	(14) 18.4	(62) 81.6	Pts. vs. NR 11.3	0.002
Relatives n=36	(3) 8.3	(33) 91.7	Pts. vs. Rel 2.5	0.1
Non-relatives n=51	(1) 1.96	(50) 98.03		
Total n=163				
* Odds Ratio, **Chi-square test, p-value				

3.2.2. *HLA-CW7* Allele Detection.

The *CW7* allele detected in 26% of patients and in lower percentage in both relatives (11%) and non-relatives (5%). *CW7* increase the risk of PSO about five times (OR 5.7). Statistical significance differences found between patients versus relatives and patients versus non-relatives. As shown in table (3-6).

Table 3-6: Distribution of *CW7* Allele Among Type I Psoriatic Patients and control.

Samples	*Cw7+* (no.)%	*Cw7-* (no.)%	*OR	**Sig
Patients n=76	(20) 26.3	(56) 73.7	Pts. vs. NR 5.7	0.002
Relatives n=36	(4) 11.1	(32) 88.9	Pts. vs. Rel 2.8	0.05
Non relatives n=51	(3) 5.9	(48) 94.1		
Total n=163				
* Odds Ratio, **Chi-square test, p-value				

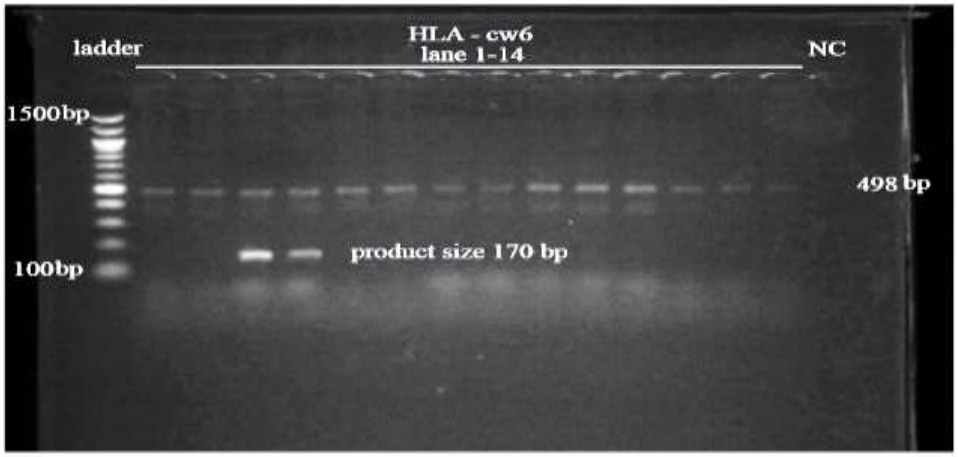
3.2.3. *HLA-CW17* Allele Detection.

A non-statistical significance difference found neither between patients and relatives nor between patients and non-relatives (p-value > 0.05). *CW17* allele detected in 31%, 38% and 29% in patients, relatives and non-relatives respectively. As shown in table (3-7).

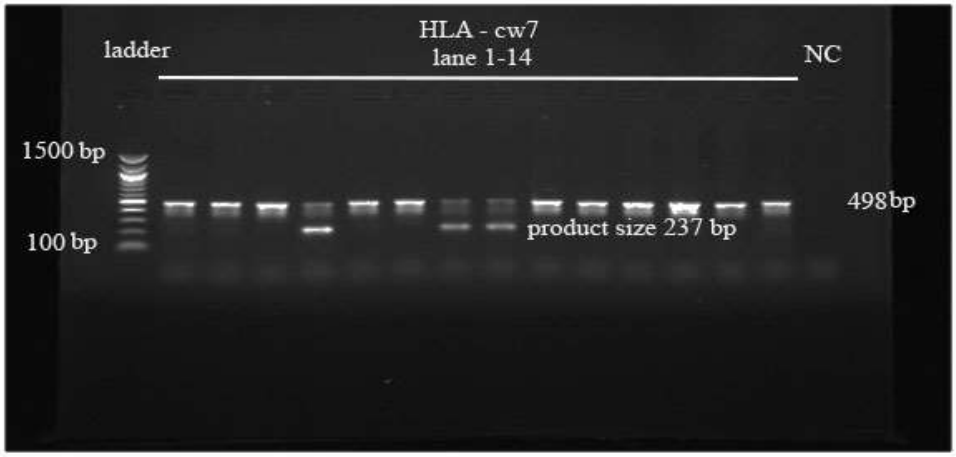
Table 3-7: Distribution of *CW17* Allele Among Type I Psoriatic Patients and Control.

Sample	*Cw17+* (no.) %	*Cw17-* (no.) %	*OR	**Sig
Patients (Pts.) n=76	(24) 31.6	(52) 68.4	Pts. vs. NR 1.1	0.5
Relatives (Rel.) n=36	(14) 38.9	(22) 61.1	Pts. vs. Rel. 0.7	0.3
Non relatives n=51	(15) 29.4	(36) 70.6		
Total n=163				
* Odds Ratio, Chi-square test, **p-value				

(A)



(B)



(C)

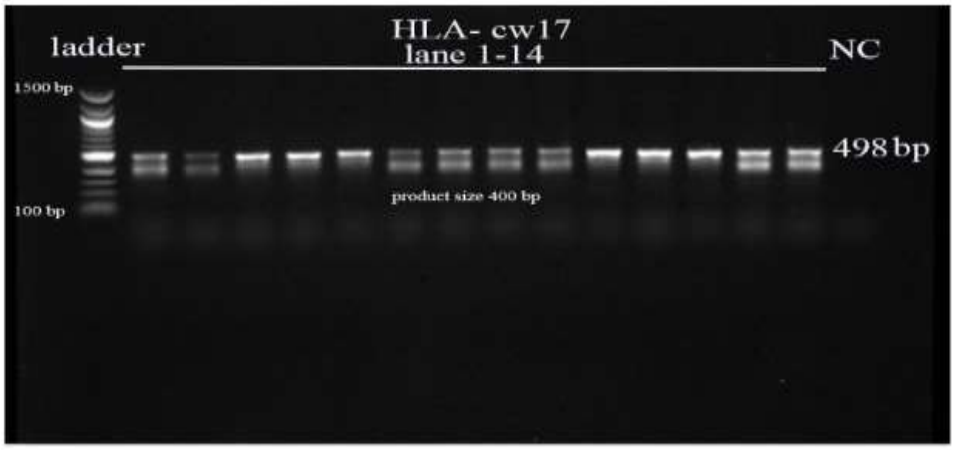
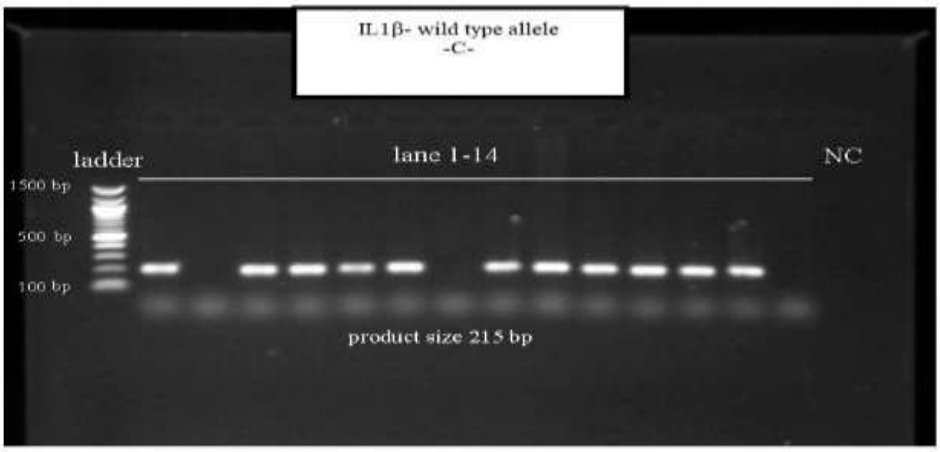


Figure 3-3: Gel Electrophoresis for PCR Products (HLA). All three procedures include control primer with 498 bp molecular size. (A) *CW6* with molecular size 170 bp. (B) *CW7* with molecular size 237 bp. (c) *CW17* with molecular size 400 bp. The desire molecular size validated by comparing to 100 bp molecular ladder.

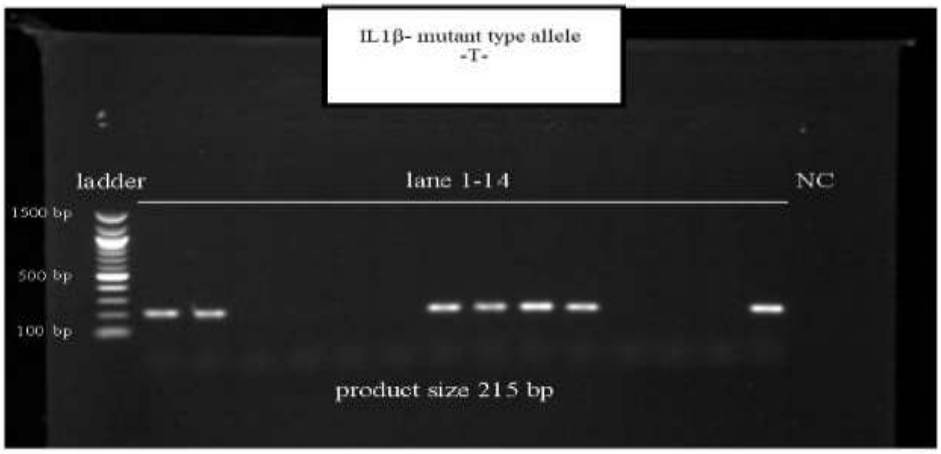
3.3. Single Nucleotide Polymorphism (SNPs) Detection for IL1β, IL6 and TNFα Among Type I Psoriatic Patient and Control.

The SSP-PCR technique employed for detection of SNPs, that use three primers for each SNP, one common forward primer and two reverse primers that differ at 3' with only one nucleotide. It depends on the 3' end discrimination of each of reverse primer for different allele. The perfectly match end allow amplification, while the unmatched end lead to amplification failure. Final result shown in figure (3-5).

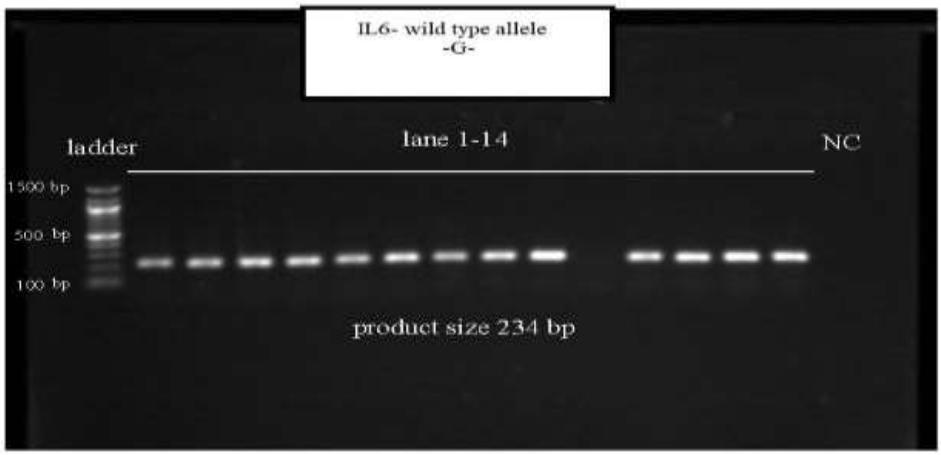
(A)


IL1β- wild type allele
-C-
ladder
lane 1-14
NC
1500 bp
500 bp
100 bp
product size 215 bp

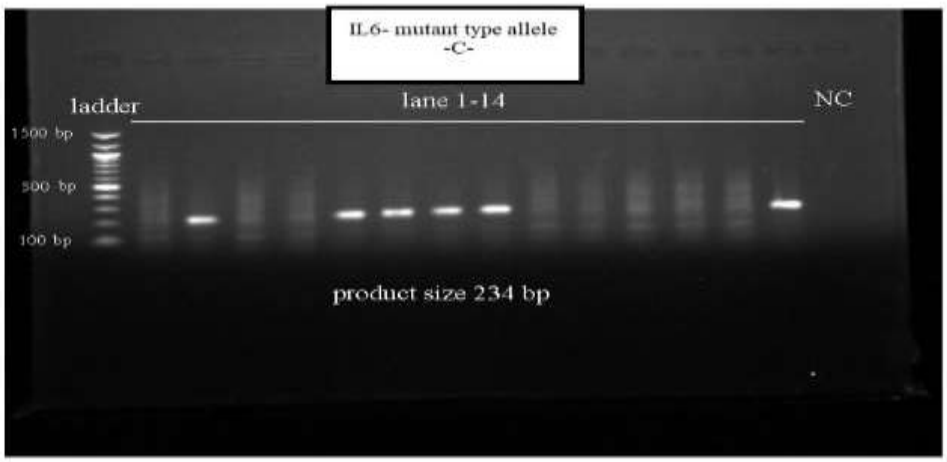
(B)


IL1β- mutant type allele
-T-
ladder
lane 1-14
NC
1500 bp
500 bp
100 bp
product size 215 bp

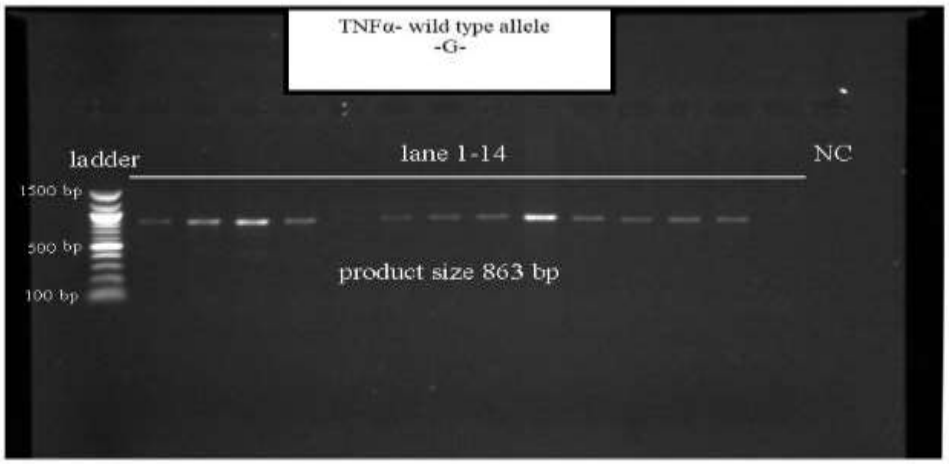
(c)


IL6- wild type allele
-G-
ladder
lane 1-14
NC
1500 bp
500 bp
100 bp
product size 234 bp

(D)



(E)



(F)

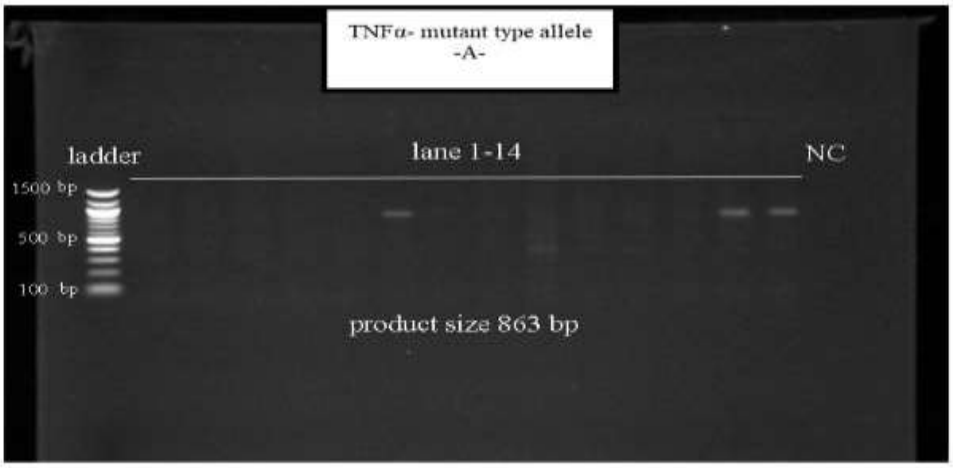


Figure 3-4: Gel Electrophoresis for PCR Products (cytokines). A- allele C for *IL1β* -511 C/T. B- allele T for IL1β -511 C/T. C- allele G for *IL6* -174 G/C. D- allele C for IL6 -174 G/C. E- allele G for *TNFα* -308 G/A. F- allele A for TNFα -308 G/A. The desire molecular size validated by comparing to 100 bp molecular ladder.

Statistical significance differences found for all three SNPs between patients and non-relatives (p-value <0.05). But non statistical significance differences between patients and relatives. As shown in table (3-8).

Table 3-8: Frequencies of Selected Cytokines SNPs in Type I Psoriatic Patients and Control.

Sample	Present (no.) %	Absent (no.) %	*OR	**Sig
IL-1β **snip**				
Patients n=76	**(41) 53.9**	**(35) 46.1**	**Pts. vs. NR 2.1**	**0.03**
Relatives n=36	**(21) 58.3**	**(15) 41.7**	**Pts. vs. Rel 0.8**	**0.4**
Non relatives n=51	**(18) 35.3**	**(33) 64.7**		
Total n=163				
IL-6 **snip**				
Patients n=76	**(25) 32.9**	**(51) 67.1**	**Pts. vs. NR 7.8**	**0.0001**
Relatives n=36	**(8) 22.2**	**(28) 77.8**	**Pts. vs. Rel 1.7**	**0.2**
Non relatives n=51	**(3) 5.9**	**(48) 94.1**		
Total n=163				
TNFα **snip**				
Patients n=76	**(15) 19.7**	**(61) 80.3**	**Pts. vs. NR 3.9**	**0.02**
Relatives n=36	**(5) 13.9**	**(31) 86.1**	**Pts. vs. Rel 1.5**	**0.3**
Non relatives n=51	**(3) 5.9**	**(48) 94.1**		
Total n=163				
*** Odds Ratio, **Chi-square test, p-value**				

3.3.1. *IL1β* -511 C/T Allele and Genotypes Frequency Among Type I Psoriatic Patients and Control.

The frequency of T allele was significantly higher in patients than non-relatives, and considered as risk factor (p-value 0.006, OR 2.12 and EF 0.19). while the C allele significantly seen at higher frequency in non-relatives (p-value 0.006). The CC genotype seen in higher frequency in non-relatives than patients, with a statistical significance (p-value 0.02). Non statistical significance differences at the allele and genotypes level between patients and relatives. As shown in table (3-9).

Table 3-9: *IL1β* Allele and Genotypes Frequencies in Type I Psoriatic Patients and Control.

IL1 β	Genotype/ allele	Patients (76)	Non relatives (51)	p-value	*OR	**EF	***PF
Genotypes (no.) %	CC	(35) 46.0	(34) 66.6	0.02	0.4		1.73
	CT	(26) 34.2	(12) 23.5	0.13	1.7		
	TT	(15) 19.7	(5) 9.8	0.10	2.3		
Allele (no.) %	C	(96) 63.1	(80) 78.4	0.006	0.5		2.33
	T	(56) 36.8	(22) 21.5	0.006	2.12	0.19	

IL1β	Genotype/ allele	Patients (76)	Relatives (36)	p-value	OR	EF	PF
Genotypes (no.) %	CC	(35) 46.0	(15) 41.6	0.4	1.2		
	CT	(26) 34.2	(12) 33.3	0.5	1.0		
	TT	(15) 19.7	(9) 25.0	0.3	0.7		
Allele (no.) %	C	(96) 63.1	(42) 58.3	0.3	1.2		
	T	(56) 36.8	(30) 41.6	0.3	0.8		

* Odds Ratio ** EF: etiological fraction *** PF: preventive fraction

3.3.2. *IL6* -174 G/C Allele and Genotypes Frequency Among Type I Psoriatic Patients and Control.

The C allele significantly increase in patients compared to non-relatives and can be consider as risk factor for PSO (p-value 0.000, OR 9.15 and EF 0.18). The CC genotype completely absent from non-relatives (p-value 0.01) and can associate with increase susceptibility to PSO. The G allele higher in non-relatives (p-value 0.00). While the GC genotype seen with high frequency in patients compared to non-relatives and also increase risk of PSO (p-value 0.001, OR 4.6 and EF 0.17). The GG genotype significantly higher in non-relatives (p-value 0.00). Non statistical significance differences between patients and relatives at the allele or genotype level. As shown in table (3-10).

Table 3-10: *IL6* Allele and Genotypes Frequencies in Type I Psoriatic Patients and Control.

IL6	Genotype/ allele	Patients (76)	Non relatives (51)	p-value	*OR	**EF	***PF
Genotypes (no.) %	CC	(8) 10.5	(0) 0.0	0.01	-	-	
	GC	(17) 22.3	(3) 5.8	0.001	4.6	0.17	
	GG	(51) 67.1	(48) 94.1	0.000	0.13		14.2
Allele (no.) %	C	(33) 21.7	(3) 2.9	0.000	9.15	0.18	
	G	(119) 78.2	(99) 97.0	0.000	0.1		32.6
IL6	Genotype/ allele	Patients (76)	Relatives (36)	p-value	OR	EF	PF
Genotypes (no.) %	CC	(8) 10.5	(1) 2.7	0.1	4.1		
	GC	(17) 22.3	(7) 19.4	0.5	1.2		
	GG	(51) 67.1	(28) 77.7	0.2	0.6		
Allele (no.) %	C	(33) 21.7	(9) 12.5	0.07	2.0		
	G	(119) 78.2	(63) 87.5	0.07	0.5		

* Odds Ratio ** EF: etiological fraction *** PF: preventive fraction

3.3.3. *TNFα* -308 G/A Allele and Genotypes Frequency Among Type I Psoriatic Patients and Control.

A non-statistical significance found between patients and relatives. But significance differences with non-relatives found. The A allele seen in high frequency in patients compared to non-relatives (11% vs 3%). The A allele considers a risk factor for PSO (p-value 0.01, OR 4.1 and EF 0.08). while the G allele significantly seen in higher frequency in non-relatives than patients (97% vs 88%) (p-value 0.01). The AA genotype completely absent in non-relatives and may increase susceptibility to PSO. The GA genotype significantly increase in patients than non-relatives, and consider a risk factor for PSO (p-value 0.04, OR 3.4 and EF 0.12). On the other hand, the GG genotype significantly higher in non-relatives than patients (p-value 0.02). As shown in table (3-11).

Table 3-11: *TNFα* Allele and Genotypes Frequencies in Type I Psoriatic Patients and Control.

TNFα	Genotype/ allele	Patients (76)	NR (51)	p-value	*OR	**EF	***PF
Genotypes (no.) %	AA	(2) 2.6	(0) 0.0	0.4	-	-	
	GA	(13) 17.1	(3) 5.8	0.04	3.4	0.12	
	GG	(61) 80.2	(48) 94.1	0.02	0.2		16.8
Allele (no.) %	A	(17) 11.18	(3) 2.9	0.01	4.1	0.08	
	G	(135) 88.8	(99) 97.0	0.01	0.2		30.2

TNFα	Genotype/ allele	Patients (76)	Relatives (36)	p-value	OR	EF	PF
Genotypes (no.) %	AA	(2) 2.6	(1) 2.7	0.7	0.9		
	GA	(13) 17.1	(4) 11.1	0.3	1.7		
	GG	(61) 80.2	(31) 86.1	0.3	0.6		
Allele (no.) %	A	(17) 11.18	(6) 8.3	0.3	1.3		
	G	(135) 88.8	(66) 91.6	0.3	0.7		

* Odds Ratio ** EF: etiological fraction ***PF: preventive fraction

3.4. Distribution of Type I Psoriatic Patients According to Age of Onset of Disease.

The average age of onset of PSO in our subjects about 17.3 years. Patients with *CW7* have an earlier age of attach (17.8 years) while patients with *IL6* -174 G>C polymorphism develop PSO later (20 years). As shown in figure (3-6).

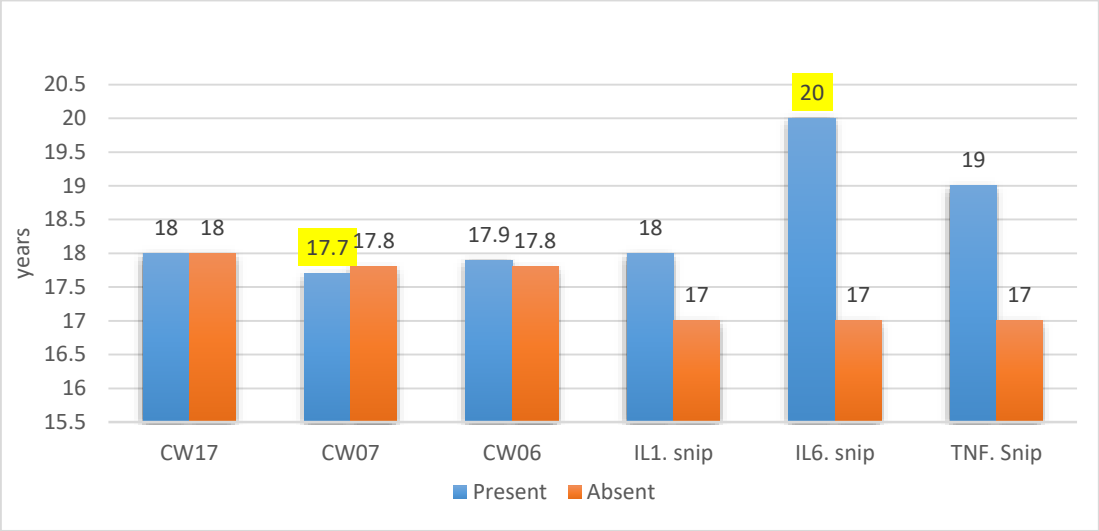


Figure 3-5: Distribution of Type I Psoriatic Patients According to Age of First Attach with Relation to Selected HLA Types and Cytokines Gene Polymorphism. there are no significant differences between all (t-test: p-value >0.05).

3.5. Comparison of Type I Psoriatic Patients with/ without Family History.

3.5.1. According to HLA Type.

The patients in this study divided into two group. Patients with family history of PSO (40) and patients without family history (36). About 33% of those without family history have *CW17* allele compared to 30% in those with family history. The *CW7* allele distribution (22% vs 30%) and *CW6* (22% vs 15%) with no statistical significance difference (p-value >0.05). As shown in table (3-12).

Table 3-12: Comparison of Patients with/ Without Family History According to HLA Type.

Family history of patients with/ without psoriasis	HLA		*OR	**Sig
	Present (no.) %	*Absent (no.) %*		
CW17				
Without family history n=36	**(12) 33.3**	**(24) 66.7**	**0.9**	**0.5**
With family history n=40	**(12) 30.0**	**(28) 70.0**		
Total n=76				
CW07				
Without family history n=36	**(8) 22.2**	**(28) 77.8**	**1.5**	**0.3**
With family history n=40	**(12) 30.0**	**(28) 70.0**		
Total n=76				
CW06				
Without family history n=36	**(8) 22.2**	**(28) 77.8**	**0.6**	**0.3**
With family history n=40	**(6) 15.0**	**(34) 85.0**		
Total n=76				
*** Odds Ratio, **Chi-square test, p-value**				

3.5.2. According to *IL1*, *IL6* and *TNF* Allele and Genotype.

According to the study results, *IL1β* allele and genotypes show non-statistical significance differences between patients with family history and patients without family history (p-value >0.05). Regarding *IL6*, the C allele significantly increase in those with family history (p-value 0.05 and OR 2.1). on the other hand, the G allele significantly increase in those without family history (p-value 0.05 and OR 0.4). The GG genotype of *IL6* is significantly increase in patients without family history (p-value 0.03 and OR 0.3).

The A and G allele of *TNFα* show non statistical significance between patients with family history from those without family history (p-value >0.05). the AG genotype significantly increase in patients with family history (p-value 0.05 and OR 3.7) while the GG seen in significantly higher frequency in patients without family history (p-value 0.03 and OR 0.2). table (3-13).

Table 3-13: Comparison of Patients with/ without Family History According to Cytokines Allele and Genotypes

	IL1 β	Family history–(36)	Family history+(40)	**p-value	*OR
Genotypes (no.)%	CC	(16) 44.4	(19) 47.5	0.5	0.8
	CT	(12) 33.3	(14) 35.0	0.5	0.9
	TT	(8) 22.2	(7) 17.5	0.4	1.4
Allele (no.)%	C	(44) 61.1	(52) 67.5	0.4	0.8
	T	(28) 38.8	(25) 32.5	0.4	1.2
	IL6				
Genotypes (no.)%	CC	(3) 8.3	(5) 12.5	0.4	1.6
	CG	(5) 13.8	(12) 30	0.07	2.7
	GG	(28) 77.7	(23) 57.5	0.03	0.3
Allele (no.)%	C	(11) 15.2	(22) 27.5	0.05	2.1
	G	(61) 84.7	(58) 72.5	0.05	0.4

	TNFα				
Genotypes (no.)%	**AA**	**(1) 2.7**	**(1) 2.5**	**0.7**	**0.9**
	AG	**(3) 8.3**	**(10) 25.0**	**0.05**	**3.7**
	GG	**(32) 88.8**	**(29) 72.5**	**0.03**	**0.2**
Allele (no.)%	**A**	**(5) 6.9**	**(12) 15.0**	**0.09**	**2.4**
	G	**(67) 93.0**	**(68) 85.0**	**0.09**	**0.4**
*** Odds Ratio, **Chi-square test, p-value**					

3.6. Association of Selected HLA Allele and Cytokine Gene Polymorphism with Type I Psoriasis Severity.

The association of severity with the selected HLA show non significance alteration in frequency between patients have the selected HLA and patients haven't (p-value >0.05). As shown in table (3-14).

Table 3-14: Association of Selected HLA Allele with Severity of Type I Psoriasis.

Severity	***Cw17*+(24)**	***Cw17*-(52)**	***p-value**	****OR**
Mild (no.)%	**(12) 50.0**	**(24) 46.1**	**0.5**	**1.2**
Moderate (no.)%	**(5) 20.8**	**(11) 21.1**	**0.6**	**0.9**
Sever (no.)%	**(7) 29.1**	**(17) 32.7**	**0.5**	**0.8**

Severity	*Cw7*+(20)	*Cw7*-(56)	p-value	OR
Mild (no.)%	(8) 40.0	(28) 50.0	0.3	0.6
Moderate (no.)%	(5) 25.0	(11) 19.6	0.4	1.3
Sever (no.)%	(7) 35.0	(17) 30.3	0.4	1.2
Severity	*Cw6*+(14)	*Cw6*-(62)	p-value	OR
Mild (no.)%	(7) 50.0	(29) 46.7	0.5	1.1
Moderate (no.)%	(2) 14.2	(14) 22.5	0.4	0.6
Sever (no.)%	(5) 35.7	(19) 30.6	0.5	1.3
** Odds Ratio, *Chi-square test, p-value				

Only IL6 show significant association with type I psoriasis severity. In which the C allele show significant increase in frequency in mild cases compare to moderate and sever cases. As it shown in table (3-15).

Table 3-15: Association of Selected Cytokines Alleles and Genotype with Severity of Type I Psoriasis.

	IL.1β	Mild (36)	Moderate (16)	Severe (24)	p-value
Genotypes (no.) %	CC	(15) 41.7	(8) 50.0	(12) 50.0	0.8*
	CT	(12) 33.3	(6) 37.5	(8) 33.3	
	TT	(9) 25.0	(2) 12.5	(4) 16.7	
Alleles (no.) %	C	(42) 58.3	(22) 68.7	(32) 66.7	0.5**
	T	(30) 41.7	(10) 31.3	(16) 33.3	

	IL6				
Genotypes (no.) %	**CC**	**(5) 13.8**	**(2) 12.5**	**(1) 4.2**	**0.3***
	GC	**(11) 30.6**	**(3) 18.8**	**(3) 12.5**	
	GG	**(20) 55.6**	**(11) 68.8**	**(20) 83.3**	
Alleles (no.) %	**C**	**(21) 29.1**	**(7) 21.8**	**(5) 10.4**	**0.05****
	G	**(51) 70.9**	**(25) 78.2**	**(43) 89.6**	
	TNFα				
Genotypes (no.) %	**AA**	**(0) 0.0**	**(1) 6.2**	**(1) 4.2**	**0.09***
	GA	**(9) 25.0**	**(3) 18.8**	**(1) 4.2**	
	GG	**(27) 75.0**	**(12) 75.0**	**(22) 91.6**	
Alleles (no.) %	**A**	**(9) 12.5**	**(5) 15.6**	**(3) 6.3**	**0.4****
	G	**(63) 87.5**	**(27) 84.4**	**(45) 93.7**	

* Fisher Exact Test ** Chi-square Test

3.7. Association of selected HLA allele with Cytokine Gene Polymorphism in type I Psoriatic Patients.

3.7.1. Association of *CW17* allele with selected cytokines genotype and allele.

A significantly association of GG genotype (p-value 0.04 and OR 0.3) of *TNFα* seen in patients who are *CW17* negative, all the AA genotype are also cw17 positive. As its shown in table (3-16). The A allele detected in 20% of those *CW17* positive (p-value 0.01 and OR 3.6) while the G allele detected in 93% in those *CW17* negative (p-value 0.01 and OR 0.3).

Table 3-16: Association of *CW17* Genotypes with Cytokines Genotype and Allele

	IL1 β	CW17		*p-value	**OR
		Present (24)	Absent (52)		
Genotypes (no.)%	CC	(10) 41.7	(25) 48.1	0.4	0.8
	CT	(9) 37.5	(17) 32.7	0.4	1.2
	TT	(5) 20.8	(10) 19.2	0.5	1.1
Allele (no.)%	C	(29) 60.4	(67) 64.4	0.4	0.8
	T	(19) 39.6	(37) 35.6	0.4	1.2
	IL6	Present (24)	Absent (52)		
Genotypes (no.)%	CC	(1) 4.2	(7) 13.5	0.2	0.3
	CG	(5) 20.8	(12) 23.1	0.5	0.9
	GG	(18) 75.0	(33) 63.4	0.2	1.8
Allele (no.)%	C	(7) 14.6	(26) 25.0	0.1	0.5
	G	(41) 85.4	(78) 75.0	0.1	2.0
	TNFα	Present (24)	Absent (52)		
Genotypes (no.)%	AA	(2) 8.3	(0) 0.0	0.09	--
	AG	(6) 25.0	(7) 13.5	0.2	2.1
	GG	(16) 66.7	(45) 86.5	0.04	0.3
Allele (no.)%	A	(10) 20.8	(7) 6.7	0.01	3.6
	G	(38) 79.2	(97) 93.3	0.01	0.3

**** Odds Ratio, Chi-square test, *p-value**

3.7.2. Association of *CW7* allele with selected cytokines genotype and allele.

The association of *CW7* with cytokine genotype and allele shown in table (3-17). None of the *CW7* positive patients have either AA or GA genotype of *TNFα* and all of them carry the GG genotype (p-value 0.005). also all *CW7* positive patients have the G allele (p-value 0.004). While the A allele detected in only 15% of those *CW7* negative though the G allele detected in 84% of them (p-value 0.004). Non-statistical association with either *IL1β* or *IL6* at the level of allele and genotype (p-value > 0.05).

Table 3-17: Association of *CW7* Genotypes with Cytokines Genotype and Allele

	IL1 β	***CW7***		****p-value**	***OR**
		Present (20)	**Absent (56)**		
Genotypes (no.)%	**CC**	**(10) 50.0**	**(25) 44.6**	**0.4**	**1.2**
	CT	**(8) 40.0**	**(18) 32.1**	**0.4**	**1.4**
	TT	**(2) 10.0**	**(13) 23.2**	**0.2**	**0.4**
Allele (no.)%	**C**	**(28) 70.0**	**(68) 60.7**	**0.2**	**1.5**
	T	**(12) 30.0**	**(44) 39.3**	**0.2**	**0.7**
	IL6	**Present (20)**	**Absent (56)**		
Genotypes (no.)%	**CC**	**(0) 0.0**	**(8) 14.3**	**0.07**	**--**
	CG	**(5) 25.0**	**(12) 21.4**	**0.5**	**1.2**
	GG	**(15) 75.0**	**(36) 64.3**	**0.3**	**1.7**
Allele (no.)%	**C**	**(5) 12.5**	**(28) 25.0**	**0.07**	**0.4**
	G	**(35) 87.5**	**(84) 75.0**	**0.07**	**2.3**

	TNFα	Present (20)	Absent (56)		
Genotypes (no.)%	AA	(0) 0.0	(2) 3.6	0.5	--
	AG	(0) 0.0	(13) 23.2	0.01	--
	GG	(20) 100.0	(41) 73.2	0.005	--
Allele (no.)%	A	(0) 0.0	(17) 15.1	0.004	--
	G	(40) 100.0	(95) 84.9	0.004	--
* Odds Ratio, Chi-square test, **p-value					

3.7.3. Association of *CW6* allele with selected cytokines genotype and allele.

A non-significant association found between *CW6* and *IL1β* or *TNFα* at the allele and genotype level (p-value >0.05). Although non significantly associated, the CC genotype of *IL6* not detected in those *CW6* positive patients (p-value >0.05). While 92% of them have GG genotype (p-value 0.02 and OR 8.2). The G allele significantly detected in higher frequency (96%) in those *CW6* positive patients (p-value 0.005 and OR 9.4) conversely the C allele detected in higher frequency (25%) in those *CW6* negative (p-value 0.005 and OR 1.0). As shown in table (3-18).

Table 3-18: Association of *CW6*Genotypes with Cytokines Genotype and Allele

	IL1 β	*CW6*		**p-value	*OR
		Present (14)	Absent (62)		
Genotypes (no.)%	CC	(7) 50.0	(28) 45.2	0.5	1.2
	CT	(4) 28.6	(22) 35.5	0.4	0.7
	TT	(3) 21.4	(12) 19.3	0.6	1.1
Allele (no.)%	C	(18) 64.3	(78) 62.9	0.5	1.0
	T	(10) 35.7	(46) 37.1	0.5	0.9
	IL6	Present (14)	Absent (62)		
Genotypes (no.)%	CC	(0) 0.0	(8) 12.9	0.2	--
	CG	(1) 7.1	(16) 25.8	0.1	0.2
	GG	(13) 92.9	(38) 61.3	0.02	8.2
Allele (no.)%	C	(1) 3.6	(32) 25.8	0.005	1.0
	G	(27) 96.4	(92) 74.2	0.005	9.4
	TNFα	Present (14)	Absent (62)		
Genotypes (no.)%	AA	(0) 0.0	(2) 3.2	0.6	--
	AG	(1) 7.1	(12) 19.4	0.3	0.3
	GG	(13) 92.9	(48) 77.4	0.2	3.8
Allele (no.)%	A	(1) 3.6	(16) 12.9	0.1	0.2
	G	(27) 96.4	(108) 87.1	0.1	4.0
* Odds Ratio, Chi-square test, **p-value					

4.1. Association of Type I Psoriasis with Some Demographic Traits.

Psoriasis is a chronic, multisystem inflammatory disease, affects both gender equally, the Pathogenesis is multifactorial, and has a bimodal age of onset (Whan et al., 2017). Early onset PSO (type I) accounting for approximately 75% of patients and occurs before the age of 40 years, Patients have a strong family history and the majority of them are CW6 positives. Late onset PSO (type II) presents after the age of 40 years, Patients have no family history and are Cw6 negative (Sunil and Rahul., 2016). This study intentionally targeted type I PSO because of its great genetic association specially to HLA type.

The results in (Table 3-1) show that there is minor shifting toward female gender with respect to incidence of PSO. Nearly same results found by Springate et al., 2017 who found that female being more likely to be diagnosed with type I PSO in compare to type II which show little difference in gender distribution. This female predominance was also demonstrated by Mercy et al., 2013.

The study also found a higher percentage of patient were in urban than rural resident. Little are the study that focus on PSO prevalence in association with residency. Salah and Bassam 2012 found that about three quarters of psoriatic patients reside city in Iraq while the rest inhabitants of rural areas or immigrated to urban areas recently. Hypothetically, there are two explanations for this finding. First, urban social and physical environment (e.g. traffic noise) contributing to increased stress (Oliver et al., 2017).

Second, skin microbiota alteration in PSO also associated with residency, based on the facts that the skin microbiota resembles those in soil, and as the early cross-talk between the developing immune system and microbiota affect the immune function in later life (Jenni et al., 2017). This can lead to the hygiene hypothesis which postulate that reduction in microbial exposure in urban area due to improved sanitary measures can promoting autoimmune disease development. In contrast to rural area were microbes specially helminth (present in mud, water, soil, plants, animals) in close contact. Immune regulatory properties of microbes from environment, especially helminthes led to their therapeutic application in experimental models and clinical studies of several immune-mediated conditions including PSO (Mathilde et al., 2015).

Another finding in (table 3-3) is that, lower percentage of patients were smoker compare to relatives and non-relatives group. The association between PSO and smoking is bidirectional, with the entrance of stress as third party, this relation become more complex. Making a triangle with reversible effect with each other's. smoking can be risky for PSO both psychologically and physiologically. While smoker do smoke to mitigate stress, smoking itself can cause stress (Natalie et al., 2013). Furthermore, although a proven relation between smoking and both prevalence and severity of PSO has been existed, patient with PSO had a higher tendency to smoking (Li et al., 2017). In Iraq, (Ata et al., 2003) found a significant association with smoking prior to the onset of the disease while no significant association after the onset of PSO. while (Khalifa et al., 2009) found that the smoker had earlier age of onset of PSO, more chronic disease and less response to treatment.

The discrepancy of current finding with several studies that showed an association between smoking and PSO (Richer et al., 2016) and (Li et al., 2012) can be easily solved because about 35% of patients in this study below 20 years and female make 52% of total patients for which smoking is inadmissible in Iraq. On the other hands about 16% of patients are active smoker and about 42% of relative are smoker make high percentage of patients a passive smoker (second hand smoker). Smoking induce oxidative stress and free radical production, increased secretion of IL2, IL12, TNF and IFNγ, and abnormal angiogenesis (Armstrong et al., 2014). Free radical production during smoking activate signaling pathways implicated in PSO, such as nuclear factor kB, while smoking byproduct (nicotine) activate T cell to produce IL17 and IL22 major cytokines involved in the PSO pathogenesis (Eun et al., 2017). Smoking also increases the production of numerous pro-inflammatory cytokines such as, IL-1, IL-6 and TNF-α while decreases the levels of anti-inflammatory cytokines such as IL-10 (Arnson et al., 2010). Passive smoking as equal as active smoking risks, and can cause serious diseases in infants and children, with female were more likely to be exposed (Hamideh et al., 2016) and (Jing et al., 2016).

4.2. Association of Type I Psoriasis with Family History.

Psoriasis is highly heritable disease with a heritability estimate of 68% (Lonnberg et al., 2013). In current study, about 53% of psoriatic patients have at least one family member affected. Several study in Dutch, Singaporean, Australian and USA found nearly same finding with minor differences due to variation in genetic background of each population (Bronckers et al., 2015).

During a study conducted on Iraqi children, about 37% of them have a positive family history of PSO (Khalil., 2008). PSO considered as a heritable disease, but not 100% as a genetic disease based on twin studies. so PSO is a complex disease that not simply explained by Mendelian inheritance rules (Hız et al., 2017). Although the inheritance pattern is still unclear, patients with childhood PSO have a positive family history, Siblings and first-degree relatives of patients show a more increased risk in developing PSO (Mak et al., 2009). The risk for developing PSO is 41% if both parents psoriatic; 14% if one parent is psoriatic, 6% if one sibling is psoriatic and only 2% when no parent or sibling is psoriatic (Hani and Muhammad., 2013).

4.3. Prevalence of Type I Psoriasis According to Severity.

The PSO severity ranges from a few scattered plaques to the involvement of the entire body surface. PSO area severity index (PASI) and body surface area (BSA) are regarded as clinician-based assessment of severity. These measures although arbitrary, can provide primary assessment to select the proper treatment regime, its measured before, during and after treatment (Al-Hamdi et al., 2006). The severity ranges from mild disease with a limited localized inflammatory skin lesion to severe disease involving widespread plaques that cover more than 10% of the body surface area (Gladman., 2015).

During current study (table 3-4), highest percentage of patients suffer from mild PSO lesion. This finding in concordance with Jashin., 2017 who state that Approximately 80% psoriatic patients have mild to moderate disease while the remainder have moderate to severe disease. In survey conducted from 2003 through 2011 in the United States, 36-49% of untreated patients presented with mild PSO, compared to 29% Among those receiving treatment (Armstrong et al., 2013).

4.4. Association of HLA-Cw6, Cw7 and Cw17 Allele with the Prevalence of Type I Psoriasis.

Recently, it becomes well establishes that PSO has complex, strong and hetero-genetically genetic background. Considering the multifactorial nature of PSO (genetic predisposition, immune dysregulation and environmental triggers), the HLA and cytokines gene polymorphism can be nominating to be responsible for both genetic predisposition and immune dysregulation. HLA-C belongs to the MHC I receptors which are critical for CD8+ T cell priming which supports their important role in the pathogenesis of PSO (Harden et al., 2015). HLA-Cw6 have been strongly linked with PSO (Marina et al., 2016). The normal frequency of CW6 vary with different population and range from 4-16%, while sharply increase in psoriatic patients to about 50% (Gourraud et al., 2014).

During current study (table 3-5,6,7), the CW6 allele significantly associated with psoriatic patients than apparently healthy non relative control. Cw7 also significantly associated with PSO. While cw17 show no significant association with PSO. These three HLA type make the mainstay of this study. The frequencies of CW6 antigen in Iraqi Arab Muslims and Kurd Muslims about 2%, while CW7 20% in Arab versus 9% in Kurd (Batool et al., 2006). Another study found that from 13 different HLA-C alleles in Iraqi Kurd seven alleles had frequencies higher than 4% including HLA CW6, CW7 and CW17 (Antonio et al., 2017). Ahmed., 2008 in his survey about HLA typing in UC patients in Iraq, detect CW6 and CW7 in 12% and 18% of healthy control respectively.

Several studies conducted in Iraq that investigate the association of HLA types with PSO. Batool., 2013 in attempt to summarize some HLA alleles related to specific diseases in Iraq identified cw7 among others as risk allele for PSO. Ahmed., 2016 revealed that cw17 (but not CW6 or CW7) among others were significantly associated with PSO in Iraqi patients. In Neighboring Countries, a study about childhood PSO in Kuwait by Nanda et al., 2000 showed a significant association with CW1. CW6 significantly increase in frequency in the type I patients compared with controls in Turkish (Mustafa et al., 2006). CW6 allele although no statistically significant, increased in patients with type I compared with controls in Omanis (Fatma et al., 2009). The global association of CW6 allele with PSO have been validated with different population, including South Asians (Aditi et al, 2016), and East Asians (Zhou, 2016), Europeans (Lenz, 2015). and Egyptian (Khalda et al., 2010).

Fine mapping studies have identified HLA-C*06:02 as strongest associate to PSO. The SNP (rs4406273) is in strong linkage disequilibrium with HLA-C*06:02 and acts as a surrogate marker (Stuart et al., 2015). Most studied populations have shown strong evidence of association between this SNP and PSO (Okada et al., 2014). But it is difficult to detect routinely because of polymorphism of HLA-C, sequence similarity to other allele, and it is 3 bases away from another SNP (Philip et al., 2015). The importance of CW6 allele associated with PSO is not only about its role in presenting autoantigen to T-cell. CW6 positive patients tend to develop extensive and sever disease, while CW6 negative patients suffer from dystrophic nail changes and PSA (Johann et al., 2002).

HLA-Cw6-positive patients responded more quickly to ustekinumab with almost 90% achieving significant improvement within 4 weeks, compared with only 60% of patients without the allele (Martina et al., 2016). CW6 allele may offer protection from PSA (John et al., 2017). Another finding in this study is that the CW7 allele significantly increase in patients than their relatives. Make it valuable risk factor for construction of PSO. While no difference found between patients and their relatives with regard to CW6 and CW17.

4.5. Association of IL1β, IL6 and TNFα Cytokines Gene Polymorphism with Type I Psoriasis.

Psoriasis is a chronic inflammatory immune-mediated skin disorder (Sunil and Rahul., 2016). Characterized by complex interaction between T reg, Th1 and Th17 (Dinuzzo et al., 2014). It is a T cell–mediated disease driven by T cells that produce high levels of IL-17 in response to IL-23 (Jason et al., 2017). Author opinion that Hypothetically, there is a cascade of events responsible for initiation and maintenance of PSO. And PSO generally known with its IL23/IL17 axis as a main event in this cascade. But several events occur upstream the IL23/IL17 axis.

This study pays more attention to the role of pro inflammatory cytokines, more specifically to IL1β, IL6 and TNFα genes. KCs are a vital contributor in the immune pathogenesis of PSO, are a rich source of antimicrobial peptides, including LL-37 and are a key innate immune cell types that act on myeloid dendritic cells through IL-1, IL-6 and TNFα early in the cascade (Alwan and Nestle., 2015). IL 17, late in the cascade, activate the KCs in immunologic and proliferative terms, giving rise to the production of IL-1, IL-6 and TNF-α (Puig at al., 2014).

The overproduction of pro-inflammatory cytokines, with persistent secretion of IL-1, IL-6 and TNF-α contribute to the development of another related disease (Audrey et al., 2016). IL-1, IL-6 and TNF-α also produce by epicardial adipose tissue and form a link between PSO and cardiovascular risk (Ines and Tiago., 2015).

The IL1β -511 T allele significantly detected in patients shown in (table 3-9). On the other hands, the C allele and CC genotype significantly increased in frequency in non-relative controls. IL-1β important in the initiation and maintenance of psoriatic plaques through induction of Th17 cells to produce IL-17, IL-17 in turn can act on KCs to produce more IL-1 family cytokines. Establishing an IL-17/IL-1 axis that play important roles in the pathogenesis of PSO (Yelin et al., 2014). IL-1 role in the pathogenesis of PSO suggested by the markedly increased IL-1β level in lesional skin (Balato., 2013). Tamilselvi et al., 2013 observed that IL-1β concentration in plasma and skin biopsies of patients was elevated compared to healthy control. Binding of IL-1β to its receptor stimulating the release of other pro inflammatory cytokines, such as IL-6 and TNFα, and inducing naïve T cell bias to Th17 (Attila et al., 2014). IL1β C/T promoter polymorphism showed significantly increased IL1B mRNA levels in individuals with TT genotype as compared to individuals having CC and CT genotypes (Naresh et al., 2014).

Current results in concordance with Nikhil et al., 2015 as he found a strong association of IL-1β -511C/T polymorphism with PSO at both genotypes and alleles. Although C/C genotype is supposed to be anti-inflammatory and logically should not be associated with PSO. Reich et al., 2002 found that the C/C genotype was associated with type II PSO. However, some author suggests that IL-1β -511 C/T polymorphism is a nonfunctional polymorphism (Bidwell et al., 1999).

While other suggest that increased IL-1β present in the psoriatic skin, is functionally inactive (Cooper et al., 1990) and (Franchi et al., 2009).

An important feature of PSO is increasing skin and serum IL-6 levels, level of IL-6 in serum regarded as a marker of the inflammatory activity as well as an indicator of treatment response, been decrease after effective treatment with methotrexate or UVB phototherapy (Andrea et al., 2014). IL-6 has pleiotropic effects include keratinocyte hyperplasia, promotion of the differentiation of IL-17-producing T cell and inhibition of Treg differentiation. An increase of IL-6 also associates with increased serum levels of IL-22 in the absence of IL-17. Th22 cells role in PSO has been confirmed, in fact IL-6 and TNF-α promote priming of Th22 (Cordiali et al., 2014).

This study results (table 3-10) show that IL6 -174 C allele, CC and GC genotype significantly increase in frequency in patients, while G allele and GG genotype frequently detected in non-relative control. The -174 G/C polymorphism in the IL-6 promoter region is a functional polymorphisms and correlate with transcription activity and levels of expression (Linfeng et al., 2016). G allele exhibit enhanced both spontaneous and inducible expression compared to C allele, and significantly associated with higher level of IL6 in healthy adults (Walaa et al., 2016).

Current result in concordance with that of Białecka et al., 2015 in that IL6 -174 G>C polymorphism associate with susceptibility to PSO (aged 45.3 ± 15.6 years), but in disagreement at the allele and genotype level, as it showed that GG genotype increase risk of PSO. Current result also in disagreement to that of Cashtry et al., 2017 which found that the GG genotype in subjects aged 30-65 years, significantly associate with patients than control.

The age of subjects included in these studies is crucial in this discrepancy, as this study include only type I PSO (< 40 years). Ahmad et al., 2015 when include type I PSO subject, found that C allele frequency was significantly higher in patients, and CC genotype significant higher frequency in patients.

According to current results the level of IL6 supposed to be lower in type I PSO compare to that of control. In Iraq, several studies (Fadhil et al., 2013), (Radhia., 2012), (Iqbal., 2010) and (Mahdi., 2014) measure the IL6 level in PSO patients irrespective to age of first attack, and found an elevated IL6 level in patients compare to control.

The TNFα is a pleiotropic, predominantly pro-inflammatory cytokine. Produce mainly by activated macrophage and by several other cells like T cells, neutrophil, endothelial cell, mast cell and other. It is responsible for several vital process including inflammation, cell growth, proliferation, differentiation, apoptosis and autoimmunity (Mujeeb et al., 2016). Polymorphisms in the promoter region of TNF-α -308 G/A involves the substitution of a guanine by an adenine, is associated with an increase in TNF-α expression levels (Linfeng et al., 2016).

Current results (table 3-11) show that the TNFα -308 A allele, AA and GA genotypes significantly increase in frequency in patients than non-relative control, while G allele and GG genotype significantly increase in non-relatives control. A study by Khalid et al., 2017 on Iraqi patients (aged 18-70 years) showed that G allele and GG genotype significantly associated with PSO than control, with an elevated level of TNFα in serum of patients than control.

Another study by Svetlana et al., 2015 showed that the AA genotype detected only in type I but not type II PSO. Jia et al., 2013 found an association between AA/GA genotype and early onset PSO.

Furthermore, the G allele may play a protective role in PSO (Li et al., 2007). While the A allele is over representing in psoriatic patients (Nikhil et al., 2015).

Based on the finding of Khalid et al., 2017 that the A allele and AA genotype associate with higher level of transcription, the TNFα level supposed to increase in type I PSO. Several study conducted in Iraq that measure the level of TNFα (Suzan., 2017), (Fadhil et al., 2013), (Mahdi., 2014) and (Talib et al., 2015) although not define an exact age groups or age of onset, all found a significant elevation of TNFα in patients compare to control.

Another important finding in current study is that there are no significance differences between patients and their relatives at the selected cytokine gene polymorphism. These finding serve two purposes. First, the inheritance of these allele is the same for all family member, affected or not. Second, giving an answer to our request to find what the patient have or haven't in compare to his relatives that make him initiate PSO. And the answer is nothing.

4.6. Association of Selected Genetic Marker with Age of Onset of Type I Psoriasis.

When making a comparison among patients according to age of first attach with regard to selected genetic marker in (figure 3-6), although non statistically significance, this study found that HLA cw7 allele associate with earliest age of first attach (mean 17 years) while IL6 -174 G\C polymorphism associate with latest age (mean 20 years). Because this is the first study that include these markers together there is no other studies to compare with.

4.7. Association of Selected HLA-C Alleles and Cytokines gene polymorphism with family history in Type I Psoriasis.

A positive family history defined as psoriatic person with at least one first degree family member affected with PSO (Haoyan et al., 2011). Study on families with multiple affected members found several susceptibility loci with the most strongly associated locus is PSOR1, the family-based studies have confirmed that HLA-C is directly involved in susceptibility to PSO (Bartłomiej et al., 2017).

The obtained results in (table 3-12) indicate that there is none statistical association between either CW6, CW7 or CW17 with a positive family history. HLA Cw6 revealed to confers susceptibility to PSV and to be the PSORS1 risk variant that has been associated with early onset of PSO and higher prevalence of family history (Proton and James., 2012). This association also proved by Ruben et al., 2003.

Other study by Annet et al., 2014 could not find any association between CW6 and family history and attribute this discrepancy to the fact that similar proportions of both group with a positive family history and a negative family history were found to have similar proportions of CW6 positivity, many patients with early onset have negative family history while patients with adult onset have a positive family history.

Unfortunately, the absence of other study that discuss the association of CW7 and CW17 with family history make comparison and discussion of these results very difficult, but by looking to Iraq community as closed one, closed mating in the family and that several generation residents the same place, a conclusion is that the inheritance of these HLA alleles was the same for both group. This conclusion enforced by CW6 finding.

At the cytokines allele and genotype level in (table 3-13), IL6 -174 C allele significantly associated with family history positive group compare to G allele in family history negative group. The G\G genotype of both IL6 and TNFα significantly associated with those negative for family history, but the TNFα A\G genotype significantly associated with those positive for family history. There is no available date about IL1β polymorphism association with family history either for PSO or other diseases to support or antagonized current result.

A study by Monika et al., 2015 Evaluate IL6 gene polymorphism (30-60 years old patients) and reveal that there is no significant difference between the IL6 −174 G/C genotype and a family history of PSO. such Lack of association also seen in rheumatoid arthritis in adults (Solbritt et al., 2002), febrile seizures or epilepsy in children (Seham et al., 2016).

These data suggest that inheritance of IL6 −174G>C polymorphism offer a better chance for initiation of type I but not type II PS within family, while have no effect with other diseases.

There is no other study involve TNFα polymorphism in association with family history of PSO to make agreement or not with it, Sangeeta et al., 2016 cannot found an association between TNFα level and family history. TNFα polymorphism association with family history proved in other disease like type 2 diabetes mellitus **(**Elva et al., 2012), coronary heart disease (George et al., 2005) but not in alopecia areata **(**Mahira et al., 2014).

4.8. Impact of Selected HLA-C Alleles and Cytokines gene polymorphism on Severity of Type I Psoriasis.

With regard to genetic markers (table 3-14), although non statistically significant for HLA cw17, cw7 and cw6. About 50% of patients carry cw17 and cw6 alleles suffer from mild PSO compare to 40% for those who carry cw7 allele. While 29% of those carry cw17 presented with sever PSO in compare to 35% of those carry cw6 and cw7. current result for cw6 show little disagreement with other studies (Johann et al., 2002) in which they found that HLA cw6 positive patients with younger age of onset tend to develop a severe form of PSO. Baurecht et al., 2015 found that Cw6 is strongly associated with the initiation of a more severe form of PSO presenting at a younger age, while Cw6 positive patients with late onset of disease and are tend to have milder severity (Bahcetepe et al., 2013).

This discrepancy attribute to that the Cw6 positivity is lower in Asian patients than in Caucasians (Sathishkumar et al., 2015). There is no comprehensive study for the association of PSO with either cw7 or cw17 to compare with about PSO severity.

Cytokines polymorphism association with PSO severity in this study (table 3-15). Show that only the C allele of IL6 significantly increase in frequency in mild cases.

In spite of the trace of studies that link some of these cytokines polymorphism to severity of PSO. Hypothetical assumption can be made that the presence or abscence of such association based on the fact that these polymorphisms influence the transcription and production rate of related cytokine. Tamilselvi et al., 2013 found a positive correlation between IL-1β levels in lesional skin biopsy and PSO activity. Yu et al., 2009 also found that the elevated circulating level of IL-1β associate with PSO severity.

Serum levels of IL-6 significantly correlated with PASI scores in PSV patients (Muramatsu et al., 2017). Increased IL-6 levels in skin and serum are a feature of PSO and correlate with clinical severity of PSV (Andrea et al., 2014). On the other hands, obesity which characterized by chronic inflammation mediated by high IL6 level show no effect on the severity of PSO (Mohammad and Mahmoud., 2017). Hadis et al., 2017 investigate the association of TNFα level with PSO severity before and after treatment and found great improvement with the decrease of TNFα level after treatment. Aikaterini et al., 2014 did not find a significant association between TNFα level and PSO severity. These inconsistencies indicate that TNF-α is produced and act locally, though, its circulating levels might be lower than at the inflammatory area (Susana and Alice., 2014).

4.9. Association of Selected HLA-C Alleles with Cytokine Gene Polymorphism in Type I Psoriasis.

To the best of our knowledge, at present this is the first study that deal with the HLA types CW6, CW7 and CW17 in association with IL1β, IL6 and TNFα cytokines gene polymorphism in type I PSO in order to identify significant association between any two of them if any in causing the early onset PSO. As mentioned above, a cascade of events responsible for initiation and maintenance of PSO lesion. In this regard, the multiple hit hypothesis can be supposed. In that, single abnormality can be tolerated by immune system and so cannot initiate the cascade, but multiple abnormality can be overwhelming the homeostasis of immune system and can initiate the cascade of PSO initiation.

The term epistasis describes the masking of one disease-causing mutation by the co-inheritance of a mutation at a separate locus, include any statistical deviation from the additive combination of two loci (Anna and Lucy., 2012).

The complexity of immune system, Networks of cell subsets and the signaling molecules interact in cascades makes it a rich environment in which to observe epistasis. The understanding of these interactions is key to understanding risk and susceptibility to autoimmune disease (Anna and Lucy., 2012). It is worthy to note that the evidence for the existence of epistasis in human diseases mainly comes from PSO (Puig et al., 2014).

Current results (table 3-16 to 18) show significant association of CW17 with A allele of TNFα that increase relative risk about three folds. CW7 on the other hands, show significant association with GG genotype of TNFα and also with G allele that increase risk of PSO. CW6 significantly associated with GG genotype of IL6 that increase relative risk about eight folds and with G allele that increase relative risk to about nine times.

Shortage in available data about studies handling the same subject make the discussion of this results very difficult. Result regarding CW6 and TNFα association in disagreement with that of Renata et al.,2016 who found significance association between simultaneous inheritance of CW6 and TNFα -308 G allele with increase susceptibility to PSO in Brazilian. This discrepancy attributed to differences in genetic constitution between the two population. Several other studies available that study the gene-gene interaction in PSO. Rajan et al., 2008 found no statistical evidence for epistasis between either IL12B or IL23R and HLA-Cw6, and demonstrate that their contribution to PSO susceptibility is statistically independent of Cw6. Epistasis interaction of Cw6 with LCE3C-3B were observed in some European, Asian, German and northern Chinese population (Aditi et al., 2016). No evidence for the epistatic effect of IL12B with HLA-Cw6 among the Indian psoriatic patients (Aditi et al., 2017). In other study, the presence of C allele or CC genotype of IL6 in the absence of CW6 decrease the risk of PSO (Andreea et al., 2013).

Another authors investigate the association of CW6 with IL6 and TNFα level, and didn't found correlation between elevated TNF-α and IL-6 with HLA-Cw6 in PSO (Sangeeta et al., 2016).

Conclusions:

1. Type I psoriasis associated with family history as more than half of patients have family history of psoriasis.
2. HLA-cw6 and cw7 significantly associated with type I psoriasis.
3. T allele of IL1β, C allele, CC and GC genotype of IL6, A allele and GA genotype of TNFα present in higher frequency in Type I psoriasis patients compared to non-relative control.
4. Patients with HLA-cw7 have earlier age of first attach, while those with IL6 G\C polymorphism have the latest.
5. The C allele of IL6 and A/G genotype of TNFα significantly associated with positive family history
6. None of the selected marker have significant effect on type I psoriasis severity except IL6 C allele with mild form.
7. Only CW7 showed significant differences between patients and their relatives making it an important marker.
8. significant association of CW17 with A allele of TNFα, CW7 with G allele and GG genotype of TNFα, CW6 with G allele and GG genotype of IL6.

Recommendations:

1. Avoidance of stressful life, with giving the immune system an opportunity to develop healthfully by avoiding hygiene obsession for children.
2. Quit smoking, or at least avoid indoor smoking by adults to minimize the risk of developing early onset psoriasis in children.
3. Inclusion of asking for psoriasis in pre marriage consultation to avoid matting between members with positive family history.
4. Construction of comprehensive nationwide study for detection of more HLA types and more cytokines polymorphism.
5. Using high resolution technique for detection of specific HLA allele that more specifically associated with type I PSO.
6. Study the haplotypes inheritance pattern to identify the exact combination of alleles responsible for type I PSO.
7. Screening of patient and his family members for selected cytokines polymorphism to identify who is at risk.
8. Identification of patient's genetic profile for selected genetic marker for tailoring of therapeutic interventions.

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QUESTIONER

1. Status: P R NR

2. Name:

3. Age:

4. Gender:

5. Rural or urban habitat:

6. Smoking behavior Active Passive

7. Age of first attach:

8. family history:

9. Severity:

الخلاصة

تعتبر الصدفية من امراض المناعة الذاتية، وهي مرض التهابي مزمن يصيب جلد الانسان. من الممكن ان تظهر بصور مختلفة. مع ذلك، تعتبر صدفية الصفائح الاكثر انتشارا. يعتبر العامل المسبب مجهولا حتى الان، ولكن عدة عوامل وراثية و مناعية وكذلك بيئية تم التعرف عليها. تصيب الصدفية كلا الجنسين ولا تظهر اي اختلاف بالاصابة نتيجة التمايز العرقي. يمكن تمييز نوعين من داء الصدفية اعتمادا على عمر المريض اثناء الاصابة. النوع الاول (المبكر) ويعتمد على الاستعداد الوراثي والنوع الثاني (المتأخر) والذي يحدث بشكل متفرق. على الرغم من ان HLA-CW6 موجود تقريبا في نصف حالات النوع الاول، الا انه عدة انواع من HLA موجودة في مجموعات عرقية مختلفة. يتميز داء الصدفية كذلك بارتفاع مستويات السايتوكينات الالتهابية مثل IL1β, IL6 ., TNFα

شارك في الدراسة الحالية ١٦٣ شخص تم تقسيمهم الى مجموعتين. مرضى الصدفية (من النوع الاول) وشملت ٧٦ مصاب ومجموعة السيطرة من الاشخاص الاصحاء ظاهريا وشملت ٨٧ شخص والتي بدورها قسمت الى مجموعتين، ٣٦ شخص اقرباء لمرضى الصدفية و ٥١ شخص ممن لم يسبق لهم الاصابة بداء الصدفية ولا يمتلكون تاريخ عائلي للاصابة بالمرض. تم سحب ٢ مل دم وريدي من كل المشاركين في انابيب مانعة للتخثر (K3-EDTA) وتم حفظها بدرجة حرارة -٢٠ درجة سيليزية. ثم تم استخلاص ال DNA واجراء التفاعل التسلسلي التضاعفي للكشف عن (HLA-CW6, CW7, CW17) وعن التغاير الجيني في (IL1β, IL6, TNFα).

متوسط اعمار المرضى بلغ ٢٦,٢ سنة. ووجدت الدراسة ان المرضى ضمن الفئة العمرية اكثر من ٣٠ سنة هم الاكثر عددا. وكذلك عدم تباين الاصابة بين الجنسين. كما وجدت الدراسة ان اكثر من ثلاثة ارباع المصابين يسكنون المدينة. عدد قليل من المرضى وجدوا مدخنين واكثر من نصف المرضى يمتلكون تاريخ مرضي للاصابة بالصدفية. اظهرت الدراسة ايضا ان النسبة الاعلى من المرضى يعانون من داء الصدفية معتدل الشدة.

النتائج اظهرت علاقة معنوية بين النوع الاول من داء الصدفية مع HLA-CW6, CW7 وكذلك علاقة معنوية مع الاليل IL1β-T ومع الاليل IL6-C والنوع الجيني IL6- CC, GC ومع الاليل TNFα-A والنوع الجيني TNFα- AA, GA. كما وجدت الدراسة ان CW7 مرتبط بالاصابة المبكرة (المتوسط ١٧ سنة) مقارنة مع بقيت الجينات المختاره بينما التغاير الجيني في IL6 مرتبط بالاصابة المتاخرة (المتوسط ٢٠ سنة). لم تظر انواع HLA المختارة علاقة معنوية مع التاريخ العائلي، بينما الاليل IL6-C وكذلك النوع الجيني TNFα-G\A اظهر علاقة معنوية مع التاريخ العائلي. كما اظهر الاليل IL6-C زيادة معنوية عند المرضى المصابين بالنوع الاول من الصدفية معتدل الشدة.

النتائج اظهرت علاقة معنوية بين الاليل TNFα-A مع HLA-CW17 وبين الاليل TNFα-G والنوع الجيني TNFα-GG مع HLA-CW7. كذلك وجدت الدراسة علاقة معنوية بين الاليل IL6-G والنوع الجيني IL6-G\G مع HLA-CW6.

استنتجت الدراسة وجود علاقة معنوية بين HLA-CW6 مع الاليل IL6-G ومع النوع الجيني IL6-G\G مما يؤدي الى زيادة خطر الاصابة بالنوع الاول من داء الصدفية. كما ان العلاقة بين HLA-CW7 مع الاليل TNFα-G والعلاقة بين HLA-CW17 مع الاليل TNFα-A تزيد من خطر الاصابة بداء الصدفية من النوع الاول

جمهورية العراق
وزارة التعليم العالي والبحث العلمي
جامعة القادسية
كلية الطب

التنميط الجيني لمواضع محددة من HLA-C مع تعدد الاشكال الجينية لبعض السايتوكينات الالتهابية في مرضى النوع الاول من داء الصدفية

اطروحة
مقدمه الى مجلس كليه الطب / جامعة القادسيه
كجزء من متطلبات نيل شهادة الدكتوراه في الاحياء المجهريه الطبيه

علاء ارحيم علي
بكالوريوس تقنيات تحليلات مرضية/بغداد ٢٠٠٣
ماجستير تقنيات تحليلات مرضية/بغداد ٢٠١١

اشراف
ا.د. منال محمد كاظم

٢٠١٨ م **١٤٣٩ هـ**