

# Plaque Psoriasis: Understanding Risk Factors of This Inflammatory Skin Pathology

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## Abstract

Covering the entire human body, the skin is considered to be one of the most important organs, since it is the first line of protection against chemical and biological external agents. Although the skin protects tissues and organs against external aggression, it can still be unbalanced by various skin diseases, such as psoriasis. This non-contagious inflammatory dermatosis is characterized by the occurrence of erythematous lesions of various sizes covered with whitish scales. This scaling of the skin is the result of a rapid renewal of the epidermis, occurring over five to seven days instead of 28 days. *Psoriasis vulgaris*, or plaque psoriasis, is the most common form of this disease and is therefore commonly referred to by the term “psoriasis”. This work is a review of the literature on plaque psoriasis, aiming at a better comprehension of the pathology at the histological level, but also to understand the genetic and environmental factors associated with this inflammatory dermatosis.

## Keywords

Plaque Psoriasis, Clinical Phenotypes, Comorbidities, Genotype-Phenotype Correlation, Susceptibility Gene

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## 1. Introduction

Psoriasis is a common, chronic inflammatory skin disease affecting 2% to 3% of the worldwide population, both men and women [1]. However, although psoriasis occurs worldwide, its prevalence varies considerably in dif-

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ferent ethnic groups. Indeed, this skin disease is more frequent in Caucasians, while it affects only 0.3% of the Chinese population [2]. Several forms of psoriasis have been identified and classified into 5 different types: guttate, pustular, erythrodermic, inverse psoriasis and plaque psoriasis (**Figure 1**) [3]. The latter form, also known as *Psoriasis vulgaris*, is the commonest form, accounting for up to about 90% of patients with this disease [4]. Therefore, that type of psoriasis is usually named “psoriasis” and, as the plaque psoriasis is the most predominant form, the majority of studies examining this skin disease are based on this form of psoriasis. This skin pathology is characterized by the presence of erythematous plaques, covered by silvery dry white scales varying in size. In addition, plaque psoriasis vary in severity and may occur only as small and single lesions at localised sites, especially on knees, elbows and the scalp, or be widespread over most of the body and disabling [5]. Beyond the physical appearance, psoriatic lesions are painful and uncomfortable, affecting the life quality of patients and causing various psychosocial problems [6] [7].

Previously, it was thought that psoriasis was caused principally by a disorder in epidermal keratinocytes, leading to their abnormal proliferation and differentiation from epidermal cells [4]. Although the exact cause of this skin disease is still not known, several studies have highlighted the deregulation of the immune system in the development of psoriatic lesions. Indeed, a study has shown the need of immune cells during successful treatment with cyclosporine A, a T cell immunosuppressant [8]. Nowadays, the disease is mainly characterized by hyperkeratosis, parakeratosis, acanthosis, a keratinization disorder where filaggrin and loricrin are under expressed, while involucrin and transglutaminase are over expressed [9]-[11], with leukocyte infiltration and an increased angiogenesis [12] [13] also occurring. In addition, genetic and environmental factors may also play a synergetic role in triggering psoriasis [4] [14]. No curative treatment is currently available to treat the disease; however, there are treatments that can alleviate the symptoms. In this work, our objective is to present a literature review of chronic plaque psoriasis briefly describing the clinical phenotypes of psoriasis, the influence of the genetic and environmental factors and the associated comorbidities.

## 2. Clinical Phenotypes of Psoriasis

Over the decades, the understanding of the disease, although still incomplete, has evolved, and enabled to offer patients a better diagnosis of their psoriasis and, by extension, to offer them the best treatments for their specific type of psoriasis. Although there are no diagnostic criteria for psoriasis, a classification of psoriasis has been proposed to assist practitioners, based on the clinical phenotypes of psoriasis, because it is known today that there are several varieties of clinical occurrence. Indeed, psoriasis, such as described above, can be variable in morphology, distribution and severity. Thereby, this classification of clinical phenotypes relies on various characteristics of psoriasis. Among these are the anatomical sites exposed to lesions, the distribution of the psoriatic



**Figure 1.** Clinical phenotypes of psoriasis. Plaque psoriasis is characterized by erythematous cutaneous lesions covered by silvery scales, often appearing on the elbow [26] (A). Plaque psoriasis may also develop in the scalp, named seborrheic psoriasis [27] (B). Flexural (inverse) psoriasis is distinguished from others by its reddish plaques without scales located in intertriginous areas [28] (C). Guttate psoriasis [29] (D). Pustular psoriasis (palmoplantar pustulosis) affects the palms and/or soles [30] (E).

lesions, their thickness and their size and the patient's age [15]-[19]. Moreover, since psoriasis affects psychosocial behavior, it is important to consider the psychological condition of the patient during the diagnosis to maximize the efficiency of the treatment. The various types and presentations of psoriasis are outlined below.

Chronic plaque psoriasis is characterized by well-defined contour plaques, covered with whitish scaly skin, and which are most commonly found on the elbows, knees, lumbosacral area and scalp [20]. Several forms of chronic plaque psoriasis can occur, which are primarily distinguished by size, distribution, and dynamics of psoriatic plaques. Early lesions can appear as small papules, which may become more inflamed and may vary in diameter. Plaque psoriasis may occur as single lesions at predisposed sites or be generalized over the body. Psoriatic lesions can occasionally dominate seborrheic regions and affect areas of the scalp and face such as cheeks, nose, ears, hair line, scalp and interscapular regions [2]. This anatomical distribution of plaque psoriasis is called seborrheic psoriasis or sebopsoriasis, since there are many morphological similarities with seborrheic dermatitis [16]. Psoriatic lesions can also be located in the flexural areas, such as the axillae, the inguinal crease, the intergluteal cleft, the inframammary region and the retroauricular folds. When flexural lesions are the only sites of involvement, the term "inverse" psoriasis is sometimes used. This type of psoriasis is distinguished from others by its reddish, shiny, humid thin plaques without scales [21]. Furthermore, plaque psoriasis should be differentiated from other uncommon types of psoriasis such as guttate psoriasis, localized and generalized pustular forms and erythrodermic psoriasis, which are all clinically distinct.

Guttate psoriasis is characterized by small drops of psoriasis over the entire body and no plaque is observed. These psoriatic lesions are located mainly in zones where friction with clothing is involved, such as lower abdomen and lower back, forearms, chest, but also on the scalp and external ear pavilion. Most commonly developed in children or adolescents, guttate psoriasis generally occurs as a result of a  $\beta$ -haemolytic streptococcal infection, such as tonsillitis, pharyngitis or an upper respiratory tract infection. This acute form of psoriasis often resolves itself, except for some cases that subsequently develop chronic plaque psoriasis [15] [22]. Guttate psoriasis, such as psoriasis vulgaris, has a strong association with the psoriasis susceptibility locus 1, PSORS1, in the major histocompatibility complex region [23]. Genetic predisposition associated with psoriasis vulgaris is discussed in the next section of this review.

Pustular psoriasis is characterized by the presence of pustules on the palms and soles only, in the palmoplantar pustulosis form, or anywhere on the body, in the generalized form [15] [24]. This variant of psoriasis can also progress with plaque psoriasis when the plaques become very inflamed and itchy [16]. Unlike guttate psoriasis, there is no evidence that the three candidate genes at the PSORS1 locus are involved in palmoplantar pustulosis, which appears to be a distinct disorder [23].

Erythrodermic psoriasis is widespread almost all over the body and may be accompanied by severe itching, swelling and pain. It can cause a state of hypothermia, anemia, risk of heart failure or acute respiratory distress syndrome [4] [7]. Erythroderma may be a life threatening condition, and could perhaps be the morphologic presentation of a variety of skin and systemic diseases [25]. Consequently, it is difficult to establish a diagnosis of the underlying disease. The development of erythrodermic psoriasis occurs when there is poor control of an already existing psoriasis, sometimes caused by an abrupt withdrawal of systemic drugs, such as corticosteroids, or in response to a drug such as lithium.

### 3. Genetic Predisposition

A knowledge of the genetic involvement in plaque psoriasis is essential in understanding the disease as well as developing effective treatments. The genetic predisposition is one factor that is known to initiate the characteristic lesions of plaque psoriasis, but is not the only one, as in fact, some psoriasis patients do not present any genetic influence. The genetic predisposition was evidenced by cases involving monozygotic twins and dizygotic twins [31]-[33], but the accurate etiology and the precise role of the genes in the pathogenesis remains unclear. Because genes play a key role in the psoriatic skin disease, understanding the correlation between the genotype-phenotype and the psoriasis susceptibility loci is essential for developing leads to new therapeutic options.

#### 3.1. Genes Can Trigger Psoriasis-Psoriasis Susceptibility Loci

The patient's genetic background influences around 35% - 50% of the psoriasis heritability, and the PSORS1 and PSORS2 are the principal locus involved [11] [34]. There are three genes in the PSORS1 locus associated with plaque psoriasis. The first one, the HLA-C, is a variation of HLA-Cw6, responsible for the codification of

MHC first class protein [35] [36]. The other two are the CCHCR1, a coiled-coil  $\alpha$  helical rod protein 1 and the CDSN, five variant alleles that encode the over expressed protein corneodesmosin. However, 36 genetic loci linked to the occurrence of psoriasis have already been identified, 21 of which are associated with European ancestry. In a recent study, 15 psoriasis-associated regions were identified that are involved in pathway immune mechanisms and show up regulated genes and down regulated genes [37].

The pro-inflammatory genes, genes encoding interleukin (IL)-12, IFN- $\gamma$ , and IFN- $\gamma$ -regulated chemokines or inflammatory mediators also influence the plaque psoriasis and can affect severity of the skin disease [38] [39]. The single-nucleotide polymorphisms (SNPs) and many genes are already associated with plaque psoriasis, such as IL-23R, IL-23A, IL-12B, LCE (late cornified envelope), HLA-Cw\*-0602, ZNF313 (zinc-finger protein 313), TNFAIP3 (tumor necrosis factor  $\alpha$  induced protein 3) [28], RNF114 (ring finger protein 114), TRAF3IP2 (TNF receptor-associated factor 3 interacting protein 2) and others. Genes expressed in keratinocytes were also identified in plaque psoriasis as LCE3B and LCE3C1 (late cornified envelope 3B and 3C1, respectively) [34]. In a comparison between lesional and non-lesional skins of plaque psoriasis patients, deregulation was observed in the expression of 23 genes [29]. It was also demonstrated that the genes IL-19, IL-20 and IL-24 affect plaque psoriasis, providing a protective effect to haplotypes CAAAC, TGGGT and CGAGT (IL-20/IL-24) [40] and an inductive effect in to haplotype CACCGAA (IL-19/IL-20) [41].

Since recent progress has been made related to genes and psoriasis susceptibility, many studies have focused on identifying genes that may help decrease the psoriatic plaque. Treatments with biologics drugs have demonstrated gene inhibition, as Adalimumab normalized the genes for innate immunity and epidermal compartment [42], while it was shown in a randomized study that Guselkumab reduced the psoriasis gene expression in patients [43]. Etanercept decreases the IL-17A genes expression [44] and a similar result was observed in patients after treatment with Brodalumab. In this latter case, the genes IL-17A and IL-17C were also down regulated, while IL-17F, responsible for the IL-17 regulation, demonstrated to be dose-dependent with the treatment [45].

### 3.2. Genotype-Phenotype Correlations

It is important to establish correlations between clinical observations and gene expression to understand the genetic risk factors of plaque psoriasis. Several studies have been conducted that have already identified the influence of IFIH1, which encodes the interferon-induced with helicase C domain 1 [46], whereas ERAP1, responsible for the codification of one amino peptidase, regulates the quality of peptides bound to MHC class I molecules, such as HLA-C\*06 [47]. The HLA-CW6 is associated with psoriasis development before 40 years of age [48] [49] and with high prevalence in British population [50]. In the IL-12B gene, some SNP has been associated with susceptibility of plaque psoriasis development and with the production of IL-12 and IL-23 in individuals of different ethnic groups [51] [52], including North American Caucasian, European and Asiatic [53]-[56].

One study included 151 psoriasis pediatric patients and 451 healthy controls, all of European descent with a primary diagnosis of plaque-type psoriasis before the age of 18 years. No significant phenotype variations between patients of different ages were found, but a correlation was identified between the genes IFIH1 and ERAP1 and the severity of the disease [57]. Another study performed in Mexican Mestizo population from western Mexico showed that there is no correlation between the SNPrs3212227 (identified in the IL-12B gene), the susceptibility to develop plaque psoriasis and levels of IL-12 and IL-23 in serum [58]. The age and the sex of the patients have no significant influence in genetic aspects of the plaque psoriasis [50]. In China, the SNP rs72474224 in GJB2 is reported as genetic susceptibility to plaque psoriasis and might contribute to the complexity of the disease [59] as well as the polymorphism rs6887695 of the IL-12B gene [60]. In contradiction with the study of Oostveen *et al.* [57], Hébert *et al.* found eight loci associated with early-onset psoriasis, HLA-C, IL-12B, TRAF3IP2, IL-23R, RNF114, IFIH1, IL-23A and HLA-A [61]. Indeed, the influence of HLA-C and IL-12B had already been described in a previous study [37] [62].

Several studies have focused on the genes involved in the onset of psoriasis before 40 years. However, the genetic influence on plaque psoriasis can also be present in the late onset psoriasis as demonstrated by Hébert *et al.*, suggesting that the late onset of psoriasis can be a type of plaque psoriasis [61]. Besides the influence in the disease onset, the genes can also be involved in the thickness of the plaque psoriasis [29] [63], including the genetic expression of IL-22, IL-19 and LCN2 in non-lesional skin of the thick plaque psoriasis patients [29]. Furthermore, one recent study evidenced the correlation between the C677T polymorphism in the methylenetetrahydrofolate reductase polymorphism and plaque psoriasis severity [64], corroborating the study of the Baiqiu *et*

al. [65].

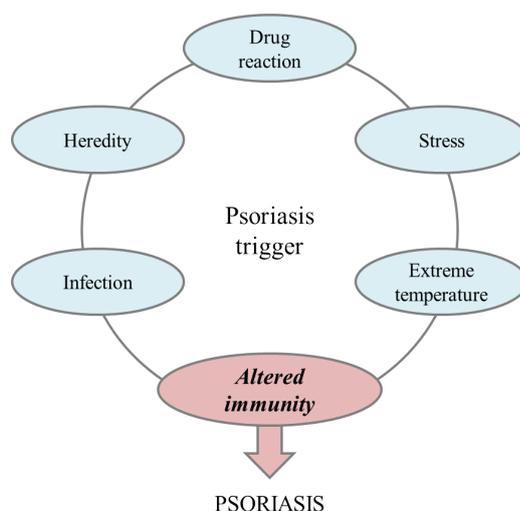
In summary, the pathway to elucidate the factors triggering plaque psoriasis involves knowledge of the genetic contribution. Accurate genetic influence in plaque psoriasis is not completely understood but is well documented, and many advances have already been achieved. However, more studies exploring that relationship are necessary to fully elucidate genetic involvement in plaque psoriasis.

#### 4. Environmental Factors in the Psoriasis Pathology

Although the exact causes of psoriasis are not fully understood, it is widely accepted that environmental factors and genetic predisposition act jointly to lead to the development of the disease. Many environmental risk factors, such as smoking habits, extreme temperature, drug reaction, stress and infections, appear to be able to trigger or exacerbate the disease [66] and are discussed below (Figure 2).

Smoking is a leading lifestyle factor that affects human health and can influence the development of psoriasis, since smoke has an important extra-pulmonary toxicity [67]. Epidemiologic studies have pointed to a strong association between psoriasis and current smokers, and between psoriasis and former smokers [68]. Psoriasis is a T cell immune-mediated disease and nicotine alters a wide range of immunological functions, including innate and adaptive immune responses [69] [70]. In fact, according to the literature, nicotine consumption results in an increased secretion of IL-12 and numerous other pro-inflammatory cytokines involved in pathologies, such as tumor necrosis factor [71]. Nicotine present in tobacco also causes dysregulated expression of vascular endothelial growth factor, an important factor in angiogenesis. Since psoriasis is characterized by an increase in angiogenesis [12], this could partly explain the relationship between smoking and psoriasis. The influence of long-term smoke exposure on the development of psoriasis also stems from the fact that smoking induces oxidative stress and free radical damage [67]. The increased presence of free radicals in the human body has the potential to trigger a cascade of systemic effects, including the development of psoriasis.

Psychological or emotional stress is one of the main reasons for the exacerbation of psoriasis patients [72]. Indeed, psychological stressors might contribute to the severity of chronic inflammatory diseases such as psoriasis by dysregulating hypothalamic-pituitary-adrenal (HPA) axis activity, where the body begins to secrete the hormone cortisone, which affects the epidermal barrier and increases the secretion of pro-inflammatory cytokines [73] [74]. Besides the psychological stress, the body may suffer physical stress trauma to the skin, like sunburn or scratches. This physical trauma can trigger psoriasis patients in the Koebner phenomenon, a phenomenon characterized by the appearance of psoriasis after skin trauma, ahead of exacerbation of psoriasis [75] [76].



**Figure 2.** Various causative factors could influence the development of psoriasis. Environmental factors such as extreme temperature, infection, stress or smoking and genetic predisposition act jointly to lead to the development of psoriasis.

The development of plaque psoriasis can also be affected by seasonal variation. In fact, psoriasis worsens in winter, because the temperature of this cold season causes a low level of humidity, which in turn may increase skin permeability, induce thickening of the epidermis and stimulate the production of inflammatory mediators [77].

Furthermore, certain drugs are known for inciting or exacerbating triggers of psoriasis. Indeed, drugs like lithium and beta-blockers can trigger psoriasis, while antimalarial drugs such as chloroquine or hydroxychloroquine may exacerbate it [78]. Lithium and beta-blockers decrease the level of cyclic adenosine monophosphate (cAMP) in keratinocytes, thus leading to an increased proliferation and decreased differentiation [79], as chloroquine or hydroxychloroquine inhibit transglutaminase in the epidermis, an important enzyme in the formation of the epidermis [80].

Microbial infections may also exacerbate pre-existing chronic plaque psoriasis, in addition to being responsible for the onset of disease in normal subjects. *Streptococcus pyogenes* ( $\beta$ -hemolytic) infections were strongly associated with the initiation of guttate psoriasis [81] while *Staphylococcus aureus* or yeast such as *Candida albicans* have been reported as being responsible for the worsening of psoriatic lesions [78]. These three microorganisms have similar mechanisms of action involving all superantigens capable of activating T cells [82].

## 5. Comorbidity

Psoriasis patients are known to have an elevated risk of developing comorbidities such as cardiovascular diseases, metabolic syndromes, and others [83]-[86]. The high presence of the pro-inflammatory cytokines, as for example, the TNF, interleukins, IFN- $\gamma$ , and C-reactive protein, can contribute to initiation of other diseases by the deregulated trafficking of the immune cells, and can be released into the systemic circulation modifying the function of the cells in different organs [87]. Plaque psoriasis treatments can contribute to attenuate risk of comorbidities or can further increase the risk. The TNF- $\alpha$  antagonists are associated with the decrease of liver comorbidities and arthropathies [88] [89], however these are also related to weight gain in patients [90] and infectious diseases [91]. Furthermore, methotrexate use is associated with reduced risks of cardiovascular diseases in comparison to non-treated patients [92], but is associated with hyperhomocysteinemia and liver fibrosis [93].

### 5.1. Cardiovascular Disease

Psoriasis patients have about a 25% increased relative risk of cardiovascular diseases [94] and have related risks for arterial stiffness [95], vascular damage, atherogenesis [84], myocardial infarction and coronary artery calcification [96] [97]. In fact, coronary disease is the most common cardiovascular comorbidity associated with psoriasis [97] [98]. Studies conducted on plaque psoriasis, with adults and children, have demonstrated the high prevalence of the relationship between plaque psoriasis and cardiovascular disease. Torres *et al.* conducted a case-control study on children that showed an increase in atherogenic factors related to the risk of cardiovascular diseases [99]. In addition, high levels of cytokines in the blood stream, such as TNF- $\alpha$ , IL-2, IL-17 and IFN- $\gamma$ , combined with altered angiogenesis and endothelial functions were studied as a possible cause of cardiovascular diseases [100] [101] and accelerated atherosclerosis [102], which is a situation present in plaque psoriasis. In one case-control study, Arias-Santiago *et al.* found four times more carotid atheroma plaques in psoriatic patients than in controls [103]. Votrubova *et al.* in a study conducted with 131 patients with chronic plaque psoriasis and 267 control patients with other skin disorders, observed relationships between psoriasis and risk factors for cardiovascular diseases such as hypertension, higher body mass index and reduced HDL cholesterol levels [104].

Since psoriasis can initiate a cardiovascular disorder, with altered risk factors, treatments alleviating plaque psoriasis may be useful for reducing those risk factors, as shown by Boehncke *et al.* [105]. After fumaric acid ester treatment, patients with clinical insulin resistance returned to normal levels, and the high-sensitive CRP serum and vascular endothelial growth factor levels were reduced, causing the improvement of endothelial cell function in patients with moderate-to-severe psoriasis vulgaris.

### 5.2. Metabolic Syndrome

Metabolic syndrome includes different conditions such as obesity, dyslipidemia, diabetes and hypertension [106]. In obese patients, the occurrence of these conditions is twice as frequent when the patients have psoriasis in comparison to patients without psoriasis or with other skin diseases [107]. This fact was confirmed in the

study of Akcali *et al.* [108], where hypertension was more frequent in patients with psoriasis than in controls. Furthermore, Rajappa *et al.* [83] showed the increase of pro-inflammatory adipokines, insulin levels and insulin resistance indices and the decrease of anti-inflammatory adipokines, adiponectin and insulin sensitivity indices in psoriatic patients in comparison with controls.

The exact mechanism involved when psoriatic patients develop another related disease is not completely understood, but genetic and environmental factors and inflammatory components are probable causes. The overproduction of pro-inflammatory cytokines, with persistent secretion of TNF- $\alpha$ , IL-1, IL-6 and others, can contribute to chronic inflammation and development of metabolic disorders [109] [110]. The high pro-inflammatory mediator levels in the pathogenesis of psoriasis are also responsible for the metabolic syndromes. In the case of obesity as comorbidity, for example, that dysregulation can increase the production of leptin, visfatin, resistin, IL-6 and a decrease in the anti-inflammatory adipokines with insulin-sensitizing properties levels [111] [112] and consequently, initiation of the disease.

Treatment of psoriasis with acitretin, ciclosporin and TNF- $\alpha$  antagonists can contribute to the development of comorbidities by the increase of serum lipid levels [113], by the increase of serum uric acid and the development of dyslipidaemia [114] and by a weight gain induced by these drugs [90]. Besides, treatment with methotrexate helps to decrease the adipokines levels in psoriatic patients by anti-inflammatory action [83]. Though the TNF- $\alpha$  antagonists possibly contribute to weight gain, studies also indicated that those drugs can help to reduce the intima-media thickness, an indicator of atherosclerosis [54].

### 5.3. Coagulation Disorders

The influence of the psoriasis in platelet activation has also been studied. The platelets are responsible for hemostasis support, and deregulation can cause several cardiovascular diseases, such as atherosclerosis, coronary vascular disease and cerebrovascular disease [115]-[117]. It has been shown, in plaque psoriasis patients, that platelets tend to aggregate and consequently cause occlusive vascular disease [115] [116]. Several platelet indices are altered in psoriatic patients, such as mean platelet volume, higher reactivity when put in contact with adenosine diphosphate, collagen and thrombin [118]. Psoriasis can initiate an increase in the concentrations of the inflammatory markers [116] [119] and the platelet activation can initiate another disorders [116] [120].

### 5.4. Other Inflammatory Disease

Psoriatic patients have high risk of some cancers, such as lymphoma and non-melanoma skin cancer [121] [122]. The increased risk of those diseases can be associated with the physiology of the disease or its treatment. With severe plaque psoriasis, the patients taking antitumoral and immunosuppressor drugs, besides the PUVA treatment, present an increased risk of tumor development [123]. Dental problems, such as periodontitis and radiographic bone loss, are other disorders that plaque psoriasis patients may develop with a higher risk than the general population [124]. Other studies have identified, in some patients, hyperuricemia, high serum uric acid and chronic kidney disease as consequences of psoriasis [125]. These cases can arise from the pathology or from the treatment, as for example, the use of nonsteroidal anti-inflammatory drugs, which is strongly linked with kidney problems [125].

## 6. Conclusion

Psoriasis is a chronic skin disorder characterized by erythematous plaque with silvery white scales. The scaly red plaque is a clinical reflection of hyperkeratosis, parakeratosis, acanthosis of the epidermis, dilated vessels, and an inflammatory infiltrate composed primarily of lymphocytes. Skin lesions may be on specific anatomic sites, such as elbows or knees, or on the entire skin surface. Although the characteristics of psoriasis are well documented, the cause of the disease remains unknown. However, two main factors that affect the onset and exacerbation of the disease have been reported: environmental factors and genetic predisposition. Both factors would act jointly in triggering the disease. This skin disease can appear at any age, but two peaks in age of onset have been reported: one at 20 - 30 years and a second at 50 - 60 years. In approximately 75% of the occurrences, the onset is before 40 years old, where the HLA-CW6 is associated. People with psoriasis are at an elevated risk of developing other chronic and serious health conditions, also known as “comorbidities”, such as cardiovascular disease, metabolic syndrome (obesity, dyslipidemia, diabetes and hypertension) and coagulation disorders.

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