

Psoriasis Risk Factors and Triggers

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PRACTICE POINTS

- HLA-Cw6 and *CARD14* are genetic factors associated with psoriasis.
- Psoriasis in the setting of human immunodeficiency virus infection may be treated with topical steroids, phototherapy, systemic retinoids, or apremilast.
- Psoriasis is a potential adverse effect in patients taking lithium or tumor necrosis factor inhibitors.
- Patients should be counseled about the role of obesity and smoking on psoriasis.

Numerous factors contribute to the onset and exacerbation of psoriasis. Genetic risk factors include HLA-Cw6 and mutations in the caspase recruitment domain family member 14 gene, *CARD14*. Environmental risk factors, including infectious diseases, medications, and lifestyle, also have been implicated. It is important for clinicians to be aware of these risk factors and triggers because they might provide insight into the pathogenesis of psoriasis as well as help patients understand more about their disease.

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Psoriasis is a chronic autoimmune skin disease affecting approximately 6.7 million adults in the United States.¹ Although its pathogenesis is not yet clear, risk factors and triggers provide insight into potential pathways by which psoriasis can occur. There is notable overlap between risk factors and triggers of psoriasis; perceived risk factors might, in fact, be triggers causing manifestation of disease in predisposed persons. In this review, we summarize the key factors contributing to onset and exacerbation of psoriasis. When learning to manage this chronic disease, it also may be helpful to

educate patients about how these elements may affect the course of psoriasis.

Genetics

The pathogenesis of psoriasis has a strong genetic component, with approximately 70% and 20% concordance rates in monozygotic and dizygotic twins, respectively.² Moreover, studies have shown a positive family history in approximately 35% of patients.^{3,4} Family-based studies have found a 50% risk of developing psoriasis in patients with 2 affected parents.⁵ However, the genetics of psoriasis are complex and are attributed to many different genes. Thus far, genes involving antigen presentation, T-cell receptor development and polarization, and the nuclear factor $\kappa\beta$ (NF- $\kappa\beta$) pathway have been identified.⁶

HLA-Cw6—The most well-studied gene implicated in psoriasis is HLA-Cw6, which encodes a major histocompatibility complex class I allele supporting psoriasis as a T cell-mediated reaction to an autoantigen.⁶ Two potential antigens for HLA-Cw6 recently have been identified: LL-37, a cathelicidin-related antimicrobial peptide, and the A disintegrin and metalloproteinase with thrombospondin motifs-like protein 5 (ADAMTSL5), found on melanocytes and keratinocytes.⁷ The percentage of psoriasis patients with HLA-Cw6 ranges from 10.5% to 77.2%, with higher frequency in white individuals than in Asians.⁷

HLA-Cw6 manifests as specific features in psoriasis, including onset of disease before 21 years of age.⁸ It also is more strongly associated with guttate-type psoriasis, greater body surface area involvement, and higher incidence of Köbner phenomenon. Patients with positive HLA-Cw6 also reported worsening of psoriasis during and after throat infection.⁹

Caspase Recruitment Domain Family Member 14—Another gene mutation implicated in psoriasis pathogenesis

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is caspase recruitment domain family member 14, *CARD14* (formerly *PSORS2*), a gene encoding a scaffolding protein important in the activation of NF- κ B.^{10,11} Missense *CARD14* mutations cause upregulation of NF- κ B through formation of a complex with adapter protein B-cell lymphoma 10 (BCL10) and mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1),¹² which, in turn, causes increased transcription of cytokines IL-8, C-C motif chemokine ligand 20 (CCL-20), and IL-36 gamma in the keratinocyte.¹³ Mutations in *CARD14* alone lead to psoriasiform skin in mice through amplified activation of the IL-23/IL-17 axis.^{14,15} Patients with a mutation in a *CARD14* variant (p.Arg820Trp) have demonstrated better response to tumor necrosis factor (TNF) inhibitors.¹⁶

Further characterization of the genetic pathogenesis of psoriasis might lead to better targeted therapies, including the possibility of MALT1 inhibitors as a treatment option.¹²

Infection

Streptococcus—The association between streptococcal infection and psoriasis was first documented more than 100 years ago, specifically the onset of acute guttate psoriasis.^{17,18} Although classically described following throat infection, psoriasis also occurs following streptococcal vulvovaginitis and perianal streptococcal infection.^{19,20}

This type of psoriasis is typically self-limited but can recur with subsequent streptococcal infections or initiate a more chronic plaque psoriasis. Patients have a 1 in 3 risk of developing chronic psoriasis within 10 years of a single episode of acute guttate psoriasis.²¹ Moreover, in many patients with existing plaque psoriasis, throat infection exacerbates psoriatic symptoms.²² The mechanism of exacerbation is likely due to cross-reactivity between streptococcal M surface antigen and human keratinocytes and might also be influenced by inherited abnormalities in immune response.²³⁻²⁶ Therefore, tonsillectomy has been studied as a possible treatment of psoriasis but is likely helpful only in patients with exacerbations of disease that are closely associated with recurrent tonsillitis.²⁷

Human Immunodeficiency Virus—The prevalence of psoriasis in human immunodeficiency virus (HIV) patients is similar to or greater than the general population.²⁸ Human immunodeficiency virus infection causes new onset of psoriasis and exacerbation of existing psoriasis; severity often is correlated with worsening immune function.^{28,29}

The clinical subtypes of psoriasis that occur most frequently with HIV include guttate, inverse, and erythrodermic, though patients may present with any subtype.²⁸ The mechanism is puzzling because HIV is primarily mediated by helper T cell 2 (T_H2) cytokines, whereas psoriasis is mainly driven by helper T cell 1 (T_H1) cytokines.³⁰ Furthermore, despite increased severity with lower CD4⁺ counts, treatments further lowering T-cell counts paradoxically improve symptoms.³¹ Current literature suggests that expansion of CD8⁺ memory T cells might be the primary mechanism in the exacerbation of psoriasis in HIV-mediated immunosuppression.³⁰

Treatment of HIV-associated psoriasis presents challenges because many therapeutics cause further immunosuppression. The National Psoriasis Foundation recommends topical preparations as first-line agents for mild to moderate psoriasis.³² For moderate to severe psoriasis, retroviral agents may be effective as first-line monotherapy or when supplemented by phototherapy with UVB or psoralen plus UVA. Retinoids can be used as second-line agents.³² For cases of severe refractory psoriasis, cyclosporine, methotrexate, TNF inhibitors, or hydroxyurea can be considered. There also is evidence that apremilast is effective without risk for worsening immune function.³³

Other Infections—Other bacteria associated with triggering or exacerbating psoriasis include *Staphylococcus aureus* and *Helicobacter pylori*.^{34,35} Fungi, such as species of the genera *Malassezia* and *Candida*, and other viruses, including papillomaviruses and retroviruses, also have been implicated.³⁴

Medications

Numerous medications can trigger psoriasis, including lithium, nonsteroidal anti-inflammatory drugs, antimalarials, beta-blockers, and angiotensin-converting enzyme inhibitors.³⁴ More recent literature suggests that TNF inhibitors also can paradoxically induce psoriasis in rare cases.³⁵

Lithium—Psoriasis is the most common cutaneous adverse effect of lithium.³⁴ It is more likely to exacerbate existing disease but also can induce onset of psoriasis; it also can cause disease that is more refractory to treatment.^{34,36} Current literature hypothesizes that lithium triggers psoriasis by interference of intracellular calcium channels through reduction of inositol, thereby affecting keratinocyte proliferation and differentiation.³⁴ Lithium also inhibits glycogen synthase kinase-3 (GSK-3), a serine threonine kinase, which, in turn, induces human keratinocyte proliferation.³⁷ However, it is unlikely lithium alone can induce psoriasis; genetic predisposition is necessary.

TNF Inhibitors—Tumor necrosis factor inhibitors such as adalimumab, etanercept, certolizumab pegol, golimumab, and infliximab are used in various inflammatory diseases, including psoriasis. Interestingly, there have been more than 200 reported cases of suspected TNF inhibitor-induced or -exacerbated psoriasis.³⁸ This phenomenon appears to occur more frequently with infliximab and is most likely to occur in the first year of treatment of Crohn disease and rheumatoid arthritis.³⁸ Plaque psoriasis is the most common form, but 15% to 26% of cases presented with 2 or more morphologies.^{38,39}

Treatment options include discontinuing therapy, though many patients experience resolution while continuing treatment or switching to another TNF inhibitor.³⁸⁻⁴⁰ Traditional topical therapies also have been used with success.⁴⁰ The pathogenesis of this phenomenon is still unclear but is thought to involve both the IL-23/helper T cell 17 (T_H17) axis and dysregulation of IFN- α in the setting of TNF suppression.³⁸

Lifestyle

Obesity is a chronic low-grade inflammatory state that can contribute to the onset of psoriasis or exacerbation of existing disease.^{41,42} Smoking also is thought to increase the risk for psoriasis, perhaps by a similar mechanism. Lee et al⁴³ found a strong positive correlation between the amount or duration of smoking and the incidence of psoriasis.

The relationship between psoriasis and alcohol consumption is less clear than it is between psoriasis and obesity or smoking; greater consumption is found in psoriasis patients, but evidence is insufficient to deem alcohol a risk factor.⁴⁴

Conclusion

Various factors, including genetics, infection, pharmacotherapeutic, and lifestyle, can all contribute to the induction or exacerbation of psoriasis. These factors can provide clues to the pathogenesis of psoriasis as well as help clinicians better counsel patients about their disease.

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